Clinical and magnetic resonance observations in cerebral small-vessel disease
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Disequilibrium in patients with atherosclerosis: relevance of pontine ischemic rarefaction

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Abstract

Background and purpose
To examine clinical relevance of isolated pontine hyperintense lesion (PHL) on MRI in patients with atherosclerosis.

Methods
Seventeen atherosclerotic patients with isolated PHL on MRI were compared with 17 patients without PHL, matched for age, sex and initial manifestation of atherosclerosis. Subjects and observer were blinded to the MRI findings. We assessed symptoms, impairment and disability with a protocolized interview and neurological examination, and disability scales.

Results
On all items patients with PHL scored worse than their controls. We found the largest differences in frequencies of symptoms of disequilibrium, difficulties with speech or swallowing, the Timed Walking Test and the body care and movement subscale of the Sickness Impact Profile. Except for disequilibrium (p=0.04), these differences did not reach statistical significance. Abnormal tandem-walking tests were more frequent in patients than in controls. Pyramidal signs were equally distributed.

Conclusions
We propose PHL as a cause of symptoms of disequilibrium in patients with atherosclerosis. Symptoms are probably elicited by dysfunction of the corticopontine fibers, the pontocerebellar fibers or the pontine nuclei.
Disequilibrium is a common symptom of the elderly with a prevalence of up to 30% in community-based studies.\textsuperscript{1,2} It is defined as a sensation of dizziness or unsteadiness when standing or walking, but not while sitting or lying down.\textsuperscript{3} Disequilibrium is a diagnostic challenge. There are many potential causes, but even after careful history and examination the cause often remains unclear in individual patients.\textsuperscript{3,4}

Leukoaraiosis (on CT-scan) or white matter lesions (on MRI) of the cerebral hemispheres is a cerebrovascular disorder that may cause disequilibrium.\textsuperscript{5,6} In 1995 Pullicino et al. reported 16 cases with “ischemic rarefaction” of the pons, that appears as a hyperintense area on T2-weighted magnetic resonance imaging (MRI). These lesions resemble supratentorial leukoaraiosis, as was histopathologically confirmed in two cases.\textsuperscript{7} Recently, we described characteristics of patients with similar pontine hyperintense lesions on T2-weighted MRI (PHL) and suggested that PHL is a manifestation of cerebral small vessel disease.\textsuperscript{8} The clinical relevance of PHL has so far only been examined in a Japanese study in a group of patients who also had supratentorial white matter lesions and pontine infarcts.\textsuperscript{9} Subjective complaints as vertigo and dizziness were found more frequently in patients with PHL.\textsuperscript{9} However, clinical studies about isolated PHL have to our knowledge not been done so far. We hypothesized that PHL may cause dysfunction of the pyramidal and cerebellar tracts and therefore cause gait or equilibrium disorders. We examined the symptoms and signs of patients with isolated PHL (without supratentorial white matter lesions) and compared them with those without PHL in a cohort of atherosclerotic patients.

Patients and Methods

For this study we examined patients with PHL, who had no supratentorial white matter lesions. These patients were identified in an ongoing prospective cohort study of 229 atherosclerotic patients, who had presented initially with either non-disabling ischemic stroke, myocardial infarction or peripheral arterial disease.\textsuperscript{10} Controls were patients from the same cohort
with neither PHL nor supratentorial white matter lesions.

We matched the controls for age, sex and the initial manifestation of atherosclerosis. For each patient with PHL a control was drawn and first matched for the initial atherosclerotic disease. Age was then individually matched as close as possible within the range of 10 years. Sex was matched as far as possible, but if this was not feasible, it was assigned a lower priority than the two other variables. The study was approved by the medical ethics committees in the participating hospitals. All patients and controls gave their informed consent.

Transversal T1-weighted spin-echo, proton density- and T2-weighted spin-echo images were made with a Siemens Magnetom 63 SP/4000 (1.5 Tesla). Two investigators (VIHK, BV) independently assessed the MRI scans without knowledge of clinical or laboratory data. We defined PHL as confluent hyperintense areas on T2-weighted or proton density-weighted images, without distinct borders. To avoid including pontine infarcts, cases with well-demarcated frank hypointense corresponding lesions on T1-weighted images were excluded. With these definitions the agreement for the presence or absence of PHL between the two observers was good (kappa = 0.63). We diagnosed PHL only if both observers independently agreed on its presence. In all other cases PHL was judged absent. Supratentorial white matter lesions were assessed on the T2-weighted and proton density-weighted images. Periventricular hyperintensities limited to small caps and pencil-thin linings were considered normal. Patients with more extended white matter lesions were excluded.

