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Original Article

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White Matter Lesions Predominantly Located in Deep White Matter Represent Embolic Etiology Rather Than Small Vessel Disease

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ABSTRACT

Background and Purpose: We investigated the correlation between the deep distribution of white matter hyperintensity (WMH) (dWMH: WMH in deep and corticomedullary areas, with minimal periventricular WMH) and a positive agitated saline contrast echocardiography result.
Methods: We retrospectively recruited participants with comprehensive dementia evaluations, an agitated saline study, and brain imaging. The participants were classified into two groups according to WMH-distributions: dWMH and dpWMH (mainly periventricular WMH with or without deep WMH.) We hypothesized that dWMH is more likely associated with embolism, whereas dpWMH is associated with small-vessel diseases. We compared the clinical characteristics, WMH-distributions, and positive rate of agitated saline studies between the two groups.
Results: Among 90 participants, 27 and 12 met the dWMH and dpWMH criteria, respectively. The dWMH-group was younger (62.2±7.5 vs. 78.9±7.3, p<0.001) and had a lower prevalence of hypertension (29.6% vs. 75%, p=0.008), diabetes mellitus (3.7% vs. 25%, p=0.043), and hyperlipidemia (33.3% vs. 83.3%, p=0.043) than the dpWMH-group. Regarding deep white matter lesions, the number of small lesions (<3 mm) was higher in the dWMH-group(10.9±9.7) than in the dpWMH-group (3.1±6.4) (p=0.008), and WMH was predominantly distributed in the border-zones and corticomedullary areas. Most importantly, the positive agitated saline study rate was higher in the dWMH-group than in the dpWMH-group (81.5% vs. 33.3%, p=0.003).
Conclusions: The dWMH-group with younger participants had fewer cardiovascular risk factors, showed more border-zone-distributions, and had a higher agitated saline test positivity rate than the dpWMH-group, indicating that corticomedullary or deep WMH-distribution with minimal periventricular WMH suggests embolic etiologies.

Keywords: Cerebrovascular Disorder Patent Foramen Ovale; Embolism

90 patients, 19 patients were excluded for the following reasons:1) the presence of WMH lesions associated with etiologies other than CSVD, such as radiation injury, leukodystrophy, multiple sclerosis, and other autoimmune encephalopathies; 2) the detection of intra/extracranial artery stenoses on brain MR angiography; 3) history of cardiac diseases that could cause embolism, such as atrial fibrillation; and 4) meeting the Boston Criteria for cerebral amyloid angiopathy (CAA).[13]

Those in the dWMH group met the following criteria:1) WMH mainly located in the deep white matter and corticomedullary junction based on FLAIR images; 2) the presence of minimal periventricular WMH <P2 (caps ≤5 mm or band ≤5 mm)[14] and no lacunes; and 3) MTA grade 2 or less on Scheltens' visual rating scale.[7] Second, we classified individuals with typical CSVD into the dpWMH group, which satisfied the following criteria in the same study period: 1) significant periventricular WMH (caps ≥10 mm and band ≥10 mm),[14] 2) at least one lacune, and 3) MTA grade 2 or less on Scheltens' visual rating scale.[7]

Dementia evaluation

The participants underwent a comprehensive dementia evaluation that included history taking, neurological examination, blood tests to exclude secondary dementia causes, brain MRI, and cognitive assessments, including the Mini-mental Status Examination (MMSE), Seoul Neuropsychological Screening Battery, and Clinical Dementia Rating-sum of the boxes. This evaluation helped to identify the underlying causes of cognitive impairment and classify the participants into either of the following categories: subjective cognitive decline, mild cognitive impairment, or dementia.[15,16]

Agitated saline contrast echocardiography (agitated saline study)

Two-dimensional echocardiography was performed using commercially available equipment (Vivid 7; GE Medical Systems, Milwaukee, WI, USA). In the apical four-chamber view, the left-to-right shunt at the atrial level was evaluated using color flow Doppler. A right-to-left intra-atrial shunt was evaluated by contrast injection (10 mL of agitated saline) at rest and by the Valsalva maneuver (VM). To investigate the presence of an extracardiac shunt, the contrast agent injection was performed when the pulmonary vein was open.[17] The direct passage from the right atrium to the left atrium across the interatrial septum or the early appearance of bubbles in the left atrium (within three to five beats) after right chamber opacification during rest or VM suggests an intracardiac shunt. The later appearance of bubbles in the left atrium (>5 beats after first observing bubbles in the right atrium) suggests pulmonary arteriovenous shunting.[18]

