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A structural MRI study of cholinergic pathways and cognition in multiple sclerosis

Yukio Kimura[a], Noriko Sato[a,*], Miho Ota[b], Norihide Maikusa[c], Tomoko Maekawa[a], Daichi Sone[a], Mikako Enokizono[a], Atsuhiko Sugiyama[a], Etsuko Imabayashi[c], Hiroshi Matsuda[c], Tomoko Okamoto[d], Takashi Yamamura[e], Hideharu Sugimoto[f]

[a] Department of Radiology, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[b] Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[c] Integrative Brain Imaging Center, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[d] Department of Neurology, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[e] Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[f] Department of Radiology, Jichi Medical University, Shimotsuke, Tochigi, Japan

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ABSTRACT

Background: White matter hyperintensities (WMH) in the cholinergic pathways are associated with cognitive performance in Alzheimer's disease. This study aimed to evaluate the relationship between the volume reduction of cholinergic pathways and cognitive function in patients with multiple sclerosis (MS).

Methods: Thirty-two MS patients underwent a brain MRI and cognitive measurements including the Mini-Mental State Examination (MMSE) and the Japanese version of the Montreal Cognitive Assessment (MoCA-J). The extent of WMH within the cholinergic pathways was assessed using the Cholinergic Pathways Hyperintensities Scale (CHIPS). Computerized WMH volumes were also obtained. FreeSurfer was used to measure regional volumes including the cortical and subcortical volumes. The correlations among the CHIPS, the WMH volume, and the clinical data were assessed, in addition to the correlations between the cognitive scores and regional volumes measured by FreeSurfer.

Results: The CHIPS score and the WMH volume were strongly positively correlated with each other ($r = 0.87$, $P < 0.001$). The CHIPS score had significantly negative correlations with the MMSE ($r = -0.49$, $P = 0.003$) and the MoCA-J ($r = -0.47$, $P = 0.005$) results. The WMH volume had significantly negative correlations with the MMSE ($r = -0.54$, $P = 0.001$) and the MoCA-J ($r = -0.57$, $P < 0.001$) results. In the analysis by FreeSurfer, both the MMSE and MoCA-J scores had significant positive correlations only with the volume of the corpus callosum.

Conclusions: The CHIPS score tended to be less sensitive to the WMH volume in cognitive function evaluation, although the difference did not reach the level of statistical significance. Thus the CHIPS method may not be as effective in MS patients.

1. Introduction

Multiple sclerosis (MS) is a common autoimmune disease of the central nervous system. Its most common symptoms are sensory and motor dysfunctions, but cognitive impairment is also seen in about 40% to 65% of MS patients [1–3].

The cholinergic neurotransmitter system plays an important role in cognitive function [4–6]. The Cholinergic Pathways Hyperintensities Scale (CHIPS) scores are visual rating scales for assessing white matter hyperintensities (WMH), specifically within cholinergic pathways. This procedure can visually evaluate the degree of the WMH lesion load on selected MRI slices located in specific anatomical structures containing cholinergic tracts [7]. Previous studies have shown that the CHIPS score was associated with the cognitive performance in Alzheimer's disease (AD) [7,8], vascular dementia [9,10], Parkinson's disease dementia [11,12], diffuse Lewy body disease [13], and schizophrenia [14]. There has been only one study evaluating the CHIPS of MS patients, which indicated that lesions targeting the cholinergic pathways were correlated with cognitive impairment in a 1.5-tesla MR system [15]. However, a few reports have found that cerebral acetylcholinesterase

* Corresponding author at: Department of Radiology, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8551, Japan.
E-mail address: snoriko@ncnp.go.jp (N. Sato).

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(AChE) activity does not seem to be related to cognitive impairment in MS patients [16,17]. Thus, there is insufficient evidence of the efficiency in MS patients, although AChE inhibitors are widely used to treat AD patients [18].

