White Matter Lesions in Patients With Localization-Related Epilepsy

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**Objectives:** White matter lesions (WML) have been proven to be associated with cognitive impairment. As (1) the decline of cognitive function is the most frequent comorbid disorder in epilepsy, and (2) patients with epilepsy have a relatively high prevalence of WML, the question is raised whether WML in patients with epilepsy are also associated with cognitive decline.

**Materials and Methods:** A high-resolution magnetic resonance imaging examination was performed at 3.0 T, comprising T1-weighted, T2 relaxometry, and fluid-attenuated inversion recovery (FLAIR) sequences. Patients with localization-related epilepsy with impaired and unimpaired cognitive functioning and a healthy control group were included. Furthermore, the performance of an automated WML detection algorithm, based on regional intensity evaluation, was assessed.

**Results:** The prevalence of WML, detected on 3.0 T FLAIR images, is 63% in healthy volunteers and 46% in patients with localization-related, cryptogenic epilepsy. No relationship between WML volume and cognitive performance was observed. The WML volumes from the automated segmentation method were found to be significantly correlated to the volumes obtained by neuroradiologic assessment.

**Conclusions:** No relations could be found between WML and cognition in the well-defined population of patients with epilepsy. Other clinical characteristics of chronic epilepsy, such as seizures, age of onset, and medication are more likely to play an important role in cognitive decline. Furthermore, the automated WML detection algorithm using a regional Z-score analysis can successfully segment and quantify the WML on FLAIR images.

**Key Words:** epilepsy, white matter lesions, fluid-attenuated inversion recovery, cognitive decline

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White matter lesions (WML) are areas of bright, high signal intensity in the white matter depicted on T2-weighted magnetic resonance imaging (MRI), and are a common finding in the brains of asymptomatic elderly individuals and in patients suffering from various neurosychiatric disorders. The pathophysiologic origins of WML are still poorly understood and are thought to include multiple factors. Potential sources for WML consist of ischemia, demyelinating disorders, gliosis, and other causes. Risk factors for WML are age, diabetes, history of stroke or heart disease, and hypertension. Both periventricular WML (pWML) and subcortical WML (sWML) have been established to be associated with cognitive impairment, particularly with declined performances of attention, memory, executive function, and frontal lobe mediated function. Also, decline of cognitive function is the most frequent comorbid disorder in epilepsy, particularly in patients with localization-related (partial) epilepsy with a temporal or frontal lobe origin. Expressions of cognitive decline may vary from memory impairment or slowing of information processing speed to even cognitive deterioration with intelligence quotient (IQ) decline.

Interestingly, the population of patients with epilepsy was previously found to have a higher prevalence of WML than healthy age-matched controls. In a recent study on the prevalence of WML in a healthy population younger than 65 years (age, 16–65 years; mean, 37 years), it was found that WML occurred in 5.3% of the participants. For similarly aged patients with epilepsy, this number is higher; Wiesmann reported a prevalence of 10% in patients with chronic epilepsy and Sanders et al reported a prevalence of 14% in patients with complex partial seizures. Additionally, Eriksson et al described a prevalence of 13% for large WML (>10 mm) and 17% for small WML (3–10 mm) in a population of epilepsy patients. This relatively high prevalence of WML in patients with epilepsy raises the question whether these lesions are also associated with a decline of cognitive function. Unfortunately, no relevant literature covers this subject.

To determine whether WML are associated with cognitive impairment in patients with chronic epilepsy, we have performed a high-resolution MRI examination at 3.0 T, comprising T1-weighted, T2 relaxometry, and fluid-attenuated inversion recovery (FLAIR) sequences. Patients with localization-related epilepsy with impaired and unimpaired cog-
nitive functioning were included. In addition, a healthy control group was included to provide normative brain MR data. A 3.0 T clinical system was used, which is known to improve neuroradiologic brain applications with respect to 1.5 T. \textsuperscript{13,16} Especially for the detection of WML, 3.0 T has been proven to have a significantly higher detection rate than 1.5 T. \textsuperscript{17-19} In addition to MRI examination, neuropsychological assessment was performed on all subjects to assess possible cognitive impairment.

The WML were examined in 2 ways: (1) visually, by an experienced neuroradiologist and (2) fully-automatically, using a computer-based WML detection technique using a regional Z-score analysis.