A positive shunt test was achieved when at least one definite microbubble was observed in the left chamber.[19-21] The amount of right-to-left shunt (RLS) was semi-quantified as follows: grade 0 (no microbubbles), grade I (1– 5 microbubbles), grade II (6–20 microbubbles), grade III (21–50 microbubbles), and grade IV (>50 microbubbles). Grade I or II was considered small RLS, and grade III or IV indicated large RLS, adopted from the grading system used for R-L shunt.[19-21]

Brain MRI acquisition

MR images from all participants were obtained using an Achieva 3.0 T MRI scanner (Philips, Best, The Netherlands), which included FLAIR and T2*GRE from all participants. The following parameters were used for the FLAIR images: axial slice thickness, 2 mm; no gap, TR of 11,000 ms; TE, 125 ms; flip angle, 90°; and matrix size, 512×512 pixels. The following parameters were used for the T2*GRE images: axial slice thickness, 5.0 mm; inter-slice thickness, 2 mm; repetition time, 669 ms; echo time, 16 ms; flip angle, 18°; and matrix size, 560×560 pixels.

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WMH assessment

WMH lesion assessment was performed by two experienced neurologists who were trained in neuroimaging rating and blinded to the participants' clinical details. WMH lesions were rated on a visual rating scale proposed by the Clinical Research Center for Dementia of South Korea (CREDOS).[14] Deep WMH was classified as D1 (<10 mm), D2 (10–25 mm), or D3 (≥25 mm) based on the longest diameter of the lesions. Periventricular WMH were classified as P1 (caps and band <5 mm), P2 (5–10 mm), or P3 (cap or band ≥10 mm) based on the maximum length measured perpendicular (cap) and horizontal (band) to the ventricle.[3,14] We assessed WMH lesions on every other FLAIR image as the images were acquired without a gap and at a thickness of 2 mm.

We only counted WMH lesions where the longest diameter was longer than 2 mm because exceedingly small, unspecified bright objects (UBOs) are considered normal, and small UBOs can be a manifestation of small perivascular spaces (<2 mm), which have been regarded as anatomic variations.[22-25] In terms of WMH distribution, periventricular lesions were defined as those located within 10 mm from the ventricular surface,[8] corticomedullary lesions as those within 4 mm from the corticomedullary junction,[26] and deep white matter lesions as those between the periventricular and corticomedullary junction areas.[26]

Confluent periventricular WMH lesions were excluded from the number of WMH lesions. Each isolated WMH lesion in the deep and corticomedullary regions, was counted as a single lesion, even if partially confluent. The size of each lesion was determined by its longest diameter.

Assessment of lacunes and microbleeds

Lacunes were counted in accordance with the standards for reporting vascular changes on neuroimaging.[27] Lacunes were defined as round or ovoid, subcortical, fluid-filled cavities (signal similar to cerebrospinal fluid) between 3 mm to about 15 mm in diameter, consistent with a previous acute small subcortical infarct or hemorrhage in the territory of one perforating arteriole according to STRIVE guidelines.[28] Considering that our FLAIR images were obtained at a thickness of 2 mm and no gap, we counted the number of lacunes on every other FLAIR image.

Microbleeds were defined as homogenous, round lesions displaying a signal loss (≤10 mm in diameter) in T2*GRE images.[29] Considering that our GRE images were obtained with a thickness of 5 mm and a 2 mm gap, we counted the number of microbleeds on every other GRE image.

Visual rating of medial temporal lobe atrophy

Medial temporal lobe atrophy (MTA) was assessed visually by an experienced neurologist.[30] The degree of MTA was rated from 0 (no atrophy) to 4 (severe atrophy). If it was asymmetric between the left and right, the more severe MTA was selected for the patient.

Image creation to compare WMH distribution between the dpWMH and dWMH groups

WMH lesions on each FLAIR-MRI slice were manually marked using MRIcro software to create a composite image of WMH spatial distribution. The T2*FLAIR-MRI images were co-registered to each individual's 3D T1 MR images, which were then registered to the Montreal Neurological Institute's 152 templates. We then applied normalized parameters to transform the co-registered T2*FLAIR MRIs using the MRI template. The manually marked lesions were subsequently re-sampled into the template space (**Fig. 2**).