The aim of this study was to examine the relationships among cognitive scores, CHIPS scores, and the WMH lesion load using an automated lesion segmentation tool in MS patients using a 3-tesla MR system. We also examined the relationships between cognitive scores and the regional volumes measured by FreeSurfer (http://surfer.nmr.mgh.harvard.edu/).

2. Materials and methods

2.1. Subjects

This retrospective study was approved by the institutional review board at the National Center of Neurology and Psychiatry Hospital, and the need for patient informed consent was waived. A review of our radiological reporting system revealed 269 suspected MS patients who underwent MRI from January 2012 to January 2016. Clinical diagnoses were made by expert neurologists according to the revised McDonald criteria [19]. The inclusion criteria were as follow: diagnosis of MS (all MS subtypes), scan by 3-tesla MR machine, and the administration of a cognitive measures assessment (Mini-Mental State Examination (MMSE) [20] and the Japanese version of the Montreal Cognitive Assessment (MoCA-J) [21]) within three weeks of the brain MR scan. Exclusion criteria included a current diagnosis of major depression, drug/alcohol abuse, and a history of any other neurologic or medical condition that could adversely affect cognition. As a consequence, 32 patients (22 females and 10 males; mean age, 45.0 years; range, 20–75) were enrolled. Clinical data included the age, gender, disease duration, and Expanded Disability Status Scale (EDSS) score [22], in addition to the MMSE and MoCA-J scores.

2.2. MRI data acquisition and processing

Imaging was performed on a 3-tesla MR system (Achieva; Philips Healthcare, Best, the Netherlands). High spatial resolution, three-dimensional T1-weighted images were used for the morphometric study. Three-dimensional T1-weighted images were acquired in the sagittal plane (repetition time [TR]/echo time [TE], 7.18/3.46; flip angle, 10°; effective section thickness, 0.6 mm; slab thickness, 180 mm; matrix, 384 × 384; field of view [FOV], 261 × 261 mm; number of signals acquired, 1, yielding 300 contiguous slices through the brain). The parameters of FLAIR images were TR/TE/inversion time (TI), 10,000/120/2,650 ms; slice thickness, 3 mm; intersection gap, 1.5 mm; matrix, 512 × 512; FOV, 230 × 230 mm; and number of signals acquired, 1.

2.3. Data analysis

2.3.1. Assessment of cholinergic pathway involvement

Based on a previous study, axial sections from FLAIR images were used to rate the WMH lesion load in the cholinergic pathways using the CHIPS method [7]. To measure the CHIPS ratings, major anatomical landmarks on four index slices in the axial plane were selected (Fig. 1 and Table 1). The first slice (low external capsule level) had four regions: the bilateral anterior and posterior regions of the external capsule. The second slice (high external capsule level) had six regions: the bilateral anterior and posterior regions of the external capsule, and the bilateral cingulate. The third slice (corona radiate level) had six regions: the bilateral cingulate, and the bilateral anterior and posterior regions of the corona radiata. The fourth slice (centrum semiovale level) had four regions: the bilateral anterior and posterior regions of the centrum semiovale. The severity of WMH was visually rated on a three-point scale for each region: 0 = normal; 1 = mild [< 50% of region involved]; and 2 = moderate to severe [≥ 50% of region involved]. Each region was weighted to account for the concentration of cholinergic fibers. The further they spread out from the nucleus basalis to the neocortical regions, the closer they came to the basalis, the more concentrated the cholinergic fibers were. Therefore, as proposed by Bocti et al. [7], we weighted the data four times for each of the four regions of cholinergic fibers within the lateral pathway at the first basal slice and the cingulate region within the medial pathway at the second slice, three times for the two regions of cholinergic fibers within the lateral pathway at the second slice, and two times for the two regions of cholinergic fibers within the lateral pathway at the third slice. The CHIPS scoring system is summarized in Fig. 1 and Table 1. A high interrater reliability (intraclass correlation = 0.96 for the total CHIPS score, 95%CI: 0.91, 0.98) was obtained by two of the authors (YK and TM). Their average ratings were used in this analysis.