A fully automated quantitative WML detection technique can be beneficial, as it may provide a more objective assessment than visual rating; furthermore, it can help to reduce the time consuming visual assessments, especially useful in trials with a large number of subjects.

The aim of this investigation is 2-fold: (1) to examine the relationship between WML, detected on 3.0 T FLAIR images, and cognition, as assessed by neuropsychological examination, in a population of patients with localization-related epilepsy, and (2) to assess the performance of an automated WML detection algorithm.

**MATERIALS AND METHODS**

**Subjects**

Patient characteristics are listed in Table 1. The study population included 33 patients with epilepsy, and 16 healthy volunteers recruited from the social milieu of the patients. All patients were asked to inquire whether family, friends, or acquaintances also liked to participate. All patients were selected during their visit at the outpatient neurology department of the local hospital or at the local tertiary epilepsy referral and care center. Data acquisition was conducted within the guidelines of the local institutional medical ethical committee overseeing human research, and every participant provided written informed consent. Inclusion criteria for the study were: localization-related, cryptogenic epilepsy with or without secondarily generalized seizures, no history of status epilepticus, and no other underlying disease that could possibly cause cognitive decline or epilepsy, progressive neurologic disorders, or symptomatic epilepsy (eg, tumors or vascular abnormalities).

The following patient data were collected: age at onset, secondarily generalized tonic-clonic seizures (SGTCS), seizure frequency per year, partial seizure frequency (including simple and complex seizures) per year, seizure focus, and drugload. Total number of SGTCS was calculated according to patient history and seizure diaries. For those patients with relatively low numbers of SGTCS, the exact number of SGTCS could be withdrawn from the patient’s history. For those with relatively high numbers of SGTCS, the number was approximated by taking into account the seizure frequency during subsequent periods, reckoning with changes in seizure frequency (for example: weekly seizures during a few months followed by a period of seizure-freedom). No SGTCS were reported in the last 2 weeks before MR scanning. Drug load was calculated by standardizing the doses of antiepileptic drugs using the ratio of prescribed daily dose to defined daily dose.\textsuperscript{20} None of the subjects reported hypertension.

**Neuropsychological Testing**

All subjects underwent neuropsychological testing and to test intelligence, the Wechsler Adult Intelligence Scale Third Edition was used.\textsuperscript{21} Based on the results of this test and the educational history of each person, a discrepancy score was derived, similarly as described by Langeland and Cheine,\textsuperscript{22} comparing the actual cognitive level with the expected level, based on premorbid educational level.

**Magnetic Resonance Imaging**

The patients were imaged with a 3.0 T whole-body unit [Philips Achieva (software release 1.5.4.0); Philips Medical Systems, Best, The Netherlands].

For every subject, the following images were acquired using the SENSE head coil with 8 channels. For anatomic reference, first a T1-weighted three-dimensional (3D) turbo field echo was acquired with the following parameters: repetition time (TR), 9.91 milliseconds; echo time (TE), 4.6 milliseconds; inversion time, 3 seconds; flip, 8-degree angle; matrix, $256 \times 256 \times 160$; field of view (FOV), $256 \times 256 \times 160$ mm$^3$; 1 mm adjacent coronal slices; scan time, 12 minutes. For T2 quantification a 3D dual-echo turbo spin echo (TSE-Dual) was performed, using the following parameters: TR, 2500 milliseconds; TE1, 10 milliseconds; TE, 110 milliseconds; matrix, $256 \times 256 \times 100$; FOV, $256 \times 256 \times 200$ mm$^3$; 2.0 mm adjacent coronal slices; acceleration (ie, SENSE reduction) factor, 1.5 in the left-right direction; k-space segmentation, 6 shots per image; scan time 10 minutes.