Fig. 2. Comparison of WMH distribution between the dWMH and the dpWMH groups. WMH lesions were manually cropped from the patients' FLAIR slices using MRIcro, co-registered to 3D T1 images, and superimposed onto MNI templates (see Methods for details). (A, B) WMH lesions from a patient in the dWMH (A) and the dpWMH (B) group were superimposed onto MNI templates. The red and blue colors indicate higher and lower frequencies, respectively, as indicated by the color bar on the far right. (C) Spatial distribution of the WMH lesions evident in both dWMH and dpWMH groups (red: WMH lesions shown exclusively in the dWMH group, blue: WMH lesions shown exclusively in the dpWMH group, green: lesions overlapping in both groups).
WMH: white matter hyperintensity, dWMH: deep-only WMH pattern in which WMHs are mainly located in the corticomedullary junction or deep white matter, accompanied by little or no periventricular WMH, dpWMH: WMH pattern that is commonly seen in individuals with cerebral small vessel disease, where main periventricular WMH with or without deep WMH is accompanied by one or more lacunes.

Statistical analyses

For descriptive statistics, we used the χ^2 test and Student's t-test to compare the clinical/imaging characteristics and shunt frequency between the groups. Post-hoc analysis was performed after pooling the dWMH and dpWMH groups. Linear regression was used to determine the association between age and the presence of cardiovascular factors.

Statistical significance was set at a two-tailed p-value of <0.05. Statistical analyses were conducted using the Statistical Package for the Social Sciences software version 25 (SPSS Inc., IBM Corp., Armonk, NY, USA).

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Data availability

Data that support the findings of this study will be made available by the corresponding author upon reasonable request.

RESULTS

Demographic characteristics

After excluding 19 of the initial 90 according to the exclusion criteria, 39 of the remaining 71 patients met either the dWMH (27/39) or the dpWMH (12/39) criteria. Of the 39 patients, 27 were classified into the dWMH group, and 12 were classified into the dpWMH group (**Table 1**). Overall, the dWMH group was younger than the dpWMH group (62.2±7.5 vs. 78.9±7.3 years,

Table 1. Demographic data of the study participants

Variables	dWMH group (n=27)	dpWMH group (n=12)	*p*-value
Age	62.2±7.5	78.7±7.3	<0.001
Female	21/27 (77.8)	8/12 (66.7)	0.463
Hypertension	8/27 (29.6)	9/12 (75)	0.008
Diabetes mellitus	1/27 (3.7)	3/12 (25)	0.043
Hyperlipidemia	9/27 (33.3)	10/12 (83.3)	0.016
The number of lacunes	0	3.3±2.5	0.001
Prevalence of TIA/CVA	0 (0)	1/12 (8.3)	0.129
Cognitive status			<0.001
SCD	17/27 (65.4)	1/12 (8.3)	
MCI	9/27 (34.6)	5/12 (41.7)	
Dementia	0 (0)	6/12 (50.5)	
MMSE	25 (28.8±1.9)	25.0±3.9	<0.001
CDR	25 (0.5±0.1)	0.7±0.5	0.015
CDR-SOB	25 (0.9±0.8)	3.0±3.3	0.005
Variables	dWMH group (n=27)	dpWMH group (n=12)	*p*-value
No. of total WMH lesions	155.6±82.3	53.3±53.1	<0.001
Longest diameter of WMH (mm)	14.7±8.1	52.5±14.8	<0.001
Anatomical distribution of WMH			
Deep WM lesion (total)	31.1±34.4	27.6±20.7	0.695
<3 mm	10.9±9.7	3.1±6.4	0.008
3–10 mm	17.3±24.4	15.6±11.9	0.776
10–20 mm	2.5±7.2	6.0±5.4	0.114
>20 mm	0.4±1.8	5.4±4.0	0.002
Corticomedullary lesions, total	124.5±75.6	25.7±40.9	<0.001
<3 mm	60.3±48.3	7.1±14.4	<0.001
3–10 mm	59.4±41.2	16.6±25.6	0.001
10–20 mm	4.2±9.9	2.4±4.0	0.416
>20 mm	0.7±2.6	1.9±3.3	0.284
Variables	dWMH group (n=27)	dpWMH group (n=12)	*p*-value
Saline shunt test	22/27 (81.5)	4/12 (33.3)	0.003
Intracardiac shunt	18/22 (81.8)	2/4 (50.0)	
Extracardiac shunt	4/22 (18.2)	2/4 (50.0)	
Shunt grade	1.8±1.2	0.5±0.9	0.003
0	5 (18.5)	8 (66.7)	
I	4 (14.8)	1 (8.3)	
II	12 (44.4)	3 (25)	
III	4 (14.8)	0 (0)	
IV	2 (7.4)	0 (0)	