2.3.2. Volumetric analysis by FreeSurfer

Brain volumes were analyzed using FreeSurfer 5.1 automated software. Image processing included the removal of nonbrain tissue with a hybrid watershed/surface deformation procedure, automated Talairach transformation, and segmentation of cortical and subcortical WM and GM. In the present study, we used cortical volumes (e.g., middle temporal, inferior parietal, inferior temporal, rostral anterior cingulate, etc.) and subcortical volumes (e.g., hippocampus, amygdala, putamen, thalamus, corpus callosum (CC), etc.). To adjust for differences in head size, the volumes for each region were divided by the intracranial volume.

2.3.3. WMH lesion segmentation

The total volume of the WMH lesion was calculated using the Lesion Segmentation Toolbox (LST version 1.2.3) [23] add-on in the Statistical Parametric Mapping (SPM8) imaging software; the total lesion volume of the WMH [mL], here named the “WMH volume,” was measured in each individual. The Lesion Segmentation Toolbox used T1-weighted and FLAIR images for lesion segmentation. GM, WM, and cerebrospinal fluid tissue classes were determined using the information from the T1-weighted scan.

2.4. Statistical analysis

First, the correlations among the CHIPS score, the WMH volume, and the clinical data (i.e., disease duration, EDSS, MMSE, MoCA-J) were assessed using Spearman's correlation analysis. Second, the significance of the difference between two correlation coefficients the CHIPS score and the WHM volume with the cognitive tests (MMSE and MoCA-J) was tested by using the standard Fisher z-transformation. Third, the correlations of the MMSE score and the MoCA-J score with the regional volumes measured by FreeSurfer were assessed using Spearman's correlation analysis.

Statistical analyses were performed with SPSS version 22 (SPSS Japan, Tokyo). The statistical significance threshold was set at $P < 0.05$. The P values were corrected for multiple comparisons and correlations using the Bonferroni method.

3. Results

The clinical features and demographics of the subjects are shown in Table 2. First, the CHIPS score and the WMH volume were strongly positively correlated with each other (Fig. 2, $r = 0.87$, $P < 0.001$). The CHIPS score had significant negative correlations with MMSE (Fig. 3A, $r = -0.49$, $P = 0.018$) and MoCA-J (Fig. 3B, $r = -0.47$, $P = 0.032$), but had no significant correlation with EDSS ($r = 0.22$, $P = 1.27$) and disease duration ($r = 0.34$, $P = 0.30$). Additionally, the WMH volume had significant negative correlations with MMSE (Fig. 4A, $r = -0.54$, $P = 0.006$) and MoCA-J (Fig. 4B, $r = -0.57$, $P < 0.003$), but had no significant correlation with EDSS ($r = 0.36$, $P = 0.22$) and disease duration ($r = 0.42$, $P = 0.081$).

