“Normal is overrated.”

(Dr. House)
Chapter 4

NORMAL-APPEARING TISSUE AT (ULTRA)HIGH FIELD
Beyond lesions: Visualisation of the ‘unseen’
4.1

Perivascular spaces in MS patients at 7 Tesla MRI: a marker of neurodegeneration?


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Abstract

Background
Virchow-Robin spaces (VRS) are associated with vascular and neurodegenerative disease. In multiple sclerosis (MS), VRS have been associated with neuroinflammation. Ultrahigh-field imaging may be used to gain insight in these contradictory findings.

Objective
Analyze VRS in MS patients using high-resolution 7 Tesla (T) MRI. Additionally, we investigated whether the widening of VRS is related to inflammatory or neurodegenerative aspects of MS.

Methods
34 MS patients and 11 healthy controls were examined at 7 T. Number and size of VRS were measured on 3D T1-weighted images. 3D fluid attenuated inversion recovery (FLAIR) images were used for MS lesion detection. Brain atrophy was quantified by computing supratentorial brain volume fraction (sBVF). VRS counts were correlated with clinical variables, lesion count and sBVF.

Results
MS patients displayed more VRS (median 11) than healthy controls (median 4), P=0.001. VRS size did not differ between both groups. VRS count in patients was associated with sBVF (rho=-0.40, P=0.02), but not with lesion count (P=0.22).

Conclusions
7T MRI reveals increased numbers of VRS in MS. The finding that VRS are associated with supratentorial brain atrophy, but not with lesion count, suggests that VRS might rather serve as a neurodegenerative than an inflammatory marker in MS.
Introduction

Perivascular spaces (PVS) surround small cerebral vessels as they penetrate the brain parenchyma. They constitute a drainage pathway for interstitial fluid, and enable leukocyte trafficking and possibly modulate immune responses, as part of the blood-brain-barrier. With increasing age, PVS are more frequently detected and appear to be larger. These enlarged PVS are visible with magnetic resonance imaging (MRI), and are also known as Virchow-Robin spaces (VRS). The most common locations for VRS are the basal ganglia, the vertex, and the ponto-mesencephalic junction in the midbrain. VRS are not limited to aging, but are found in many disorders, mostly of vascular or neurodegenerative nature. In multiple sclerosis (MS) however, VRS have been linked to neuroinflammation rather than to neurodegeneration. Although inflammatory-mediated lesions are the pathological hallmark of MS, it is recognized that the disease has a prominent neurodegenerative aspect that is more strongly associated with clinical disability. Until to date, there is an ongoing debate on what triggers the disease; some authors even believe that neurodegeneration might be a causative agent in MS.

Previous studies that investigated VRS in MS have been performed at 1.5 Tesla (T) MRI. Due to the small size of VRS, visibility may be hampered at lower field strengths. Increased spatial resolution at 7 T may result in improved detection of VRS. The aim of this study was to analyze frequency and size of VRS in MS patients, at 7 T. Additionally, the radiological link between VRS and inflammation is revisited: we aim to relate VRS to neuroinflammatory (MS lesion counts) and to neurodegenerative aspects of the disease (brain atrophy).

Methods

Participants

In this study, we included 34 (65% female) MS patients and 11 (55% female) age- and gender-matched healthy controls without vascular or neurological comorbidity. The MS group had a mean age of 43 years (SD=7.9), a mean disease duration of 9.4 years (SD=5.8), and consisted of 22 relapsing-remitting (RR), 5 secondary-progressive (SP), and 7 primary- progressive (PP) MS patients. Clinical disability of the patients was measured using the Extended Disability Status Scale (EDSS). The study was approved by our institutional review board and all participants signed written informed consent prior to participation.