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**TABLE 1. Patient Demographics and Characteristics**

<table>
<thead>
<tr>
<th>Healthy Volunteers</th>
<th>Patients With Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>40 (13)</td>
</tr>
<tr>
<td>Age range</td>
<td>23-36</td>
</tr>
<tr>
<td>Sex</td>
<td>10F/6M</td>
</tr>
<tr>
<td>IQ</td>
<td>115 (13)</td>
</tr>
<tr>
<td>Cognitive discrepancy score</td>
<td>8 (9)</td>
</tr>
<tr>
<td>sWML (mm$^3$)</td>
<td>203 (350)</td>
</tr>
<tr>
<td>pWML score</td>
<td>1.1 (1.1)</td>
</tr>
<tr>
<td>Age of onset (yrs)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total no. SGTCS</td>
<td>23 (50)</td>
</tr>
<tr>
<td>Total no. partial seizures</td>
<td>N/A</td>
</tr>
<tr>
<td>Seizure focus$^1$</td>
<td>N/A</td>
</tr>
<tr>
<td>Drugload</td>
<td>N/A</td>
</tr>
</tbody>
</table>

| Values are mean (standard deviation) |

F indicates female; M, male; IQ, intelligence tested with the Wechsler Intelligence Test for Adults III; scores are full scale IQ; N/A, not applicable; LF, left frontal; BF, bilateral frontal; LT, left temporal; RT, right temporal; BT, bilateral temporal; LFT, left frontotemporal; RFT, right frontotemporal; M, multiple foci; U, unknown.

$^1$Two-tailed $P < 0.05$ (Bonferroni correction).

$^1$Based on the electromyogram.

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A T2-weighted TSE FLAIR was acquired with the following parameters: TR, 11 seconds; TE, 125 milliseconds; inversion delay, 2.8 seconds; matrix, 512 × 512 × 90; FOV, 256 × 256 × 180 mm²; 2 mm adjacent coronal slices; scan time, 5 minutes. The images of 1 patient with epilepsy were excluded because of ghosting artifacts.

WML Scoring

The FLAIR scans were reconstructed into isotropic transverse images (with voxel size 1 × 1 × 1 mm³) using the software package MRiKer. Images were analyzed by an experienced neuroradiologist to obtain estimates of the total volume of sWML and the extent of pWML. WML were scored according to the criteria by Achten et al from the Rotterdam Scan study, a method that has been validated extensively.

For this purpose, FLAIR image stacks analyzed using custom software (GIANT) on a Macintosh G3 computer. This program allowed systematic inspection and manual demarcation of regions of interest. At each level, SWML were scored using predefined region of interest masks [i.e., circles with a diameter of 1–3, 6, and 12 mm, to correspond approximately with WML lesion diameters of small (1–3 mm), medium (3–10 mm), or large (>10 mm) regions, respectively. Lesions were identified on the FLAIR image, and a mask that matched the region of interest best was fitted over the lesion. After inspection and delineation of all sWML in a stack, the program generated an output file containing the number and size of all lesions at each level of the scan. These data were transferred to a standard spreadsheet to yield a total sWML volume score for each patient. In this procedure, regions of interest were inflated to spheres with the same diameter, with corresponding volumes of 4.2, 113, and 905 mm³, respectively. Next, the overall sWML volume was calculated. Periventricular WML severity, ranging between 0 and 3, was scored for frontal and occipital regions (“caps”) and the medial periventricular lining (“bands”) separately, which were then summed to an overall periventricular WML score.

Image Analysis

All image processing was performed using customized software in Matlab (The Mathworks, Natick, MA), based on SPM5 software routines (Wellcome Department of Cognitive Neurology, London, UK).

Preprocessing

First all MR images were visually inspected for image artifacts, and if necessary, excluded from analysis. Further image preprocessing included: (1) T2 and cerebrospinal fluid (CSF) mapping, (2) skull stripping, (3) spatial normalization, (4) tissue segmentation, (5) person-specific whole cerebrum mask creation, and (6) localization of ventricles.

1. T2 and CSF mapping was based on the images obtained from the T2-relaxometry. The T2 was calculated (in milliseconds) on a voxel-by-voxel basis using the signal intensities of the images obtained at the 2 TE, as described earlier using the following equation:

\[ T2 = \frac{TE_2 - TE_1}{\ln\left(\frac{SI_1}{SI_2}\right)} \]

where TE1 is the first TE of 22 milliseconds, and TE2 is the second TE of 110 milliseconds, SI1 and SI2 are the signal intensities corresponding to TE1 and TE2, respectively. A percentile volume CSF map was calculated by attributing voxels individually to a CSF percentage (\(\Delta_{CSF}\)) on a scale of 0% to 100%. The \(\Delta_{CSF}\) was based on the T2 value of the voxel as calculated from the TSE-FLAIR images. For this, the T2 relaxation rate (i.e., 1/T2) was assumed to be a fractional volume weighted sum of CSF (T2 > 2500 milliseconds) and uniform brain tissue (T2 < 110 milliseconds); 1/T2 = \(\Delta_{CSF}/T2\)CSF + (1 - \(\Delta_{CSF}\)/T2 tissue. For large T2 values (i.e., T2 > 2500 milliseconds), \(\Delta_{CSF}\) was set to 100%.