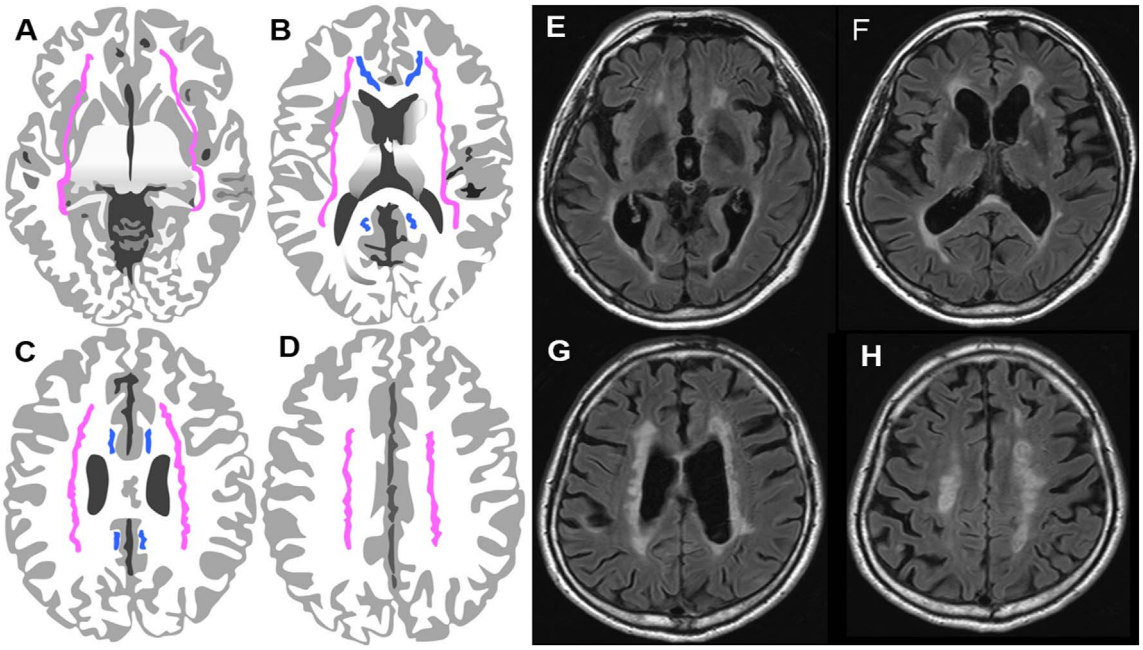

Fig. 1. CHIPS scoring illustrated on a schema and FLAIR sequence MR images. To measure the CHIPS ratings, major anatomical landmarks on four index slices in the axial plane were selected: low external capsule (A, E), high external capsule (B, F), corona radiate (C, G), and centrum semiovale (D, H). The colored lines indicate the medial (blue) and lateral (red) cholinergic pathways. Each region was weighted to account for the decreasing concentration of cholinergic fibers as they spread out from the nucleus basalis to neocortical regions (maximum weight of 4 for the first slice; minimal weight of 1 for the fourth slice) (see Table 1). Examples of CHIPS scores are shown in E–H. (E) Low external capsule: anterior (right = 0, left = 0, factor = × 4, total = 0); posterior (right = 1, left = 1, factor = × 4, total = 8). (F) High external capsule: anterior (right = 1, left = 1, factor = × 3, total = 6); posterior (right = 0, left = 1, factor = × 3, total = 3); cingulate (right = 0, left = 0, factor = × 4, total = 0). (G) Corona radiata: anterior (right = 2, left = 2, factor = × 2, total = 8); posterior (right = 2, left = 2, factor = × 2, total = 8); cingulate (right = 0, left = 0, factor = × 1, total = 0). (H) Centrum semiovale: anterior (right = 1, left = 2, factor = × 1, total = 3); posterior (right = 1, left = 2, factor = × 1, total = 3). The total CHIPS score is 39. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
The Cholinergic Pathways Hyperintensities Scale.

Level of slices	Regions	Score[a]	Factor	Total score
1. Low external capsule	Anterior of LP	0-1-2	× 4	0-4-8
	Posterior of LP	0-1-2	× 4	0-4-8
2. High external capsule	Cingulate of MP	0-1-2	× 4	0-4-8
	Anterior of LP	0-1-2	× 3	0-3-6
	Posterior of LP	0-1-2	× 3	0-3-6
3. Corona radiata	Anterior of LP	0-1-2	× 2	0-2-4
	Posterior of LP	0-1-2	× 2	0-2-4
	Cingulate of MP	0-1-2	× 1	0-1-2
4. Centrum semiovale	Anterior of LP	0-1-2	× 1	0-1-2
	Posterior of LP	0-1-2	× 1	0-1-2

LP = lateral pathway; MP = medial pathway.
[a] 0 = none; 1 = mild (< 50% of area); 2 = severe (≥ 50% of area).

Table 2
Demographic and clinical characteristics of the study sample.

