Through the looking glass: Risk factors, radiological hallmarks and cognitive function in cerebral small vessel disease

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Perivascular distribution of white matter hyperintensities in cerebral small vessel disease: A 7 Tesla MRI study

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ABSTRACT

Background The exact aetiology of white matter hyperintensities (WMHs) remains elusive. Involvement of both arterioles and venules have been implicated. We investigated anatomical involvement of small arterioles and venules in WMHs, using ultra high field imaging (7T MRI) with particular interest in differences in periventricular and deep WMHs.

Methods Thirteen patients (age 63±13 yrs) with a recent lacunar infarct underwent 7T MRI. Presence of a hypo-intensity, suggestive for a blood vessel, in each WMH was noted using the axial, sagittal and coronal FLAIR images. Hypo-intensities were considered blood vessels when they 1) could be visualized in at least two perpendicular planes, 2) appeared linear/tortuous in at least one plane and 3) were completely surrounded by hyperintense signal in at least one plane. Subsequently, the presence of a venule within each WMH was evaluated with 3D multi-echo gradient imaging. If a venule was found at the anatomical location of a WMHs in >2 planes, this was counted as a present venule in the WMH.

Results We counted 232 WMHs (interpatient range 0–50). 69.8% of all counted WMHs contained a central blood vessel (interpatient range 33%–100%). Periventricular WMHs were more likely to contain a central blood vessel than deep WMHs (88.4% vs 56.9%, p<0.0001). Of all WMHs, 55.6% contained a venule. Periventricular WMHs were also more likely to contain a venule than deep WMH (79.3% vs 39.5%, p<0.001).

Conclusions This study shows that WMHs often contain a small blood vessel, which can be visualized using 7T MRI. Our findings suggest a role for venules as well as arterioles in the development of WMHs, possibly dependent on anatomical location.
INTRODUCTION

White matter hyperintensities (WMHs) of presumed vascular origin are focal hyperintense lesions seen on T2-weighted Magnetic Resonance Imaging (MRI). They are commonly seen in elderly patients with cerebral small vessel disease (CSVD), and have been associated with cognitive dysfunction, dementia and altered gait, although they can also be clinically silent. There is a considerable amount of pathological heterogeneity between WMHs, although they appear similar on conventional MRI. Involvement of the small cerebral blood vessels have been proposed, including both arterioles and venules. Arteriosclerosis and endothelial dysfunction in the arterioles are presumed to cause chronic ischemia and leakage of the blood-brain barrier and may therefore cause WMHs. However, abnormal venules have also been implicated as a possible contributor and venous collagenosis has been described in patients with WMHs. The exact role of venules in the development of WMHs is still unclear.

Anatomical location of WMHs is often used to distinguish different types of WMHs. In epidemiological studies, periventricular WMHs are more strongly associated with classical risk factors such as hypertension, contribute more to brain atrophy and are more strongly associated with cognitive dysfunction compared to deep WMHs. This suggests that periventricular and deep WMHs may have different aetiologies. Given the different vascular territories of periventricular and deep white matter it could be that part of aetiological difference is explained by differing underlying vascular pathologies. Conventional 1.5 Tesla and 3.0 Tesla MRI cannot detect detailed differences between WMHs. Ultra high field 7 Tesla (7T) MRI has an increased signal-to-noise ratio and enhanced spatial resolution compared to 3T MRI, and could provide new insights in the aetiology of WMHs. We performed an explorative 7T MRI study in cerebral small vessel disease patients to quantify the amount of blood vessels within WMHs with particular attention to venules. Moreover, given the possible distinction between anatomical localisation, we hypothesized that the proportion of blood vessels and venules would differ between periventricular and deep WMHs.