Neither the clinical investigator (LHZ) nor the patients were informed about the MRI-findings. All subjects were interviewed about problems with walking and equilibrium. We assessed symptoms and signs with a structured interview and physical examination. The question concerning disequilibrium was: “Did you suffer from dizziness or unsteadiness (on walking or standing) during the past year?” (see Appendix A). We paid special attention to gait, tandem-walking in a straight line, the Romberg test and pyramidal signs. Broad-based gait, variable stride-length or circumduction were considered abnormal. Tandem-walking was considered abnormal, if, after practicing once, the patient made more than two deviations
from a 5 meters straight line. If the patient stepped aside during the Romberg test, it was considered abnormal. Speed of walking was measured with the Timed Walking Test. Disability was assessed with the following scales: Rivermead Mobility Index, Hauser Ambulation Index, and “body care and movement”- and “ambulation”-subscales of the Sickness Impact Profile. These scales are given in appendix A.

Statistical analysis

We analyzed the variables in the two groups univariately with the Wilcoxon matched pair signed rank sum test to compare medians, the sign test for ordinal data, and the McNemar’s test for frequency data. A p-value of ≤ 0.05 was considered significant. Since this is an explorative study we were also interested in trends. Therefore we did not correct for multiple comparisons. We considered multivariate analysis inappropriate because of the small number of patients.

Results

In the cohort of 229 patients with symptomatic atherosclerosis we identified 20 patients with isolated PHL and described their characteristics in a previous study. In summary, there were strong associations with higher age, supratentorial white matter lesions and lacunar infarcts but not with hypertension, cardiac disease, smoking, hypercholesterolemia and diabetes mellitus. We compared the patients with isolated PHL with twenty controls from the same cohort. Two patients refused and one patient had bilateral amputated legs due to peripheral arterial disease. These three patients and their controls were excluded. Matching was successful concerning initial atherosclerotic disease (non-disabling ischemic stroke, myocardial infarction or peripheral arterial disease) and age. A full pairwise match for sex was not possible, but both groups were balanced for this variable.

To examine the exact location of PHL, patients MRI’s were drawn on sheets and superimposed on each other. PHL was most frequently located
in the central regions of the ventral part of the pons with relative sparing of the midline (figures 1 and 2). The mesencephalon and the medulla oblongata had a normal appearance.

Clinical data and results are given in the table. Three patients and controls had had a minor ischemic stroke, 7 pairs myocardial infarction and 7 pairs had peripheral arterial disease. These conditions had been diagnosed on average 3.6 years before the present study. There were no

Table. Characteristics of 34 patients with and without pontine hyperintense lesions on T2-weighted MRI (PHL).

<table>
<thead>
<tr>
<th></th>
<th>Patients with PHL (n = 17)</th>
<th>Patients without PHL (n = 17)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, yr</td>
<td>66 (47-80)</td>
<td>65 (47-77)</td>
<td></td>
</tr>
<tr>
<td>disequilibrium</td>
<td>12 (71%)</td>
<td>5 (29%)</td>
<td>0.04&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>difficulties with speech or swallowing</td>
<td>8 (47%)</td>
<td>2 (12%)</td>
<td>0.07&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>abnormal tandem-walking</td>
<td>10 (59%)</td>
<td>6 (35%)</td>
<td>0.29&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Babinski’s sign</td>
<td>5 (29%)</td>
<td>4 (24%)</td>
<td>1.00&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Timed Walking Test, sec.</td>
<td>9.6 (6.1-32.2)</td>
<td>8.7 (6.0-12.7)</td>
<td>0.07&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rivermead Mobility Index&lt;sup&gt;†&lt;/sup&gt;</td>
<td>14 (4-15)</td>
<td>15 (12-15)</td>
<td>0.34&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Häuser Ambulation Index&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1 (0-5)</td>
<td>1 (0-2)</td>
<td>0.34&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sickness Impact Profile&lt;sup&gt;‡&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>body care &amp; movement, %</td>
<td>4.3 (0.0-40.1)</td>
<td>0.0 (0.0-9.6)</td>
<td>0.05&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>ambulation, %</td>
<td>10.6 (0.0-49.6)</td>
<td>4.2 (0.0-44.4)</td>
<td>0.11&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>†</sup>median (range), <sup>‡</sup>McNemar’s test, <sup>‡</sup>Wilcoxon matched pairs signed rank sum test, 1sign test
Rivermead Mobility Index: 15 = no restriction >= 0 = maximal restriction
Häuser Ambulation Index: 0 = asymptomatic >= 9 = restricted to wheelchair, unable to transfer
Sickness Impact Profile: 0% = no dysfunction >= 100% = maximal dysfunction
other vascular events afterwards. One patient with myocardial infarction had a previous medical history of TIA, and 2 patients with stroke and one control with peripheral arterial disease had a previous history of myocardial infarction. Twelve of the 17 patients (71%) with PHL complained about disequilibrium versus 5 of the 17 controls (29%). Eight patients (47%) had difficulties with speech or swallowing versus 2 controls (12%). Five patients complained of clumsiness in arm or leg against 4 controls. All patients had normal eye movements. Babinski’s signs were equally distributed: 5 patients and 4 controls. Only one patient (with PHL) had an abnormal Romberg test. Abnormal tandem-walking was more frequent in patients (10) than in controls (6). On all scales the patients with PHL scored worse than their controls: longer median Timed Walking Test, lower scores in the Rivermead Mobility Index, more restrictions on the Hauser Ambulation Index and more dysfunction on the SIP scales. However, except for disequilibrium (p=0.04), these differences did not reach statistical significance.