2. Based on the T2 = 110 milliseconds T2-weighted image, brain tissue was segmented from nonbrain tissue using the brain extraction tool skull stripping algorithm.

3. The FLAIR, \(\Delta_{CSF}\), and T2 map were spatially transformed into common coordinates (dimension 217 × 217 × 181, 1 × 1 × 1 mm³-sized voxels) along with the spatial normalization procedure of the T2 = 110 milliseconds image into the standard brain space defined by the Montreal Neurologic Institute T2 template. Also, the T1-weighted image was spatially transformed into Montreal Neurologic Institute standard brain space using the T1 template.

4. The normalized T1-weighted images were segmented to yield a gray matter (GM), a white matter (WM), and a CSF map.

5. Based on the whole cerebrum maps created with WFU PickAtlas and the skull-stripped normalized T2 weighted image, for each patient a specific whole cerebrum map was created. Tissue was segmented from CSF by applying the threshold \(\Delta_{CSF} < 5\%\) for each voxel.

6. Using the obtained \(\Delta_{CSF}\) map from the WFU PickAtlas and the ventricle masks, individual ventricle maps could be created.

Automated Detection and Measurement of Volumes of WML

The major steps of the WML volumetric estimation were as follows:

1. Regional Z-score analysis of FLAIR intensities, (2) filtering deviation flair hyperintensity clustered based on size, location with respect to ventricles, maximal Z-score, and gray matter contribution.

1. For each pixel within the person-specific whole cerebrum mask for the FLAIR image, a Z-score was derived based on the mean and standard deviation of the intensities of all pixels within a sphere with diameter 2 cm around the pixel. Because the algorithm uses different locally obtained parameters for each voxel, the method enables different deviation scores for each WML cluster. This potentially offers more precise WML segmentation than determining Z-scores based on global information.
2. All pixels, with a Z-score higher than 2 were selected. Subsequently, only clusters with a size of more than 26 pixels were selected (a cube, i.e., pixel, has 26 connectivity corners). Furthermore, clusters were excluded if the percentage of GM was higher than 50%. Then, pixels were either classified sWML or pWML, based on the distance of each cluster to the ventricles, which had to be more or less than 0.7 cm, respectively. For sWML clusters, the maximum Z-score had to exceed 4. Finally, the total number of both sWML and pWML voxels was counted to obtain volumes in cubic millimeter.

Comparison of Visually and Automatically Obtained WML Volumes

The level of agreement between the 2 different WML assessment methods, namely (1) visually, by an experienced neuroradiologist, and (2) automated, using a computer-based WML detection technique, was evaluated. For this purpose, the intraclass correlation (ICC) coefficient was calculated using a 1-way random model. Additionally, the Spearman rank correlation coefficient was determined. As the 2 measures for pWML that were compared use different metrics, it was investigated whether there is a correlation between these measures rather than an absolute agreement.

Statistical Analysis

Visually obtained sWML and pWML values were compared with IQ, cognitive discrepancy score, and age, all using the Spearman rank correlation.

Additionally, differences between patients with epilepsy and healthy volunteers were assessed using a Student t test (IQ, cognitive discrepancy score, and age) or the non-parametric Mann-Whitney U test (sWML and pWML). Multiple end point testing was corrected for using the methods described by Hochberg. Statistical significance was inferred when \( P < 0.05 \).

