White matter hyperintensities in cholinergic pathways may predict poorer responsiveness to acetylcholinesterase inhibitor treatment for Alzheimer disease

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Research Article

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Abstract

Background

Acetylcholinesterase inhibitor (AChEI) drug regimens are the mainstay treatment options for patients with Alzheimer disease (AD). Herein, we predicted clinical responses to AChEI treatment from baseline neuroimaging parameters.

Methods

Between 2020 and 2021, we recruited 101 individuals with a clinical diagnosis of probable AD. Each participant underwent complete neuropsychological testing and 3T brain magnetic resonance imaging (MRI). Responsiveness to donepezil, as assessed after 12 months, was designated as less than two points of regression in Mini-Mental State Examination scores. We also evaluated MRI images by examining scores on the Cholinergic Pathways Hyperintensities Scale (CHIPS), Fazekas scale, and medial temporal atrophy (MTA) scale.

Results

In our cohort, 52 patients (51.4%) were classified as responders. We observed significantly higher CHIPS scores in the nonresponder group (21.1 ± 12.9 vs. 14.9 ± 9.2, P = 0.007). Age at baseline, education level, sex, Clinical Dementia Rating sum of boxes scores, and three neuroimaging parameters were tested in regression models. Only CHIPS scores predicted clinical response to AChEI treatment.

Conclusion

WMHs in the cholinergic pathways, not diffuse white matter lesions or hippocampal atrophy, correlated with poorer responsiveness to AChEI treatment. Therefore, further investigation into the role of the cholinergic pathway in AD is warranted.

Background

Alzheimer disease (AD) is the most common neurodegenerative disease affecting older adults. Although various chronic conditions, genetic and environmental factors contribute to AD, the exact causes of AD development and progression remain unclear. A notable postulation in AD research is that cognitive decline and behavioral symptoms are linked to reductions in acetylcholine (Ach) in the brain. This chemical is involved in learning, memory, attentional processes, circadian rhythmicity, and the modulation of neuroinflammation [1, 2]. A systematic review of 22 clinical trials reported that patients with AD exhibited improvements in cognitive function following acetylcholinesterase inhibitor (AChEI) treatment [3]. A meta-analysis of studies on AChEI treatment for AD noted the mitigation of neuropsychiatric symptoms and improvements in the ability of perform activities of daily living [4]. Thus, restoring cholinergic activity in the brain constitutes a mainstream treatment for AD.

Responsiveness to AChEIs varies among individuals, and numerous determinants have been examined. Factors such as genetic backgrounds, concomitant medication, and plasma drug concentrations are associated with treatment outcomes. Furthermore, a recent review determined that up to five genes correlate strongly with treatment response [5]. In addition, pathological risk factors related to AD may also correlate with treatment response. For example, apolipoprotein E (APOE)-e4 allele status, by far the most relevant genetic risk factor for AD, has been linked with both responsiveness and nonresponsiveness to AChEIs [6, 7].

Hippocampal atrophy and white matter hyperintensities (WMHs), the most notable MRI findings of AD, are highly correlated with disease progression and correspondent to underlying pathological changes [8, 9]. These markers have been employed in predicting responses to AChEIs, with inconsistent results. Some studies have indicated that hippocampal atrophy is a stronger determinant of responses to AChEI treatment [10, 11], whereas others have concluded that WMHs are the stronger determinant [12, 13]. An overview of findings from relevant studies, including significant neuroimaging parameters, is presented in Table 1.

Responses to AChEI treatment can also correlate with the integrity of the cholinergic system in the brain. Neurodegeneration can compromise this integrity through cortical-Ach-secreting neurons or cholinergic pathways damage. The intactness of cortical-Ach-secreting neurons also come from intact cortical cholinergic activities and basal forebrain neurons. A study measuring cortical acetylcholinesterase activity through positron emission tomography (PET) observed reduced cortical cholinergic activity, which is correlated with poor responses to AChEIs in patients with AD [14]. In a longitudinal study involving patients with AD undergoing AChEI treatment, the reduction in the basal forebrain volume was a significant predictor of the global cognitive response [15]. In sum, this evidence demonstrates the importance of intact cortical-Ach-secreting neurons to AChEI responsiveness.