MRI protocol

Imaging was performed on a whole body 7T MRI system (Achieva, Philips Healthcare, Best, the Netherlands), with a slew rate of 200 T/m/s and maximum gradient strength of 40 mT/m, using a 16-channel phased-array head coil (Nova Medical Inc, Wilmington, Massachusetts, US). The protocol included a three-dimensional (3D) T1-weighted sequence (MPRAGE, TR = 7.0 ms, TE = 2.9 ms, TI = 1129 ms, flip angle 8°, acquired resolution 0.8x0.8x0.8 mm³, reconstructed resolution 0.49x0.49x0.4 mm³, acquisition time 13 min 06 s) for VRS detection and atrophy measurements, and a 3D fluid attenuated inversion recovery (FLAIR) sequence (TR = 8000 ms, TE = 303 ms, TI = 2325 ms, flip angle 100°, acquired resolution 0.8x0.8x0.8 mm³, reconstructed resolution 0.49x0.49x0.4 mm³, acquisition time 9 min 43 s) for lesion detection. Both sequences were reconstructed in axial direction, with all slices parallel to a line through the floor of the pituitary gland and the fastigium of the fourth ventricle (HYFA-angle). No intravenous contrast was administered.
VRS and lesion measures

VRS were manually delineated on the axially reformatted T1-weighted images by one of the authors (IDK) under supervision of an experienced neuroradiologist (MPW), using MIPAV software (Medical Image Processing, Analysis & Visualization, National Institute of Health; mipav.cit.nih.gov). VRS were defined as dot-like structures (running through-plane) visually isointense to the CSF on T1,\(^3\) and therefore hypointense with respect to surrounding cortical GM. Longitudinal VRS (running in-plane) were excluded from analysis since these would bias the area and largest diameter variables (see below). In case of doubt, the corresponding FLAIR image was used to differentiate between a VRS and an MS lesion.

Per subject, VRS were counted and the area and largest diameter were measured for each VRS at five levels in the brain. These five levels correspond to regions where VRS are common, and were selected using predetermined anatomical landmarks, that were easily reproducible across subjects. The following anatomical landmarks were used to select the different levels: a) handknob, including VRS in the vertex; b) crus anterius, at its widest; c) anterior commissure; and d) transition between third ventricle and aqueduct, including VRS in the basal ganglia, and e) peduncles, at the largest interpeduncular distance, including VRS in the midbrain. Examples of the five different scoring levels and orientation are shown in figure 1. Total MS lesion counts (white and gray matter) were assessed on the 7T FLAIR images. Details of the lesion scoring and classification process used in the current study have been published before.\(^{16}\)

Atrophy measures

Supratentorial brain atrophy was quantified using the FreeSurfer 5.3 processing stream.\(^{17,18}\) First, the high-resolution T1-weighted images were downsampled by a factor of 2, resulting in a volume with voxel size 1.0 x 1.0 x 0.8 mm. Then, FreeSurfer estimates intracranial volume (ICV) by linearly registering the T1-weighted image to Talairach space, corrects for bias field inhomogeneities and segments the white matter (WM) using voxel-wise classification. Holes in the WM (i.e. hypointense lesions or VRS) are subsequently filled and the hemispheres are separated using cutting planes derived from Talairach space. Based on the resulting WM segmentation, an initial white matter surface is created for each hemisphere. These surfaces are subsequently nudged to obtain an accurate delineation of the pial surface. Volumetric measurements are finally performed using these surfaces and the initial volumetric segmentation. The FreeSurfer processing stream, which was originally developed for 1.5T and 3T data, required several modifications to cope with the field inhomogeneities present in our 7T data. First, the default linear registration to Talairach space was replaced by a linear registration using FLIRT (part of FSL 5.0.4; http://www.fmrib.ox.ac.uk/fsl).\(^{19}\) This made the registration much more robust to signal loss in the cerebellum and substantially improved the accuracy of ICV estimation. Second, it is known that a higher frequency modulation is required to correct the faster corrupting bias field at greater field strength.\(^{20}\) Therefore, the so-called knot distance parameter of the N3 bias field correction algorithm used in FreeSurfer was lowered to 25 mm. This substantially improved bias field correction. Finally, brain atrophy was quantified by computing supratentorial brain volume fraction (sBVf). Here sBVf was defined as supratentorial brain volume (sBV) divided by ICV, where sBV was defined as total brain volume (using the previously obtained pial surface) excluding the cerebellum, brainstem and ventricles. The cerebellum was excluded from atrophy analysis as it often suffered from low signal intensity. An example segmentation used for atrophy quantification is displayed in figure 2.
Figure 1. Five different levels in the brain used for Virchow-Robin spaces (VRS) analysis. T1-weighted images of a 63-year-old female multiple sclerosis (MS) patient. The panels show, from top to bottom, the five different levels in the brain used for VRS analysis, on which the chosen anatomical landmarks are visible: (a) handknob, including VRS in the vertex; (b) crus anterius at its widest; (c) anterior comissure; and (d) the transition between third ventricle and aqueduct, including VRS in the basal ganglia; and (e) peduncles, at the largest interpeduncular distance, including VRS in the midbrain.