Values are presented as mean ± standard deviation or number (%).
dWMH: deep-only WMH pattern in which WMHs are mainly located in the corticomedullary junction or deep white matter, accompanied by little or no periventricular WMH, dpWMH: WMH pattern that is commonly seen in individuals with cerebral small vessel disease, where main periventricular WMH with or without deep WMH is accompanied by one or more lacunes, TIA: transient ischemic attack, CVA: cerebral vascular accident, SCD: subjective cognitive decline, MCI: mild cognitive disorder, MMSE: Mini-mental Status Examination, CDR-SOB: Clinical Dementia Rating-sum of the boxes, WMH: white matter hyperintensity.

p<0.001). Compared to the dWMH group, the dpWMH group showed a higher prevalence of hypertension (29.6% vs. 75%, p=0.008), DM (3.7% vs. 25%, p=0.043), and hyperlipidemia (33.3% vs. 83.3%, p=0.043). The participants in the dWMH group (28.8±1.9) showed higher MMSE scores than those in the dpWMH group (25.0±3.9) (p<0.001).

In the post-hoc analysis using linear regression, after pooling the dWMH and dpWMH groups, younger age was correlated with a lower presence of cardiovascular factors (R^2=0.370, B=0.10, p<0.001).

Comparison of WMH burden and distribution between groups

The total number of WMH lesions was higher in the dWMH group (155.7±82.3) than in the dpWMH group (53.3±53.1) (p<0.001). The diameter of the largest lesion was larger in the dpWMH (52.5±14.8) group than in the dWMH group (14.7±8.1) (p<0.001) (**Table 2**).

In terms of deep WMH, the number of small lesions (<3 mm) was higher in the dWMH group (10.9±9.7) than in the dpWMH group (3.1±6.4) (p=0.008), whereas the number of large lesions (>20 mm) was lower in the dWMH group (0.4±1.8) than in the dpWMH group (5.4±4.0) (p=0.002).

The total number of corticomedullary lesions was higher in the dWMH group (124.5±75.6) than in the dpWMH group (25.7±40.9) (p<0.001). In particular, the number of small lesions (<10 mm) was higher in the dWMH group than in the dpWMH group (<3 mm: 59.4±41.2 vs. 16.6±25.6, p<0.001; 3 mm –10 mm: 59.4±41.2 vs. 16.6±25.6, p=0.001) (**Table 2** and **Fig. 3**).

As shown in **Fig. 2A**, WMH lesions in the dWMH group were located between the territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) (external border zone) or in the white matter along and slightly above the lateral ventricle, between the deep and superficial arterial systems of the MCA, or between the superficial systems of the MCA and ACA (internal border zone). The frequency map revealed that the WMH lesions in the dpWMH group were predominantly located in the periventricular area, followed by the contiguous deep white matter area (**Fig. 2B**). The WMH distribution in the two groups showed distinct patterns, although they partly overlapped (**Fig. 2C**).

Table 2. Characteristics and distribution of WMH between the groups

Variables	dWMH group (n=27)	dpWMH group (n=12)	*p*-value
No. of total WMH lesions	155.6±82.3	53.3±53.1	<0.001
Longest diameter of WMH (mm)	14.7±8.1	52.5±14.8	<0.001
Anatomical distribution of WMH			
Deep WM lesion (total)	31.1±34.4	27.6±20.7	0.695
<3 mm	10.9±9.7	3.1±6.4	0.008
3–10 mm	17.3±24.4	15.6±11.9	0.776
10–20 mm	2.5±7.2	6.0±5.4	0.114
>20 mm	0.4±1.8	5.4±4.0	0.002
Corticomedullary lesions, total	124.5±75.6	25.7±40.9	<0.001
<3 mm	60.3±48.3	7.1±14.4	<0.001
3–10 mm	59.4±41.2	16.6±25.6	0.001
10–20 mm	4.2±9.9	2.4±4.0	0.416
>20 mm	0.7±2.6	1.9±3.3	0.284