RESULTS

WML and Cognition

In 6 of the 16 healthy volunteers (38%), and 9 of the 32 patients with epilepsy (28%), severe sWML (>100 mm\(^3\)) were detected by the neuroradiologist. Mild sWML (0–100 mm\(^3\)) were detected in 4 (25%) and 6 (19%) of the volunteers and patients, respectively. Six healthy volunteers (38%) and 17 patients with epilepsy (53%) did not have any detectable sWML. Prevalence of no (pWML = 0), mild (pWML = 1), and severe (pWML > 1) periventricular WML were (44%, 19%, and 38%) and (50%, 19%, and 31%) for controls and patients, respectively.

Spearman rank correlation of WML and IQ and cognitive discrepancy score did not yield any statistically significant relations (\( P > 0.6 \)). In contrast, both pWML and sWML significantly increased with age [\( \rho = 0.42 \) (\( P < 0.05 \)], and \( \rho = 0.55 \) (\( P < 0.05 \)], respectively]. Patients with epilepsy had significantly lower IQ values (\( P < 0.05 \)) and cognitive discrepancy scores (\( P < 0.05 \)), compared with healthy controls. No differences in pWML or sWML between patients with epilepsy and healthy volunteers were found (\( P > 0.7 \)). A separate analysis of the WML volumes obtained from the automatic detection algorithm and cognitive and clinical characteristics yielded similar results.

Automated WML Detection

The WML volumes from the automated segmentation method were found to be significantly correlated to the visual assessment. Spearman \( \rho \) for the sWML was 0.7 (\( P < 0.05 \)). The ICC coefficient for the sWML was 0.92. The correlation between the overall visually obtained pWML score and the automated pWML volume detection, as assessed using the Spearman’s \( \rho \), was 0.65 (\( P < 0.05 \)). Figure 1 illustrates the agreement between the 2 methods. The automated assessment tends to overestimate the number of WML for patients with a low number of WMLs, as indicated by the visual assessment. However, for patients with a high number of WMLs, the number of WMLs is underestimated. In Figure 2, an example of both automated sWML and pWML assessment in a patient with epilepsy is given.

DISCUSSION

WML and Cognition

The most notable result is that the prevalence of WML (both mild and severe) of 63% in healthy volunteers and 46%
in patients with epilepsy is much higher than earlier reported values in healthy volunteers (5%)\(^{11}\) and patients with epilepsy (10%–17%).\(^{12-14}\) There are several possible explanations for this apparent disagreement. First, in the current study high spatial resolution imaging was performed using a 3.0 T clinical MRI, whereas the other studies were mostly performed on a 1.5 T MRI or even a computed tomography scanner. It has previously been shown that MRI is preferable over computed tomography to detect white matter abnormalities,\(^{35}\) and that a 3.0 T MRI has a higher detection rate of WML than 1.5 T.\(^{17-19}\) Additionally, in the current study, a FLAIR sequence was used, with a chosen optimal inversion delay to suppress signal of CSF, optimal TE to enable highly sensitive contrast in signal intensity between normal WM and WML, and 2-mm thin slices to facilitate the detection of small lesions. In the other studies, WML were examined either using possible suboptimal FLAIR sequences,\(^{15,14}\) or even using only T2-weighted or proton density weighted sequences.\(^{11,13}\) Hence, a higher prevalence of WML in the current study seems plausible. Furthermore, it is not clear what exact definition was applied to differentiate normal WM from WML. Most likely the threshold to define WML was set higher, which would result in a lower WML prevalence. Finally, the exact characteristics regarding etiology and age of the patients with epilepsy described in these studies are not clear. It is hard to determine whether our population of patients, aged 18 to 65 years, with localization-related, cryptogenic epilepsy matches the other epilepsy populations described.

The main goal of this study was to examine whether there is a relationship between WML and cognition in a well-defined population of patients with localization-related epilepsy. IQ and cognitive discrepancy scores were statistically lower in patients with epilepsy compared with the healthy control group. However, no differences were found between the 2 groups in both pWML and sWML values. Furthermore, there was no relationship between cognitive measures (IQ and discrepancy score) and WML measures.
Therefore, it seems that WML do not play a major role in chronic epilepsy related cognitive decline. Literature on the possible associative relationship among WML, cognition, and epilepsy is scarce. Previously, de Reuck et al investigated in an elderly patient population (age range, 52–81 years) with late-onset epileptic seizures, WML, and cognitive decline, whether the seizures are associated with WML. 36 Position emission tomography was applied to detect possible abnormal vascular processes underlying the epileptic seizures. It was found that patients with WML and seizures had a greater decline of regional blood flow and oxygen consumption in cortical areas than patients with WML, but without seizures. It was suggested that late-onset seizures and WML could be two independent expressions of an encephalopathy leading to decline of mental functions. It has also been observed that stroke (age range, 19–85 years and 50–80 years, respectively) patients have a higher risk of seizures if WML can be detected. 47, 38 It is important to realize that all these publications refer to a population of patients with epilepsy that is distinctively different from the population included in this study. Most notably, the population included in this study is relatively young, and did not have a history of stroke, which could possibly have caused cognitive decline or epilepsy.