Figure 2. Segmentation used for atrophy quantification at 7 Tesla magnetic resonance imaging (MRI). Example of the segmentation used for atrophy quantification in a 54-year-old female multiple sclerosis (MS) patient, in coronal, axial and sagittal orientation. The red and yellow lines indicate the pial and white matter (WM) surfaces respectively; the segmentation colors correspond to the standard FreeSurfer coloring scheme.
Statistical analysis
Statistical analyses were performed using the SPSS software package, version 20.0 (SPSS, IBM, Chicago, IL, USA). Kolmogorov-Smirnov tests and visual inspection of the histogram were used to assess normality of the variables. Results are presented as means (SD) when normally distributed and as medians (range) in case of non-normal distribution. Group differences were tested using the Mann-Whitney U-test or the Kruskall-Wallis test. Fisher’s exact test was used to test for gender differences. In MS patients, correlations of VRS counts with age, disease duration, lesion counts and sBVF were assessed using Spearman’s rank correlation coefficient. P-values of <0.05 were considered as statistically significant.

Results
Table 1 summarizes demographic, clinical and MRI data per group. Details on VRS measures and group differences are displayed in table 2. In both the MS patients and the controls, VRS were detected at all five levels of the brain, although not at each level in every subject. The differences in presence of VRS between MS patients and healthy controls varied between the levels. For example, VRS were detected in almost all MS patients (97%) and all controls at the level of the anterior commissure (level c). However, in the convexity of the brain (level a), VRS were detected in 77% of the MS patients and in 46% of the controls. Examples of VRS in an MS patient and a healthy control are illustrated in figure 3. As can be seen in this figure, the signal intensity of VRS at 7T FLAIR was high in both MS patients and healthy controls, in contrast to standard field strengths.

Table 1. Demographic, clinical and MRI data of MS patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>22/12</td>
<td>6/5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.0 (SD=7.9)</td>
<td>38.8 (SD=10.5)</td>
</tr>
<tr>
<td>EDSS</td>
<td>4 (0-7.5)</td>
<td>-</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>9.4 (SD=5.8)</td>
<td>-</td>
</tr>
<tr>
<td>VRS count</td>
<td>11 (1-66)</td>
<td>4 (2-24)</td>
</tr>
<tr>
<td>VRS area (mm2)</td>
<td>2.9 (1.2-17.5)</td>
<td>2.9 (1.9-7.0)</td>
</tr>
<tr>
<td>VRS cross-section (mm)</td>
<td>2.1 (1.0-11.9)</td>
<td>2.1 (1.4-3.1)</td>
</tr>
<tr>
<td>Lesion count</td>
<td>77.2 (SD=65)</td>
<td>1.6 (SD=2.3)</td>
</tr>
<tr>
<td>sBVF</td>
<td>0.60 (SD=0.06)</td>
<td>0.65 (SD=0.04)</td>
</tr>
</tbody>
</table>

The total number of VRS per subject was significantly larger in MS patients than in healthy controls. In the MS group, a total of 508 VRS were detected (median 11 per patient) compared to 73 VRS in the healthy controls (median 4 per subject) (P=0.001). When distinguishing the five different brain levels, most VRS were detected at the level of the anterior commissure (level c): 186 in the MS group and 42 in the healthy controls. However, for this level, the difference between MS patients and healthy controls did not reach statistical significance (P=0.07). In contrast, the superior brain areas did display more VRS in MS patients compared to healthy controls, respectively P=0.03 at level a, and P=0.002 at level b. No difference in the number of VRS could be detected between the clinical subtypes of MS.