Values are presented as mean ± standard deviation.
WMH: white matter hyperintensity, dWMH: deep-only WMH pattern in which WMHs are mainly located in the corticomedullary junction or deep white matter, accompanied by little or no periventricular WMH, dpWMH: WMH pattern that is commonly seen in individuals with cerebral small vessel disease, where main periventricular WMH with or without deep WMH is accompanied by one or more lacunes, WM, white matter.

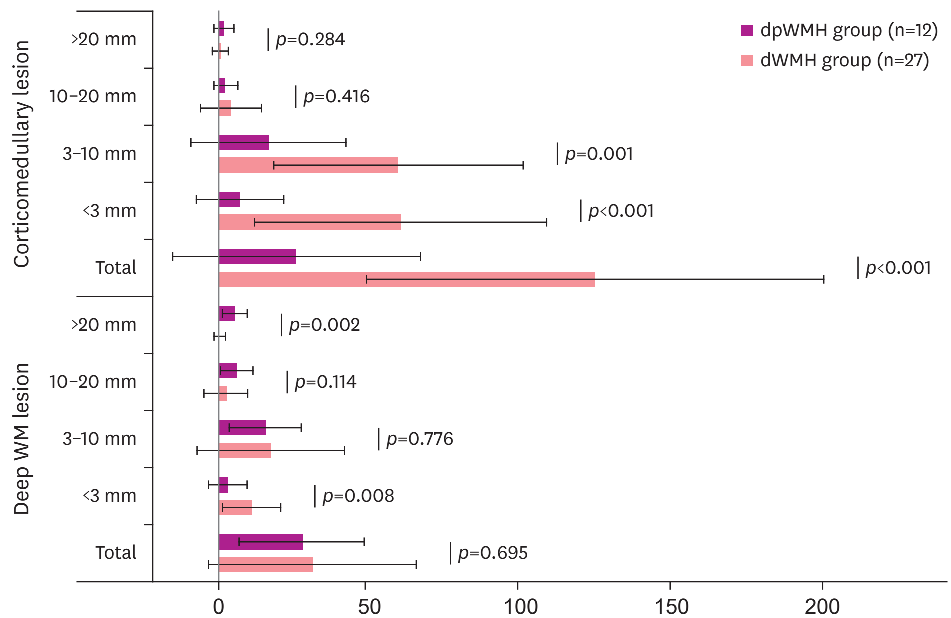

Fig. 3. Comparison of WMH distribution according to lesion size between the dWMH and dpWMH groups. The figure demonstrates that, in terms of deep white matter lesions, the number of small lesions (<3 mm) was higher in the dWMH than the dpWMH group, whereas the number of large lesions (>20 mm) was lower in the dWMH than the dpWMH group. In terms of corticomedullary lesions, the total number of lesions was higher in the dWMH than the dpWMH group, especially the number of small lesions was higher in the dWMH than the dpWMH group.
WMH: white matter hyperintensity, dWMH: deep-only WMH pattern in which WMHs are mainly located in the corticomedullary junction or deep white matter, accompanied by little or no periventricular WMH, dpWMH: WMH pattern that is commonly seen in individuals with cerebral small vessel disease, where main periventricular WMH with or without deep WMH is accompanied by one or more lacunes.

Comparison of shunt frequency between the dWMH and dpWMH groups

The dWMH group showed higher positivity in the agitated saline study than the dpWMH group (81.5% vs. 33.3%, p=0.003). The mean shunt grade of the dWMH group (1.8±1.2) was significantly greater than that of the dpWMH group (0.5±0.9) (p=0.003). All dpWMH individuals with positive saline tests belonged to Grade I or II, whereas 27.3% (6/22) of dWMH individuals with positive saline tests belonged to the large R-L shunt category (Grade III or IV). Of the 22 participants in the dWMH group who showed positivity in the agitated saline shunt study, four had extracardiac shunts. In the dpWMH group, of the four patients who showed positivity, two had extracardiac shunts (**Table 3**).