	(n = 32)
Female: male	22:10
Age (years)	45.0 ± 12.8
Disease duration (years)	12.3 ± 8.4
EDSS	4.3 ± 1.9
MMSE	26.6 ± 5.1
MoCA-J	22.1 ± 7.4
CHIPS score	27.0 ± 19.1
WMH volume (mL)	25.9 ± 24.9

Note: EDSS indicates Expanded Disability Status Scale; MMSE, Mini-Mental State Examination; MoCA-J, Japanese version of Montreal Cognitive Assessment; CHIPS, Cholinergic Pathways Hyperintensities Scale; WMH, WM hyperintensities.

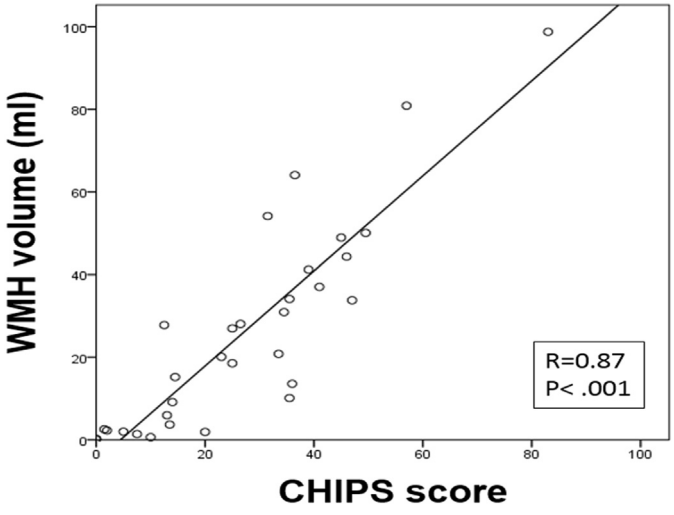

Fig. 2. Relationship between the CHIPS score and the WMH volume. The CHIPS score had a strongly positive correlation with WMH volume.

Second, the difference between the correlation coefficient for the CHIPS score and that for the WHM volume with the cognitive tests (MMSE and MoCA-J) was not statistically significant (P = 0.83 and 0.60, respectively).

Third, in the FreeSurfer analysis, the regional volumes that showed significant positive correlations with the MMSE score were the CC mid-anterior (r = 0.61, P = 0.03) and CC posterior (r = 0.64, P = 0.01). The regional volumes that showed significant positive correlations with the MoCA-J score were CC mid-anterior (r = 0.61, P = 0.03), CC central (r = 0.60, P = 0.04), and CC posterior (r = 0.61, P = 0.03).