MATERIALS AND METHODS

Subjects

Fifteen patients suspected of a lacunar infarct and admitted to the neurology ward of the University Medical Center Utrecht and the Academic Medical Center, without contra-
indication to undergo 7 Tesla MRI, were enrolled between December 2009 and September 2012. All patients were included within five days after onset of their symptoms. An acute lacunar infarct was diagnosed based on clinical presentation and diffusion weighted imaging (DWI) of the study MRI. This study was approved by the local ethics committee of the University Medical Center Utrecht and written informed consent was obtained from all participants.

**Image acquisition**

All patients were scanned on a 7T MRI scanner (Philips Healthcare, Cleveland, OH, USA). The protocol contained five sequences: 1) 3D multi-echo gradient echo for combined time-of-flight angiography and susceptibility weighted imaging for angiography, and detection of microthrombi and microbleeds, 2) DWI to identify ischemic lesions, 3) 3D T1-weighted imaging; 4) T2-weighted imaging and 5) 3D Magnetized Prepared Fluid Attenuated Inversion Recovery (3D MP-FLAIR).

**Image analysis**

All images were analyzed in viewing software (DICOM viewer, Philips Industries; MEVISLAB version 2.5). Using T1-weighted images, T2-weighted images and DWI the lacunar infarct was identified. WMHs were identified on axial 3D MP-FLAIR images. Due to improving scanning techniques during the study, the spatial resolution varied from 0.4–0.8 mm. Because of the spatial resolution of 0.8 mm, a WMH had to be at least 2.4 mm (3 x 0.8 mm) to harbour a visible hypo-intensity that was completely surrounded by a WMH. Therefore, a WMH had to be ≥3 mm to be counted. WMHs were classified as periventricular (≤1 cm distance from the ventricle in) or deep (>1 cm distance from the ventricle). Anatomical region as noted (frontal, parietal, temporal, occipital, insular). Large confluent WMHs were not counted as WMHs. Absence or presence of a hypo-intensity in each WMH was noted using the axial, sagittal and coronal FLAIR images. Hypo-intensities were considered blood vessels when they 1) could be visualized in at least two perpendicular planes, 2) appeared linear/tortuous in at least one plane and 3) were completely surrounded by hyperintense signal in at least one plane (to avoid the inclusion of adjacent rather than central blood vessels). If there were multiple hypo-intensities present within a WMH, it was counted as “present blood vessel”. Subsequently, the axial, sagittal and coronal FLAIR images were compared with the three echo gradient images with increasing echo times. Venules were defined in the same way as hypo-intensities and had to have increasing hypo-intensity with increasing echotimes.
If a venule was found at the anatomical location of a WMHs in >2 planes, this was counted as a present venule in the WMH. Examples of present hypo-intensities and venules are shown in Figure 8.1. Presence and number of microbleeds were scored for every patient. WMH load was also assessed using the ARWMC scale.11

Statistical analysis
Prevalence of WMHs, blood vessels and venules was reported for individual patients and the study sample. McNemar testing was used to test for a difference between the proportion of periventricular WMHs with a blood vessel compared with deep WMHs. This was repeated to test for a difference in the proportion of periventricular and deep WMHs with a central venule. To adjust for age and sex, we used a logistic regression model with presence of blood vessel or venule as outcome and location of WMH (deep and periventricular, age and sex as determinants). Additionally, we adjusted for size of the WMH as the chance of finding a blood vessel increases with the size of the WMH. The product of the largest width and length was used as an estimate for size of the WMH. Finally, because the highest density of venules and largest venules are located periventricular, we additionally adjusted for presence of a venule in the logistic regression analysis with blood vessel as outcome measurement.

RESULTS
Two of the fifteen enrolled patients were excluded from the analysis: one patient was finally diagnosed with conversion disorder instead of a lacunar infarct and in the second the image quality was insufficient due to motion artefacts. For the analysis using the echo gradient images, 2 additional patients were excluded, because of insufficient quality of these images. Baseline characteristics are shown in Table 8.1. The mean age (SD) of the 13 patients was 63 (± 13 years) and 69% were female. 69% of patients had a history of hypertension and 31% had a history of lacunar infarcts. The newly diagnosed lacunar infarcts were located in the basal ganglia (n=4), internal capsule (n=2), corona radiate (n=2), mesencephalon (n=2), medulla oblongata (n=1), centrum semiovale (n=1) and thalamus (n=1).