DISCUSSION

In the current study, we performed agitated saline contrast echocardiography in dpWMH and dWMH groups and examined whether the two groups differed in terms of shunt frequency. The dWMH group displayed higher positivity compared to the dpWMH group in the agitated saline studies. Among the 27 participants in the dWMH group, 18 had cardiac shunts, and four had extracardiac shunts. Among the 12 participants in the dpWMH group, two had cardiac shunts, and two had extracardiac shunts. Our findings suggest that dWMH patterns based on MRI may be associated with embolic etiologies, such as cardiac/extracardiac shunts, rather than small-vessel disease caused by atherosclerosis. In addition, the participants in the dWMH group had fewer vascular risk factors and were younger than those in the dpWMH group. The results of this study indicate that the dWMH pattern identified in FLAIR images represents embolic etiologies, which have not been comprehensively studied to date.

Table 3. Comparison of shunt positivity between the dWMH and dpWMH groups

Variables	dWMH group (n=27)	dpWMH group (n=12)	*p*-value
Saline shunt test	22/27 (81.5)	4/12 (33.3)	0.003
Intracardiac shunt	18/22 (81.8)	2/4 (50.0)	
Extracardiac shunt	4/22 (18.2)	2/4 (50.0)	
Shunt grade	1.8±1.2	0.5±0.9	0.003
0	5 (18.5)	8 (66.7)	
I	4 (14.8)	1 (8.3)	
II	12 (44.4)	3 (25)	
III	4 (14.8)	0 (0)	
IV	2 (7.4)	0 (0)	

Values are presented as number (%) or mean ± standard deviation.
dWMH: deep-only WMH pattern in which WMHs are mainly located in the corticomedullary junction or deep white matter, accompanied by little or no periventricular WMH, dpWMH: WMH pattern that is commonly seen in individuals with cerebral small vessel disease, where main periventricular WMH with or without deep WMH is accompanied by one or more lacunes, WMH: white matter hyperintensity.

Previous studies reported that the distribution of WMH was associated with underlying etiologies. Typical CSVD is associated with vascular risk factors, predominantly pWMH.[7] In contrast, a greater number of corticomedullary and deep WMH lesions can be identified in older patients with atrial fibrillation.[31] Intracranial atherosclerotic plaques are also associated with deep WMH lesions, especially on the ipsilateral side.[32] In addition, subcortical spots of WMH rather than peri-basal ganglia WMH may be seen in CAA.[33] In the present study, we excluded patients with atrial fibrillation and intracranial artery stenosis. We also ensured that our participants did not meet the Boston criteria for CAA.[13]

A few previous studies investigated the correlation between the distribution of WMH and the presence of PFO, but the results were inconsistent. One study reported that the radiologic findings of patients with PFO, one of the most common causes of cardiac embolism, showed a pattern similar to that of our dWMH group.[9] However, another study reported that both deep and periventricular WMH was associated with the presence of PFO in Alzheimer's disease (AD).[34] However, that study involving AD patients did not exclude participants who had intra/extracranial artery stenoses, previous stroke, or CAA. Again, our study strictly excluded embolic etiologies other than PFO and extracardiac shunts that could be detected in the agitated saline study. Such exclusions may have increased the robustness of the association between the dWMH pattern and the presence of cardiac/extracardiac shunts.

Among the 90 patients who underwent an agitated saline study with transthoracic echocardiography and brain MRI/MRA in the current study, 39 were categorized into two groups (dWMH and dpWMH groups) based on the distribution of WMH. Clinical characteristics and radiologic findings differed between the two groups. In terms of clinical characteristics, the participants in the dWMH group were younger and had higher MMSE scores than those in the dpWMH group (**Table 1**). In the post-hoc analysis, using linear regression, after pooling the dWMH and dpWMH groups, younger age was correlated with a lower presence of cardiovascular factors. These data are compatible with the risk of paradoxical embolism (RoPE) score, which is used to identify pathogenic versus incidental PFOs in patients with cryptogenic stroke.[35] Therefore, the white matter lesions in our dWMH group may be associated more with embolic causes such as PFOs rather than CSVD, which is closely linked to vascular risk factors such as hypertension, DM, and hyperlipidemia.