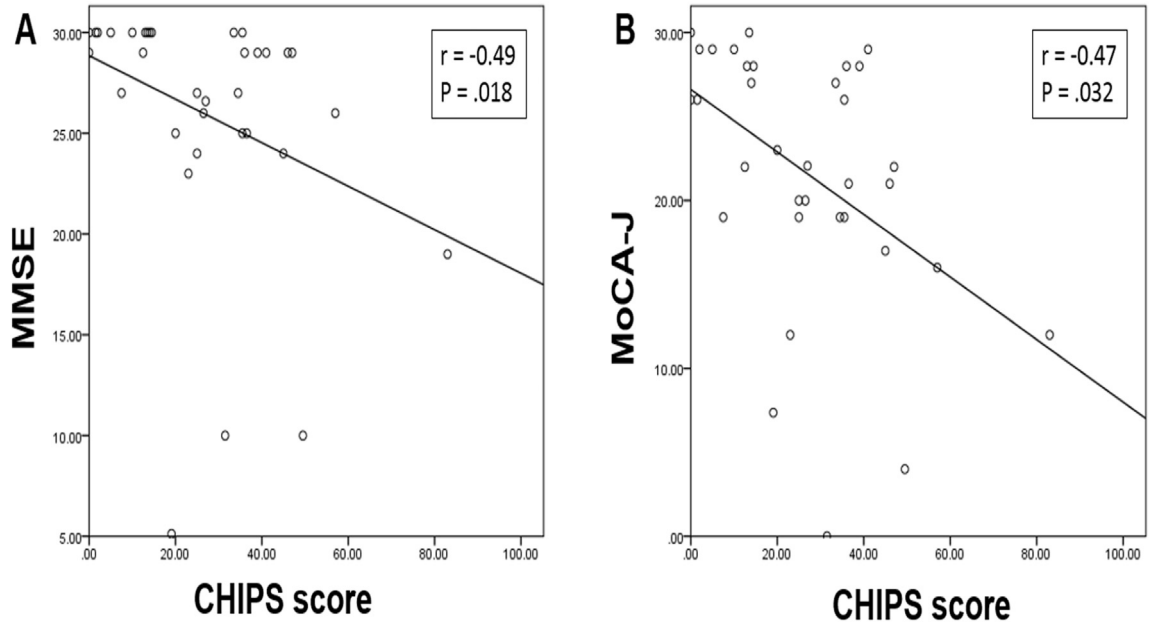

Fig. 3. Relationship between the CHIPS score and MMSE (A) and MoCA-J (B). The CHIPS score had significantly negative correlations with both MMSE and MoCA-J.

4. Discussion

In the current study, we demonstrated significant negative correlations between the CHIPS score and cognitive performance and a strong positive correlation between the CHIPS score and WMH volume. Although the difference was not significant, the WMH volume tended to have higher correlations with the MMSE and MoCA-J scores than the CHIPS score had, which probably indicated that the WMH volume determined by the computer algorithm was superior to the CHIPS score in estimating cognitive performance, although the visually assessed CHIPS score is easier to evaluate. Additionally, CC atrophy was correlated with cognitive scores. CC atrophy may thus be a sensitive marker for cognitive impairment in MS patients, as some studies have reported [24,25].

There has been only one study evaluating the CHIPS score of MS patients. In that study, the CHIPS score had higher correlations with cognitive performance than the WMH volume had in patients with MS [15]. However, our study showed that the WMH volume had a stronger correlation with cognitive performance than the CHIPS score. One of the reasons for this may have been that high-field-strength MRI improved the detectability of the computer algorithm because of the greater signal-to-noise ratio of 3-tesla MRI compared with 1.5-tesla MRI. The earlier study was done using a 1.5-tesla MRI. Another possible reason is that the detection capability may have been improved due to development of the analysis software.

In patients with AD, Bocti et al. reported that the CHIPS method was reliable and showed stronger correlations with cognitive performance than a general WMH rating scale [7]. MS lesions are histopathologically heterogeneous, consisting of areas with demyelination, remyelination, edema, inflammation, gliosis and axonal loss [26,27]. MS does not involve a selective reduction of cholinergic neurons as in AD. A PET study using the tracer ^{11}C-methyl-4-piperidinyl propionate, which is an established radioprobe for the measurement of AChE activity, showed an inverse correlation between AChE activity and cognitive impairment in MS patients [16]. This is in contrast to other neurodegenerative diseases like AD [28,29], Parkinson's disease dementia [30,31], diffuse