To check the symptoms of disequilibrium, we examined the individual items of the Rivermead Mobility Index and the Sickness Impact Profile. The most common symptom scored on the Rivermead Mobility Index was that patients could not run or walk fast (item 15: “Are you able to run (or walk fast) 10 meters in 4 seconds without limping?”). The most frequently reported problems on the Sickness Impact Profile concerned balance and walking uphill or stairs (item 2 “I do not walk up and down hills”, item 4 “I
do not maintain balance”, item 7 “I walk by myself but with some difficulty, for example limp, wobble, stumble, have stiff leg”, item 9 “I go up and down stairs more slowly, for example, one step at a time, stop often”.

Discussion

We found that patients with PHL significantly more often report disequilibrium than do controls. On all physical examination and clinimetric items patients scored worse than did controls. Statistical significance on most individual scales was not reached, probably because of the small sample size. It should be noticed, that we did not correct for multiple comparisons (a total of 10), since we were interested in trends in this explorative study. The fact that symptoms, signs and disability scales all point to the same direction, strongly indicates that our findings are valid. Bias was prevented by blinding patients and observer to the MRI findings. Our results are in accordance with a previous Japanese study, of which only an English abstract is available. In this study, patients with PHL more frequently complained of “vertigo-dizziness” than controls and than patients with pontine infarcts. However, patients with supratentorial white matter lesions were included. It is known, that such lesions are also associated with disequilibrium. In our study we examined patients with isolated PHL.

PHL is mainly located in the central area of the ventral part of the pons (figure 2), where the corticospinal tracts cross the pontocerebellar fibers and the pontine nuclei. The pontine nuclei receive corticopontine projections from the ipsilateral frontal and parietal lobes. From these nuclei efferent pontocerebellar fibers pass through the middle cerebellar peduncle to the cerebellum, where they relay on the globose and emboliform nuclei and project to the cerebellar hemispheres. Theoretically, PHL might affect the function of the corticospinal, corticopontine or pontocerebellar fibers. The more dorsally located medial lemniscus, reticular nuclei, medial longitudinal fasciculus and reticulospinal and tectospinal tracts and the more caudally located vestibular nuclei are spared. We found no differences in the frequency of pyramidal signs between patients and controls, but more
patients had abnormal tandem-walking compared with controls. These findings and the location of PHL suggest that disequilibrium in these patients is caused by dysfunction of the corticopontine fibers, the pontocerebellar fibers or their connections in the pontine nuclei.

Isolated lesions of pontine nuclei or of the tracts that traverse through the middle cerebral peduncle have neither been described in man, nor have been studied in animal models.\textsuperscript{18} Ventral pontine lacunar infarcts, especially the anterolateral infarcts, may cause the syndrome of ataxic hemiparesis, or bilateral leg ataxia with only slight or absent paresis.\textsuperscript{19,22} In these lesions the corticopontine or pontocerebellar fibers are mainly destroyed.\textsuperscript{19,23} In our patients symptoms of disequilibrium and abnormal tandem-walking might be the only manifestation of impaired function of the same structures. Although subtle, this may lead to increased disability, as suggested by the worse scores on the disability scales. More specifically, the most common complaint was that they could not run fast, walk fast, or walk uphill or stairs. Patients also more frequently reported difficulties with speech or swallowing. There were no other lesions on MRI in the brainstem than PHL, that could explain these symptoms, and we postulate that these symptoms may also be attributable to PHL.

The regions in the ventral pons, where PHL is predominantly present (figure 2), are situated in a borderzone area of the penetrating pontine arterioles.\textsuperscript{24,25} Pathologic changes of these arterioles, such as lipohyalinosis, may cause ischemia with subsequent loss of myelin and oligodendroglia cells.\textsuperscript{7} Other observations also suggest a link between disequilibrium and cerebrovascular disease. Dizzy patients more often take aspirin, and more frequently have a history of cardiovascular disease and signs of vascular lesions on MRI of the brain.\textsuperscript{1,5,8} In our previous study we found a strong association with supratentorial white matter lesions and lacunar infarcts.\textsuperscript{10} These findings suggest a common pathophysiology, namely small-vessel disease. In the histopathologic studies of Pullicino et al. the same microscopical changes were seen both in PHL and supratentorial white matter lesions.\textsuperscript{7}

Our current findings suggest that PHL, induced by micro-angiopathic changes leading to ischemia in the perfusional borderzones in the central pons, may be a cause of disequilibrium in patients with atherosclerosis.
Chapter 4

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References