Cholinergic pathways, comprising bundles of AChE-rich fiber projecting from basal forebrain neurons, constitute another essential factor influencing cholinergic integrity. Cholinergic pathways in postmortem human brains were examined through the acetylcholinesterase histochemistry method [16]. The current study used the Cholinergic Pathways Hyperintensities Scale (CHIPS), a visual rating system, to assess lesions on cholinergic projections [17]. We postulated that WMHs in the cholinergic pathways would be a determinant of AChEI responsiveness. Individuals with higher CHIPS scores may have less intact cholinergic pathways and poorer responsiveness to AChEIs.

Methods

Study design

We performed a retrospective cohort study between 2020 and 2021, recruiting participants with clinical diagnosis of probable AD from the memory clinic of Cardinal Tien Hospital. To classify responses to AChEI treatment, we reviewed and analyzed patients' baseline data (demographic information, clinical characteristics, and neuroimaging data from medical records) and cognitive changes over time, as

evaluated from their Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and CDR sum of boxes (CDR-SB) scores. We obtained the informed consent from all participants and/or their legal guardian(s). The study was conducted in accordance with the tenets of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board (IRB) of Cardinal Tien Hospital (IRB no.: CTH-107-2-1-067).

Participant recruitment

We recruited individuals with dementia (very mild to moderate) who were taking donepezil, an AChEI, for at least 12 months. At their initial visit, all participants had completed clinical evaluation and neuropsychological assessment and undergone magnetic resonance imaging (MRI). Their age, MMSE scores, and global CDR scores ranged from 70 to 85 years, 15 and 24 points, and 0.5 and 2 points, respectively. They all met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association corresponding to a clinical diagnosis of probable AD dementia. Individuals with stroke, parkinsonism, mixed dementia, or other neurological disorders, including anxiety or major depressive disorder, were excluded. The starting dose of 5 mg was slowly titrated up to 10 mg, which was then maintained for at least 12 months. We assigned the participants into the responder and nonresponder groups according to the following criteria. Responders were those whose MMSE and CDR scores remained stable or improved following treatment. Nonresponders were those whose CDR scores regressed following treatment. Table 2 presents the detailed demographic, clinical, and neuropsychological pretreatment data for the responder and nonresponder groups.

Table 2
Baseline demographic and cognitive functions of individuals with probable AD

	Responders (n = 52)	Nonresponders (n = 49)	P value
Age at baseline, years (mean) (SD)	76.6 (7.4)	79.3 (7.1)	0.059
Education, years (mean) (SD)	7.7	7.8	0.900
Women, n (%)	34 (65.4)	30 (61.2)	0.665
Hypertension, n (%)	35 (67.3)	33 (67.3)	0.99
Type 2 diabetes mellitus, n (%)	21 (40.4)	16 (32.7)	0.42
APOE4 carrier status, n^0/n^1 (%)	11/26 (42.3)	2/17 (11.8)	0.034
Baseline MMSE score (mean) (SD)	19.0 (5.1)	19.7 (5.1)	0.503
Baseline CDR score (mean) (SD)	0.75 (0.4)	0.83(0.5)	0.362
CDR 0.5, n (%)	34 (65.4)	30 (61.2)	0.567
CDR 1, n (%)	14 (26.9)	12 (24.5)	0.567
CDR 2, n (%)	4 (7.7)	7 (14.3)	0.567
Baseline CDR-SB score (mean) (SD)	4.2 (2.8)	4.6 (3.5)	0.527

SD standard deviation; MMSE Mini-Mental State Examination; CDR Clinical Dementia Rating; CDR-SB CDR sum of boxes; n^0 number of APOE4 carriers; n^1 number of patients with APOE genotyping results.