The size of VRS, as measured by the area and the largest diameter, was not different between MS patients and controls. A graphical overview of VRS counts and sizes in MS patients and healthy controls is displayed in figure 4.
**Table 2.** VRS count and size in MS patients (n=34) and HC subjects (n=11)

<table>
<thead>
<tr>
<th>Anatomical location</th>
<th>MS group total (%)</th>
<th>MS median per subject (range)</th>
<th>HC group total (%)</th>
<th>HC median per subject (range)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N subjects with VRS</td>
<td>34 (100%)</td>
<td>11 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Level a</td>
<td>26 (76%)</td>
<td>5 (45%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Level b</td>
<td>24 (71%)</td>
<td>2 (18%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Level c</td>
<td>33 (97%)</td>
<td>11 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Level d</td>
<td>25 (74%)</td>
<td>5 (45%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Level e</td>
<td>20 (59%)</td>
<td>5 (45%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total count</td>
<td>508 (100%)</td>
<td>11 (1-66)</td>
<td>73 (100%)</td>
<td>4 (2-24)</td>
<td>0.001</td>
</tr>
<tr>
<td>- Level a</td>
<td>137 (27%)</td>
<td>2 (0-26)</td>
<td>16 (22%)</td>
<td>0 (0-11)</td>
<td>0.03</td>
</tr>
<tr>
<td>- Level b</td>
<td>57 (11%)</td>
<td>1 (0-12)</td>
<td>2 (3%)</td>
<td>0 (0-1)</td>
<td>0.002</td>
</tr>
<tr>
<td>- Level c</td>
<td>186 (37%)</td>
<td>5 (0-13)</td>
<td>42 (58%)</td>
<td>4 (1-9)</td>
<td>0.07</td>
</tr>
<tr>
<td>- Level d</td>
<td>59 (12%)</td>
<td>1 (0-7)</td>
<td>8 (11%)</td>
<td>0 (0-3)</td>
<td>0.08</td>
</tr>
<tr>
<td>- Level e</td>
<td>69 (14%)</td>
<td>(0-13)</td>
<td>5 (7%)</td>
<td>0 (0-2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Total area (mm²)</td>
<td>1647.0</td>
<td>2.9 (1.2-17.5)</td>
<td>222.9</td>
<td>2.9 (1.9-7.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>- Level a</td>
<td>419.9</td>
<td>2.9 (1.2-6.0)</td>
<td>50.1</td>
<td>2.9 (1.9-4.1)</td>
<td>0.75</td>
</tr>
<tr>
<td>- Level b</td>
<td>191.6</td>
<td>2.9 (1.9-17.5)</td>
<td>5.8</td>
<td>2.9 (2.6-3.1)</td>
<td>0.93</td>
</tr>
<tr>
<td>- Level c</td>
<td>595.2</td>
<td>2.9 (1.9-11.1)</td>
<td>132.8</td>
<td>2.9 (1.9-7.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>- Level d</td>
<td>194.0</td>
<td>3.0 (1.9-14.2)</td>
<td>23.8</td>
<td>2.6 (1.9-4.6)</td>
<td>0.30</td>
</tr>
<tr>
<td>- Level e</td>
<td>246.4</td>
<td>2.9 (1.7-14.2)</td>
<td>10.5</td>
<td>2.6 (1.9-3.4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Total largest diameter (mm)</td>
<td>1172.8</td>
<td>2.1 (1.0-11.9)</td>
<td>154.3</td>
<td>2.1 (1.4-3.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>- Level a</td>
<td>313.0</td>
<td>2.1 (1.0-4.5)</td>
<td>33.1</td>
<td>2.0 (1.6-2.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>- Level b</td>
<td>139.9</td>
<td>2.2 (1.5-11.9)</td>
<td>4.0</td>
<td>2.0 (2.0-2.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>- Level c</td>
<td>423.3</td>
<td>2.1 (1.4-5.0)</td>
<td>94.2</td>
<td>2.1 (1.4-3.1)</td>
<td>0.92</td>
</tr>
<tr>
<td>- Level d</td>
<td>128.7</td>
<td>2.1 (1.4-4.9)</td>
<td>16.8</td>
<td>2.0 (1.4-2.9)</td>
<td>0.55</td>
</tr>
<tr>
<td>- Level e</td>
<td>167.9</td>
<td>2.1 (1.0-5.0)</td>
<td>8.0</td>
<td>2.0 (1.6-2.5)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