In terms of radiological findings, it is not surprising that the spatial distribution of WMH differed between the dWMH and dpWMH groups because we set the selection criteria to be predominantly located in deep areas, whereas the spatial distribution of WMH in the dpWMH group was mainly located in the periventricular areas. However, it is noteworthy that the WMH lesions in the dWMH group were especially located in border zones or watershed areas, which are known to be selectively vulnerable to microembolic infarcts.[36] The deep white matter and corticomedullary junction in the border zone areas are considered to be the point at which the arteriole and collateral circulations end. Small emboli that may have escaped from the cardiac/extracardiac shunt can block small-diameter vessels and may eventually cause the WMH embolic pattern.[37] A marked difference in shunt frequency was observed when comparing the dWMH and dpWMH groups. The incidence of PFO in the general population or healthy individuals was reported to be quite high, approximately 30% in different studies, and varied by age (34.3% for 0 to 30 years, 25.4% for 40 to 80 years, and 20.2% for over 90 years).[38] The shunt positivity in our dpWMH group (33.3%) was comparable to the PFO positivity in the normal population in previous studies, whereas our dWMH group showed drastically higher shunt positivity (81.5%), indicating that dWMH patterns may be associated with embolic etiology rather than SVD caused by arteriosclerosis. According to previous studies, if the RoPE score is in the range of 9–10 in patients with cryptogenic embolic stroke, the frequency of PFO is 73% (95% confidence interval [CI], 66–79%), and the PFO attributable fraction is 88% (95% CI, 83–91%).[12] Therefore, the high positive rate (81.5%) in our study may be acceptable, albeit higher than expected, given that the mean RoPE score in the dWMH group was 6.0±1.1 (min. 4–max. 8).

The association between the dWMH pattern and higher shunt positivity may have clinical implications. Although antiplatelet monotherapy is commonly administered to patients with CSVD, including lacunar infarcts, whether antiplatelet treatment for CSVD, especially at an asymptomatic disease stage, is beneficial remains controversial.[39,40] In contrast, recent studies not only reported that PFO closure might be more effective in preventing recurrent stroke caused by paroxysmal embolism than medical therapy,[41-44] but also suggested that patients with embolic etiologies, especially PFO, where intervention (PFO closure) is not possible, should be treated with oral anticoagulants (e.g., non-vitamin K antagonist oral anticoagulants, NOAC) rather than aspirin.[41,42,45-48] Therefore, the dWMH pattern may help clinicians have a high index of suspicion for cardiac/extracardiac shunts and pursue in-depth investigations and more aggressive interventions, such as PFO closure or NOAC administration. Given that small, asymptomatic WMH lesions located in the deep WM or corticomedullary junction of young individuals (accompanied by few vascular risk factors) have been commonly overlooked in clinics to date, the findings of this study underscore the clinical significance of dWMH patterns observed in brain MRI.

This study had several limitations. First, there might have been selection bias because this study was based on a small number of participants retrospectively recruited from a single center. Therefore, prospective, multicenter, randomized studies involving larger sample sizes are warranted. Second, diagnostic uncertainty remains because transthoracic echocardiography with an agitated saline study is not the gold standard test to detect cardiac/extracardiac shunts.[49] Third, our data lack the confidence to suggest that the dWMH pattern was independent of an R-to-L shunt because age and vascular risk factors were not controlled when the WMH patterns of the two groups were compared. However, age and vascular risk factors in individuals with CSVD were reported to be positively correlated with the number of WMH lesions.[50,51] Furthermore, in this study, individuals with the dWMH pattern had more corticomedullary and deep WMH lesions, although they were young and had few vascular risk factors. Therefore, the comparison of WMH lesions between the two groups without controlling for age and vascular risk factors may not entirely contradict our association between the dWMH pattern and R-to-L shunt. Lastly, the occurrence of additional WMH according to antiplatelet or oral anticoagulant use or PFO closure should be investigated further in future studies.

The dWMH group with younger age and fewer cardiovascular risk factors showed more border-zone distributions and higher positivity in the agitated saline test than the dpWMH group. This indicates that corticomedullary or deep WMH distribution with minimal periventricular WMH may suggest embolic etiologies.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Distribution of white matter lesions in the dWMH group. FLAIR images of the dWMH group show small, scattered white matter hyperintense lesions in the deep white matter and corticomedullary junction.

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