Image acquisition

All participants received whole-brain MRI scan (3.0 T, MAGNETOM Skyra, Siemens, Taipei, Taiwan). The MRI acquisition protocol is presented as follows: whole-brain axial and sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (FLAIR repetition time [TR]/time to echo [TE] = 3550/98 ms) with a 5-mm slice thickness, axial T1-weighted sequence (TR/TE = 2200/3 ms) with a 3-mm slice thickness, and high-resolution coronal T1-weighted three-dimensional (3D) magnetization-prepared rapid gradient-echo image (TR/TE = 2200/5 ms) with a 1-mm slice thickness. Two well-trained raters (YCL and LHL) who were blinded to the clinical data assessed all the MRI images. The interrater correlation coefficient was 0.92.

Medial temporal atrophy scale

The medial temporal atrophy (MTA) scale is a visual rating system for assessing the size of the hippocampus relative to the surrounding cerebrospinal fluid space [18]. For each side of the hippocampus, the scale ranges from 0 to 4 points. A coronal T1-weighted 3D brain MRI sequence was

employed. We measured both sides of the hippocampus and calculated the total MTA score by summing the scores for the left and right sides.

Fazekas scale

Scores on the Fazekas scale, which is used to quantify the degree of diffuse WMHs [19], ranges from 0 (normal) to 3 (confluent).

CHIPS

The CHIPS was also employed to evaluate the severity of WMHs, which was assessed through four anatomical landmarks: central semiovale, corona radiata, and the upper and lower portions of the external capsule. Each landmark was measured bilaterally from anterior to posterior (Fig. 1), with scores ranging from 0 to 2 (0: normal, 1: mild, 2: moderate to severe; Fig. 2). Because the density of cholinergic fiber differs depending on the cut, the subtotal score of each landmark was multiplied by various factors.

Statistical analysis

All analyses were conducted using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). The independent t test was performed for between-group comparisons of baseline demographic data (e.g., age, education level, and cognitive status) and MMSE, CDR, CDR-SB, and neuroimaging data (scores on the CHIPS, Fazekas scale, and MTA scale). Categorical variables were analyzed using the chi-square test and Fisher's exact test. Next, we performed Pearson correlation analysis to determine the effects of all intervariable correlations. Finally, we conducted logistic regression analysis with responses to donepezil treatment as dependent variable and visual ratings (CHIPS, Fazekas and MTA scales in separate models) as independent variable, adjusting for age, sex, education level and CDR-SB.

Results

Of the 101 participants, 64 (63.4%) had very mild dementia, 26 (25.7%) had mild dementia, and 11 (10.9%) had moderate dementia, and 52 (51.5%) patients responded to donepezil treatment. After 12 months of treatment, significant decreases in MMSE, CDR, and CDR-SB scores relative to baseline were observed in the nonresponder group. By contrast, the responder group exhibited slight regression (Table 3). Women were the majority in both the responder and nonresponder groups (65.4% and 61.2%, respectively), and no between-group sex differences were noted. Furthermore, 43 participants had APOE genotyping results, with the responder group having a significantly higher percentage of APOE e4 carriers than the nonresponder group (42.3% vs. 11.8%, P = 0.034). No significant differences in baseline cognitive function or other demographic variables were detected. The demographic data of both the groups are presented in Table 2.