MS = multiple sclerosis; HC = healthy control; VRS = Virchow Robin Space

* P-values < 0.05 were considered statistically significant

**Figure 3.** Virchow-Robin spaces (VRS) in multiple sclerosis (MS) patient and healthy control. Axial T1-weighted images showing VRS in superior levels in the brains of (a) a 27-year-old female healthy control subject and (b) a 54-year-old female MS patient. Corresponding fluid-attenuated inversion recovery (FLAIR) image of this MS patient is shown in (c).
MS patients had on average 77 lesions per subject, versus 2 in the healthy control group. Mean sBVF was lower in MS patients (0.60, SD=0.06) compared with controls (0.65, SD=0.04) (P=0.01), indicating more supratentorial brain atrophy in MS patients. The number of VRS in MS patients was negatively associated with sBVF (rho=-0.40, P=0.02). In addition, it was positively associated with age (rho=0.42, P=0.01) and disease duration (rho=0.41, P=0.02), but interestingly not with lesion count (P=0.22). There was also no correlation between VRS count and disability as measured by EDSS (P=0.96).

**Discussion**

In this study, we investigated VRS in MS patients using high-resolution 7T MRI. We compared their frequency and size to those of healthy controls and aimed to gain more insight into the substrate of the widening of VRS.

**MS patients show more VRS, especially in superior areas of the brain**

Our results confirmed the presence of VRS in both MS patients and healthy controls, using 7T MRI. We detected significantly more VRS in MS patients than in healthy controls, with a median VRS count of 11 per MS patient and 4 per healthy control, across 5 commonly affected levels in the brain. This difference in VRS count was particularly true for VRS in superior areas of the brain (levels a and b in our rating system).

Although both groups displayed the highest number of VRS at the level of the anterior commissure (level c), VRS count at this level did not differ between MS patients and healthy controls. This might be explained by the fact that also in the healthy population it is common to have VRS in this region. Heier et al. showed that 35% of healthy individuals have VRS in the basal ganglia, whereas only 13% have VRS at the convexity of the brain. Using 2T MRI, Achiron and colleagues detected more VRS in the convexity of the brains of patients with early
MS (55%) compared with healthy controls (7%). Another study in early MS patients, at 1.5 T, showed a higher number of VRS at the convexity of the brain in MS patients, whereas no significant differences in basal ganglia and midbrain VRS numbers were observed between MS and healthy controls. Our study at 7T MRI detected VRS in the vertex of 77% of the MS patients, versus 46% in the vertex of the healthy controls. At the level of the anterior commissure, VRS were detected in 97% of the MS patients versus 100% of the healthy controls. The higher detection rates of VRS in our study can be explained by the ultrahigh field and high image resolution.

In the MS group, a few very large VRS were found. However, no systematic difference could be detected in the size of the VRS between MS patients and healthy controls. No other study investigated the size of VRS in MS patients with area or diameter variables, though one earlier report described VRS volume in MS patients to be larger than in healthy subjects. Furthermore, no difference in the number and sizes of VRS could be detected between disease subtypes. This can be due to the limited number of patients in the progressive subgroups.

Until now, VRS are described to be visually isointense to CSF on all MRI sequences. Nevertheless, when quantitatively measured, the VRS signal diverges from ventricular and subarachnoid CSF. This could be explained by partial volume effects, but might also be explained by an actually different content. Our observation that VRS at 7T FLAIR had high signal intensity and were not suppressed equally as CSF, indeed suggests that the content of VRS is not similar to CSF.