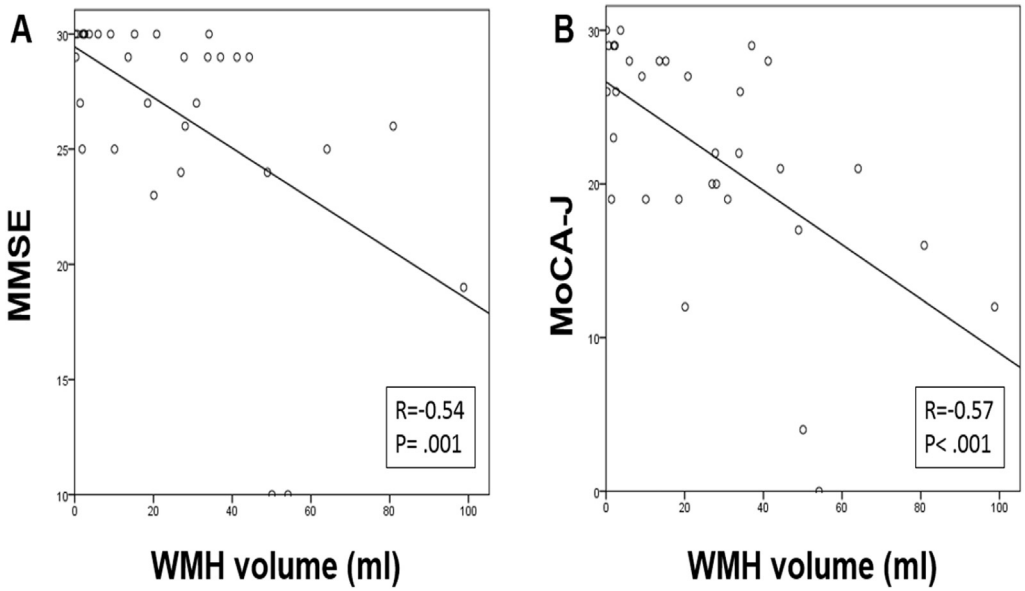

Fig. 4. Relationship between the WMH volume and MMSE (A) and MoCA-J (B). The WMH volume had significantly negative correlations with both MMSE and MoCA-J.

Lewy body disease [32], and age-associated periventricular leukoaraiosis [33], in which a positive correlation has been found between AChE activity and cognitive impairment. These observations confirm the theory of an imbalance of acetylcholine synthesis and degradation in MS. Sternberg suggests that MS cognitive impairment may arise from a sympathovagal imbalance rather than a cholinergic deficit [34]. AChE inhibitors, which were initially developed to treat cognitive impairment in AD, have recently been tried in other cognitive disorders, including MS. However, the therapeutic effects of AChE inhibitors in cognitively impaired MS patients are inconsistent and remain unsatisfactory [35]. Although the relationship between the CHIPS score and AChE activity was not strictly established in previous studies, it can be assumed based on a previous study in which patients in a high CHIPS group had a higher treatment effect by AChE than patients in a low CHIPS group [8]. Therefore, it is possible that the CHIPS method would be less effective in evaluating cognitive function in MS patients compared with patients whose cholinergic neurons were selectively damaged as in AD.

In the present study, there were significant correlations between cognitive scores and the volume of CC. This finding was supported by previous studies showing that CC atrophy is correlated with cognitive impairment [24,25]. Because the CC is composed of interhemispheric fibers traversing the bilateral cerebral white matter, it plays an important role in complex cognitive tasks. CC atrophy may result from axonal disruption owing to white matter damage [36,37]. The CC is commonly involved in MS, while it is normally relatively resistant to age-dependent changes. Therefore, we agree with a previous report that CC atrophy could be a sensitive marker for cognitive impairment in MS patients [25].

Our study has several limitations. First, this was a retrospective and single center study. Therefore, the possibility of unintended selection bias in the selection of patients could not be fully excluded. Second, we did not classify the participants into the three subtypes of MS (primary progressive, relapsing–remitting and secondary progressive). However, all patients fulfilled the inclusion criteria for cognitive impairment, and cognitive impairment has been identified in all subtypes of MS [38–40]. Further longitudinal study would show the differences among the subtypes.

5. Conclusions

Our data demonstrated significant negative correlations between the CHIPS score and cognitive performance and a strong positive correlation between the CHIPS score and WMH volume. The WMH volume on the computer algorithm was superior to the CHIPS score in estimating cognitive performance in MS patients. To explain this finding, it was speculated that selective damage of the cholinergic neurons did not occur in MS patients. Although the difference was not significant, the CHIPS score tended to be less sensitive than the WMH volume for cognitive function evaluation. The CHIPS method may not be as effective in MS patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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