Table 3
Comparisons of cognitive function before and after 12 months of donepezil treatment in participants

	Responders		P value	Nonresponders		P value
	T0	T1		T0	T1	
MMSE score, mean (SD)	19.0 (5.1)	19.8 (4.9)	0.384	19.7 (5.1)	13.0 (5.8)	0.000
CDR score, mean (SD)	0.7 (0.4)	0.6 (0.3)	0.078	0.8 (0.5)	1.2 (1.7)	0.001
CDR-SB score, mean (SD)	4.2 (2.8)	4.4 (2.8)	0.769	4.6 (3.5)	8.0 (4.7)	0.000

SD standard deviation, MMSE Mini-Mental State Examination; CDR Clinical Dementia Rating; CDR-SB CDR sum of boxes; T0 pretreatment; T1 posttreatment

On baseline MRI images, mean CHIPS scores were significantly lower in responders (14.9 ± 9.2 vs. 21.1 ± 12.9, P = 0.007; Table 4). Neither the Fazekas nor MTA scores exhibited any between-group differences. Notably, CHIPS scores (r = 0.19, P = 0.046) and MTA scores (r = 0.27, P = 0.006) were correlated with age, but the response to donepezil and age at baseline did not show any correlations. Because vascular risk factors are highly related to cognitive impairment, we examined the links between the comorbidities of hypertension and diabetes mellitus with responses to donepezil. No significant correlations were detected. The multiple logistic regression analysis revealed a significant association between CHIPS scores and responses to donepezil (b = 0.950, standard error [SE] = 0.020, P = 0.013) after adjustments for baseline age, sex, education level, and CDR-SB scores (Tables 5 and 6). However, neither the Fazekas scores (b = 0.676, SE = 0.323, p = 0.227) nor MTA scores (b = 1.090, SE = 0.099, P = 0.388) was associated with responses to donepezil .

Table 4
Baseline neuroimaging parameters in the responder and nonresponder groups

	Responders	Nonresponders	P value
Total MTA score, mean (SD)	2.2 (2.5)	2.1 (1.9)	0.879
CHIPS score, mean (SD)	14.9 (9.2)	21.1 (12.9)	0.007
Fazekas score, mean (SD)	1.2 (0.6)	1.4 (0.6)	0.136

MTA medial temporal atrophy; CHIPS Cholinergic Hyperintensities Pathway Scale

Table 5
Stepwise logistic regression for prediction of responsiveness of donepezil

Models		SE	(Exp)B	95% CI	P value
1	Age at baseline	0.029	0.948	0.896–1.003	0.063
2	Age at baseline	0.029	0.948	0.896–1.003	0.064
	Sex	0.421	0.847	0.371–1.933	0.694
3	Age at baseline	0.029	0.948	0.895–1.003	0.061
	Sex	0.453	0.874	0.732–2.051	0.757
	Education level	0.045	0.987	0.904–1.079	0.777
4	Age at baseline	0.031	0.938	0.884–0.996	0.077
	Sex	0.438	0.861	0.365–2.033.	0.733
	Education level	0.049	1.011	0.917–1.114	0.828
	CDR-SB score	0.066	0.983	0.863–1.120	0.800

Note: Stepwise logistic regression of prediction of responsiveness to donepezil with age at baseline, gender, and education level as independent variables.

SE standard error; CI confidence interval; CDR-SB Clinical Dementia Rating sum of boxes; MMSE Mini-Mental State Examination

Discussion

This study clarified the relationship between the integrity of the cholinergic tract and responsiveness to donepezil. At baseline, responders had significantly lower CHIPS scores than nonresponders (Table 4). The proportion of APOE carriers is higher in responders (42.3% vs. 11.8%). Overall, nonresponders exhibited greater clinical regression in cognitive function than responders (Table 3). We conducted logistic regression analysis to predict responses to AChEI treatment by using scores on the CHIPS, Fazekas scale, and MTA scales as variables. Considering that age, education level, and baseline dementia severity may influence the rate of cognitive decline, adjustments were made for these factors. Our results suggest that the severity of WMHs in the cholinergic pathway helps predict responsiveness to AChEI treatment.