VRS count related to brain atrophy in MS, but not to lesion load
To explore the relationship of VRS with other radiological hallmarks of MS, we correlated the number of VRS with measures of lesion load and brain atrophy. To our knowledge, this is the first study to implement brain atrophy measurements, one of the best predictors for clinical deterioration in MS, at 7T MRI. As expected, lower supratentorial brain volume (as measured by sBVF) was observed in MS patients compared to healthy controls. Our results furthermore show that the number of VRS in MS patients is related to supratentorial brain volume, age and disease duration, but not to lesion load. Which of these variables is the strongest predictor of VRS count in MS patients cannot be deduced from our data, since the sample size is too small to perform regression analysis. In healthy controls however, there was no association of VRS count with age or sBVF. This suggests that in our sample, the number of VRS is more related to a neurodegenerative (considering neurodegeneration as a part of declining sBVF) than to an inflammatory disease process. Hypothetically, the increase in VRS count in MS could be a form of local brain atrophy, but further research has to verify this. Our results are contradictory to an earlier report by Wuerfel et al., who measured VRS at 1.5 T in 45 MS patients and 30 healthy controls. They found no differences in the number of VRS, but they did find a larger VRS volume in MS patients. This volume increase coincided with contrast enhancement of MS lesions, but not with whole brain atrophy. The authors hypothesized a role of VRS as an inflammatory marker of MS activity in the brain. The discrepancy with the current study can firstly be explained by the sample of MS patients investigated. Where the present study included MS patients with the whole spectrum of MS disease types, Wuerfel et al. only studied RRM5: a disease type with a strong inflammatory nature, whereas the neurodegenerative aspect of MS is more prominent in the progressive phase. Second, Wuerfel investigated patients with inactive and active disease, whereas we studied patients without recent relapses. Furthermore, there was
a difference in the methodology of VRS quantification: where we measured VRS number and size of the VRS manually, Wuerfel et al. used semi-automatic measurements to quantify VRS number and volumes. Additionally, they measured MS lesion volumes where we counted MS lesions, and the present study does not include an analysis of contrast enhancing MS lesions, which was included in the study by Wuerfel and colleagues. However, contrast-enhancing MS lesions provide extra information on activity and severity of neuroinflammation, whereas the presence of lesions as such is already a marker for neuroinflammation, and hence sufficient to answer our study aim. Moreover, the use of higher field strength (7 T vs 1.5 T) might have a considerable influence. As mentioned before, with high resolution at 7T MRI we were able to detect the smallest VRS, in MS patients as well as in healthy controls, while at 1.5 T only rather large VRS can be seen. Lastly, we used much more advanced atrophy measurements including the filling of hypointense lesions and VRS, which are known to have a negative impact on the accuracy of brain volume measurements.25

We have shown that VRS were numerous at different levels of the brain, at ultrahigh-field 7T MRI. Additionally, we have used 7T MRI for the first time to quantify brain atrophy in MS patients, where the achievements of 7T studies have previously been confined to neuroinflammatory disease aspects, such as MS lesion detection and perivenous distribution of lesions.26,27 However, our study has some limitations, including the limited size of our sample. Therefore, we were not able to perform multiple linear regression to identify the main predictors of VRS in MS, or perform analyses per disease type. Another limitation is that the VRS were outlined manually and assessed visually; this probably is the reason that most of the measured VRS sizes are similar (approximately 2mm largest diameter). This might be the smallest VRS size visible for the rater’s eye at 7T MRI. Moreover, VRS were scored on 2D reformatted slices, which could have led to a systematic underestimation of the number of VRS compared to a 3D approach, as tubular structures were not counted as VRS. The last limitation of our study concerns the cross-sectional study design. The present work suggests that VRS could be used as a radiological marker for neurodegeneration in MS. Future follow up studies are necessary to provide information on the relevance of VRS in terms of the correlation with physical or cognitive disability, for differentiating MS clinical subtypes, or predicting disease progression. Further quantitative MRI studies are necessary to investigate the actual content of VRS and confirm the clinical and radiological relevance of our results, particularly with regard to the correlation with atrophy measures.

In conclusion, MS patients displayed more VRS compared to healthy controls, especially in superior areas of the brain. VRS in MS patients were associated with supratentorial brain atrophy, but not with lesion load. This suggests that VRS might serve as a sign of neurodegeneration in the broader sense rather than an inflammatory radiological marker in MS.

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References