**Automated WML Detection**

Previously, several methods have been explored to automatically or semiautomatically segment the WML. These methods include intensity thresholding, K-Nearest Neighbor classification to segment GM, CSF, and WM, artificial neural networks, and fuzzy connected algorithms (for some recent overviews see Refs. 39–41). For intensity thresholding, a WML volume is calculated by collecting the hyperintense voxels after counting the number of voxels exceeding a predefined threshold of intensity. In other studies, WML were segmented from normal tissue by defining a global cut-off threshold on the images. 12–44 For example, Hirono et al applied a threshold of 3.5 standard deviations of the intensity value of the normal WM, 46 and Jack et al obtained a cut-off from the height of the FLAIR intensity histogram. 45 In another publication, Wen and Sachdev used a threshold, which was derived from the mean and standard deviations of the gray matter, white matter, and CSF. 47 These methods use only a single global intensity threshold to segment the WML for the whole brain or for each slice of the brain images. We have chosen to analyze FLAIR intensities on a regional level. This is in agreement with clinical practice, where a neuroradiologist examines brain images by looking for local signal intensity alterations. Often in automated WML detection techniques, only visual inspection or volume measurements WML is considered and no distinction is made between pWML and sWML. A few groups have explored semiautomated or automated methods to divide WML into the categories pWML and sWML. For example, Swartz et al applied a 3D classification algorithm to separate pWML from sWML. 45 In other studies, nonlinear image registration methods using anatomic maps were applied to distinguish between pWML and sWML. 46 Our method takes into account the distance of a WML cluster with respect to the nearest ventricular space.

The WML segmentation results using the current automated method were compared with the WML visual ratings. A relatively high correlation (r > 0.65, and ICC = 0.92) between the WML quantifications from the automated method and the neuroradiologic grades demonstrated that this automated method can successfully segment and quantify the WML on FLAIR images. ICC values reported in the literature of the agreement of automated and visual assessed WML are: 0.98 (in 100 elderly patients, >65 years), 49 0.82 to 0.96 (in 6 multiple sclerosis patients, mean 40.5 years). 47 We would like to stress that the examined study population is only known to have relative mild WML. Populations consisting of asymptomatic elderly individuals, or patients with multiple sclerosis, dementia, or Alzheimer disease can have much severe forms of WML, which is likely beneficial for the detection qualities of the proposed technique.

Also, one should realize that the process of setting the threshold by which voxels are estimated to be hyperintense is still susceptible to errors resulting from artifacts (eg, ghosting). In this regard, improved three-dimensional FLAIR procedures using techniques such as nonselective adiabatic inversion may yield better quality and are less prone to flow artifacts. 48 However, even in fully automated methods, visual inspection to assess the quality of the MRI data and possible artifacts remains mandatory. 17 It remains difficult to evaluate the merits of any WML detection method, without a gold standard as histopathology. Nevertheless, the described method represents a technique to automatically detect and quantify WML, which highly correlates with neurologic assessment.

**CONCLUSIONS**

The prevalence of WML detected on 3.0 T FLAIR images, is 63% in healthy volunteers and 46% in patients with localization-related, cryptogenic epilepsy. Despite this high prevalence of the WML, no relations could be found between WML and cognition in the well-defined population of patients with epilepsy. Other clinical characteristics of chronic epilepsy, such as seizures, age of onset, and medication are more likely to play an important role in cognitive decline. Furthermore, the automated WML detection algorithm using a regional Z-score analysis can successfully segment and quantify the WML on FLAIR images, which was validated by a high correlation between the WML quantifications from the automated method and the visual grades.

**REFERENCES**