A substantial body of evidence indicates that diffuse WMHs in the brain are associated with the clinical severity of amnestic MCI [20] and AD [21], as well as with cognitive decline in these conditions. However, the link between cholinergic modulation and AChEI response remains to be established [11]. Herein, the severity of WMHs in the cholinergic pathways was the only difference between the responder and nonresponder groups. Moreover, adjusting for the effect of global cognitive function (CDR-SB scores), more WMHs in the cholinergic pathways were associated with poorer responsiveness to AChEI treatment.

Our results demonstrate that WMHs in the cholinergic pathway play a more decisive role in determining responsiveness to AChEI treatment than do WMHs in general. Similar observations have been presented in the literature, with one study reporting that white matter lesions in the frontal lobe and basal ganglia significantly reduced responsiveness to AChEI treatment [12]. Mounting evidence suggests links between the distribution or location of WMHs in the brain and cognition [20, 22]. One investigation noted that specific white matter tracts in the brain contributed more significantly than others to the conversion of MCI to AD and the progression of AD [23]. Overall, our findings align with those of other studies. Tracking the reduction of specific white matter tracts may be a promising direction to pursue in research on the monitoring of AD progression and responses to AChEI treatment.

The specific mechanism underlying the correlation between WMHs in the brain and the progression of MCI to AD or the progression of AD has yet to be elucidated. Several hypotheses have been advanced. Most studies predominantly regarded WMHs as a presentation of small vessel disease [21,24]. However, WMH is sometimes considered a vascular form of amyloid deposition, not necessarily associated with vascular risk factors such as hypertension or stroke. In one study, the severity and topographic pattern of WMHs was correlated with amyloid load and amyloid distribution in the brain [25]. On the other hand, WMHs could be driven by neurodegeneration. WMHs may damage the subcortical neurological circuit and cause cognitive decline. Herein, the mean age of the nonresponders was slightly higher (79.3 ± 7.1 years vs. 76.6 ± 7.4 years). Nonresponder groups may exhibit more neurodegenerative pathological changes than responder groups. It seems higher CHIPS scores in nonresponders was more likely due to neurodegeneration instead of small vessel disease. Cohort studies employing neuroimaging modalities such as amyloid PET to examine cerebral microbleeds as a marker of diffuse vascular and neurodegenerative brain damage may provide further insight into the pathophysiological implications of WMHs. Some earlier studies predicted responses to AChEI treatment by considering hippocampal size [10, 11]. In one investigation, poor response was associated with younger age at AD onset and more severe hippocampal atrophy, but WMHs did not contribute to the prediction of this response [11]. Notably, because the median follow-up duration in that study was 46.6 months, hippocampal atrophy possibly reflected the clinical progression of AD rather than poor responses to AChEI treatment. Given that hippocampal volume has been established as meaningful predictor of MCI conversion and cognitive decline [10, 26]. However, evidence supporting its role in predicting responses to AChEI is inconsistent (Table 1). Most of our participants had mild dementia (CDR score: 0.5 to 1); in other words, these patients were in a relatively early stage of the clinical course. Therefore, we believe that the integrity of the cholinergic system (in particular the cholinergic pathway) was the primary determinant of responsiveness to AChEI treatment in this group.

As many articles indicated, the APOE4 allele has been correlated with amyloid accumulation and the severity of WMHs in AD [27]. APOE4 is not only the most notable genetic risk factor for AD; it also increases the risk of cardiovascular disease, stroke, and other neurogenetic disorders [28]. The responder group in our study had a higher proportion of APOE4 positivity than the nonresponder group (42.3% vs. 11.8%). APOE4 has been implicated in enhancing the effects of AChEIs [29]. However, a meta-analysis

[30] indicated that APOE4 does not significantly affect responses to AChEI treatment. Whether APOE4 status influences the effects of AChEI treatment may need more work and a larger cohort.