We counted 232 WMHs in total (interpatient range 0–50). The median ARWMC score was 7 (interpatient range 0–14). Deep WMHs were slightly more prevalent than periventricular WMHs (59% vs 41%). WMH were most common in the centrum semiovale (41%), corona radiate (40%) and basal ganglia (including internal and external capsule) (13%). Frontal
Table 8.1  Baseline characteristics and results (n=13)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Location infarction</th>
<th>Number of WMHs</th>
<th>% blood vessel present / % venule present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>77</td>
<td>Corona radiate L</td>
<td>9</td>
<td>50% / 25% / 100% / 100% / 78% / 67%</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>76</td>
<td>Basal ganglia L</td>
<td>30</td>
<td>79% / 29% / 88% / 69% / 83% / 50%</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>76</td>
<td>Mesencephalon R</td>
<td>6</td>
<td>none / 100% / na / 100% / na</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>72</td>
<td>Mesencephalon L</td>
<td>11</td>
<td>67% / 33% / 75% / 75% / 73% / 64%</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>57</td>
<td>Internal capsule L</td>
<td>10</td>
<td>67% / 0% / 100% / 75% / 80% / 30%</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>74</td>
<td>Centrum semiovale L</td>
<td>16</td>
<td>63% / 50% / 100% / 88% / 81% / 69%</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>52</td>
<td>Corona radiate L</td>
<td>20</td>
<td>42% / 25% / 100% / 75% / 65% / 45%</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>48</td>
<td>Internal Capsule L</td>
<td>26</td>
<td>60% / 54% / 91% / 73% / 73% / 73%</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>65</td>
<td>Basal ganglia L</td>
<td>54</td>
<td>63% / 53% / 73% / 91% / 65% / 61%</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>69</td>
<td>Thalamus L</td>
<td>39</td>
<td>40% / 32% / 86% / 79% / 56% / 49%</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>47</td>
<td>Putamen R</td>
<td>3</td>
<td>0% / 0% / 50% / 100% / 33% / 66%</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>44</td>
<td>Medulla oblongata R</td>
<td>8</td>
<td>50% / na / 100% / na / 63% / na</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>45</td>
<td>Putamen R</td>
<td>0</td>
<td>na / na / na / na / na / na</td>
</tr>
</tbody>
</table>

na = not applicable.
WMH were most common (52%), followed by parietal (27%) and insular WMHs (11%).

70% of all counted WMHs contained a central blood vessel (interpatient range 33%–100%). Periventricular WMHs were more likely to contain a central blood vessel than deep WMHs (88% vs 57%, p<0.0001). In the logistic regression model, a periventricular WMH had an increased chance to contain a central blood vessel compared to a deep WMH (OR=5.4, 95% CI 2.6 to 11.5, p<0.001). This association attenuated but remained statistically significant after additionally adjusting for surface area of the WMHs (OR=3.9, 95% CI 1.8 to 8.6) and did not change after adjusting for presence of venules.

Of all WMHs, 56% contained a venule. Of all hypointensities on FLAIR, 63% was based on a venule. In 39% of the WMHs without a hypointensity on FLAIR a venule was still found.

Presence of a blood vessel and presence of a venule were significantly correlated (r=0.216, p<0.001). There was a significantly higher proportion of periventricular WMHs with a central venule compared to deep WMHs (79% vs 40%, p<0.001). In logistic regression analyses, a periventricular WMH had an increased chance to contain a venule (OR=5.8, 95% CI 3.0 to 11.1). This association attenuated but remained statistically significant after additionally adjusting for surface area of the WMHs (OR=2.6, 95% CI 1.3 to 5.5).