This study has some limitations. First, changes in cognitive function were only evaluated through MMSE and CDR scores. However, responses to AChEI treatment may differ between specific cognitive domains. Prospective studies can compare the difference between specific cognitive domains before and after AChEI treatment. Second, only some of the participants had APOE genotyping results. Thus, an association between APOE and responses to AChEI cannot be established. Third, we examined cholinergic pathways, general WMHs, and hippocampal atrophy by using visual rating scale. Future studies can employ neuroimaging techniques such as diffusion tensor imaging or automated volumetry.

Conclusions

Overall, 51.5% of the participants responded to AChEI treatment, as assessed through 12 months of follow-up. Our results suggest that WMHs in the cholinergic pathway, not diffuse white matter lesions or hippocampal atrophy, are correlated with poorer responsiveness to AChEI treatment. Therefore, further explorations into the role of the cholinergic pathway in AD are imperative.

Abbreviations

AD: Alzheimer's disease

WMH: White matter hyperintensity

AChEI: Acetylcholinesterse inhibitor

MCI: Mild cognitive impairment

3T: 3.0 Telsa

MRI: magnetic resonance imaging

CR: corona radiata

EC: external capsule

MMSE: Mini-mental status examination

CDR: Clinical dementia rating

CDR-SB: Clinical dementia rating- sum of box

CHIPS: Cholinergic Pathways Hyperintensity Scale

MTA: medial temporal atrophy

NIA-AA: National Institute of Neurological and Communicative Disorders and Stroke-

Alzheimer's Disease and Related Disorders Association

APOE4: Apolipoprotein E4

PET: Positron emission tomography

DTI: Diffuse tensor imaging

Declarations

Ethics approval and consent to participate

Written informed consents from each patient was obtained for publication of this retrospective cohort. All methods were carried out in accordance with relevant guidelines and regulations or Declaration of Helsinki. Institutional review board of Cardinal Tien Hospital, Taipei, Taiwan, approved the study. (IRB: CTH-107-2-1-067).

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due on our policy statement of sharing clinical data only on request but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

YCL, CJC and LHL contributed to writing and revised the manuscripts. SCW and WLL contributed to preparing and sorting data. YCL and LHL contributed to interpreting the neuroimages and CFH contributed to supervise the interpretation of neuroimages. All authors read and approved final manuscript.

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Figures

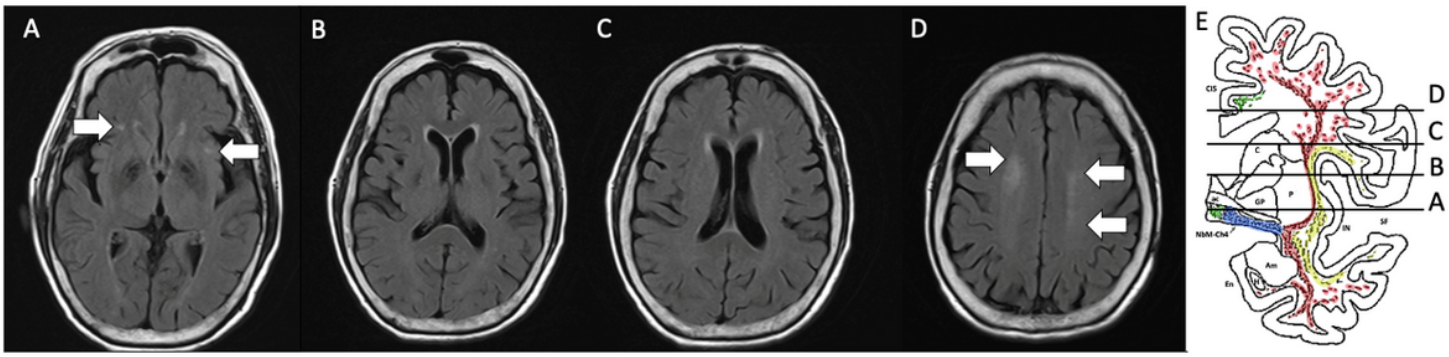

Figure 1

Sample of T2-weighted-FLAIR sequence brain MRI images of four anatomical landmarks for CHIPS score assessment

(A) Lower portion of the external capsule: anterior (right = 1, left = 1), posterior (right = 0, left = 0); add scores and multiply by a factor of 4 for a subtotal of 8 (B) Upper portion of the external capsule: anterior (right = 0, left = 0), posterior (right = 0, left = 0), cingulate (right = 0, left = 0); add scores and multiply by a factor of 3 for a subtotal of 0 (C) Corona radiata: anterior (right = 0, left = 0), posterior (right = 0, left = 0), cingulate (right = 0, left = 0); add scores and multiply by a factor of 2 for a subtotal of 0 (D) Central semiovale: anterior (right = 2, left = 1), posterior (right = 0, left = 1); add scores and multiply by a factor of 1 for a subtotal of 4. Total CHIPS score: 12 (E) Redrawing of a schematic of cholinergic pathway trajectories with permission from Mesulam MM. [16]

Note: CHIPS: Cholinergic Pathways Hyperintensity Scale

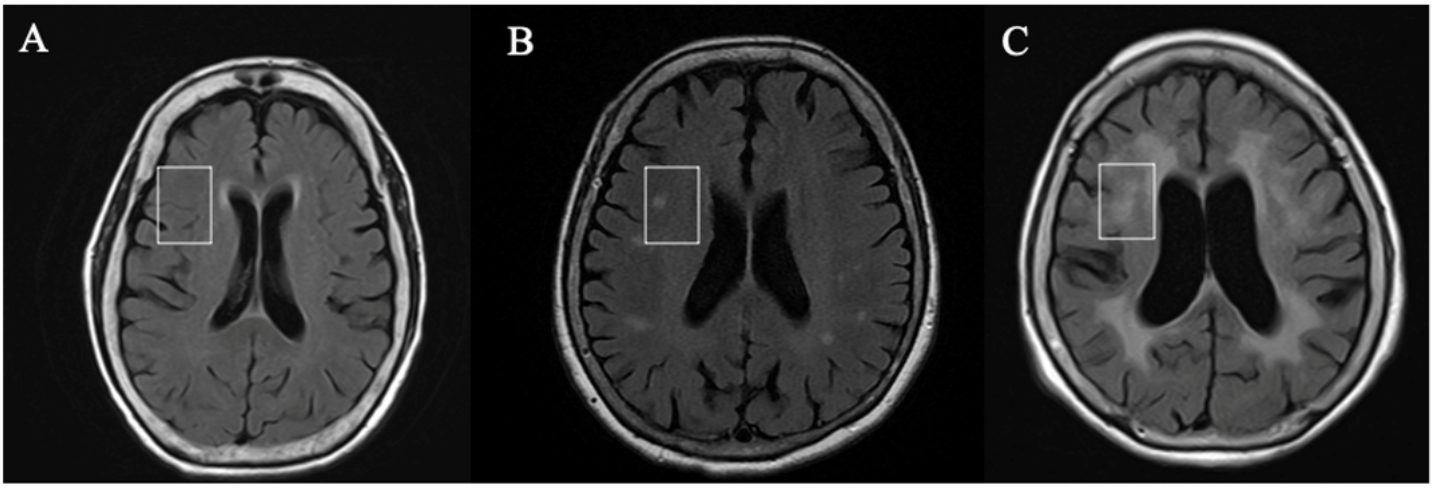

Figure 2

Brain MRI images of WMH severities corresponding to CHIPS scores as circumscribed by white rectangles

(A) Absence of WMHs (CHIPS score: 0) (B) Mild WMHs (CHIPS score: 1), as indicated by the WMHs occupying less than 50% of the marked area (C) Moderate-to- severe WMHs (CHIPS score: 2), as indicated by the WMHs occupying more than 50% of the marked area

Note: WHM white matter hyperintensities, CHIPS: Cholinergic Pathways Hyperintensity Scale