Figure 8.1 Example of a central blood vessel in a periventricular WMH. Axial FLAIR images (A) with a WMH marked by the box; the magnification shows the WMH containing several vessels marked by the white arrows. On the right the corresponding sagittal image (B) of the same WMH.
DISCUSSION

In this explorative 7T MRI in patients with an acute lacunar infarct, a remarkably high number of WMHs (70%) contained a hypo-intensity at 7T MRI, compatible with a small blood vessel. Of these, 63% (56% of all WMHs) were based on a present venule. These results underline the perivascular distribution of WMHs and their probable vascular origin in cerebral small vessel disease, and suggest that both arterioles and venules are involved in the development of WMHs.

No other studies report on the proportion of blood vessels and venules in WMHs in small vessel disease patients. One study concerning central veins in WMHs at 7T MRI in patients

Figure 8.2  Example of a venule in a periventricular WMH. Axial FLAIR images (A) with a WMH with blood vessel (arrow); gradient echo images with increasing echo time (B, C, D) showing a venule on the same location as the hypo-intensity on FLAIR.
with multiple sclerosis used patient controls with WMH that were considered to be of vascular origin. In these controls, only 30% of the WMHs contained a central venule, in contrast to 55.6% in this study. However, this patient control group did not have CSVD but consisted of patients with chance WMHs on imaging and presence of a vascular risk factor. In contrast, all included patients in this study were carefully phenotyped and had a lacunar infarct within 7 days before the MRI.

We found that periventricular WMHs were more likely to contain a central blood vessel than deep WMHs. It could be hypothesized that different pathological processes are responsible for periventricular and deep WMHs. This is supported by evidence that periventricular and deep WMHs differ regarding their risk factors and clinical consequences. Given their predominant periventricular location, we tentatively suggest that venules play a more important role in cerebral small vessel disease than previously thought. Indeed, we found a statistically significant difference between the proportion of periventricular WMHs with a venule and the proportion of deep WMHs (79.3% vs 39.5%, p<0.001) even after adjusting for size of the WMH, hereby accounting for chance findings. Previous research already described venous collagenosis and venous tortuosity in leukoaraiotic lesions and suggested that venous pressure in combination with arteriolar ischemia could underlie WMHs. Our results are in line with these pathologic findings and suggest involvement from both arterioles and venules in cerebral small vessel disease. Possibly, according to anatomical location, arterioles (in deep WMH) or venules (periventricular WMH) could play the predominant role in the development of a WMH. It could be that the difference in proportion of WMHs with a blood vessel is found because deep WMHs are often smaller in size than periventricular WMHs and are therefore statistically less likely to contain a central blood vessel or venule. However, after adjustment for lesion size, the difference remained statistically significant.

Strengths of this study are the carefully phenotyped cohort of patients with an acute lacunar infarcts. Ultra high field imaging allowed us to visualize vascular structures within WMHs. Ultra high field imaging have shown before to be more sensitive in detecting markers for cerebral small vessel disease, such as microbleeds.

Limitations include the small sample size and the absence of histopathological material. Although we clearly defined hypo-intensities as blood vessels, if a venule was absent, we cannot be sure whether these central hypo-intensities were in fact arterioles or rather dilated perivascular spaces instead. However, this does not disqualify the notion that most of the WMHs are centered around a central blood vessel, as perivascular spaces usually harbour a blood vessel. Also, this does not disqualify the significant difference in proportion of
periventricular and deep WMHs containing a blood vessel as these limitations would apply to both locations.

In conclusion, using ultra high field MRI, we found that the majority of WMHs contain a small arteriole of venule, often related to their anatomical location. This has not been shown before and underlines the prominent role of small blood vessels in the development of WMHs. Moreover, we found evidence that venules play a more dominant role than previously thought, especially in periventricular WMHs.

REFERENCES


