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MAJOR PAPER

Characterization of the Growth of Deep and Subcortical White Matter Hyperintensity on MR Imaging: A Retrospective Cohort Study

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Purpose: In elderly patients, deep and subcortical white matter hyperintense lesions are frequently observed on MRI; however, the growth process of these lesions is unclear. The aims of this retrospective cohort study were to elucidate the growth characteristics of deep and subcortical white matter hyperintense lesions, and to insight their etiology.

Materials and Methods: We enrolled 103 patients (1610 lesions) whose deep and subcortical white matter hyperintense lesions were monitored for 3 or more years by MRI examination. The area of each hyperintense lesion was measured using a tracing method in the first and last MRI examinations. The annual rate of increase in the area of each lesion was calculated, and using the Pearson product-moment correlation coefficient the correlation between the annual rate of increase in area and the interval between the first and last MRI examinations was determined.

Results: The paired *t*-test showed a significant increase in the mean area of all the deep and subcortical white matter hyperintense lesions between the first and last MRI examinations ($P < 0.001$). However, hyperintense lesions had decreased in the area or disappeared in 227 (14.1%) lesions in the last MRI examination, particularly in patients with diabetes. The mean annual rate of increase in area of all hyperintense lesions was 0.013 ± 0.021 cm^2 per year. The annual rate of increase in area and the interval between the first and last MRI examinations showed a weak negative correlation ($r = -0.121$; $P < 0.01$).

Conclusion: Decrease in the area and the disappearance of the subcortical white matter hyperintense lesions, and a decline in the annual rate of increase in the lesion area with time suggest that the interstitial fluid accumulation associated with dysfunctional drainage around the vessels may be involved in the possible etiologies of deep and subcortical white matter hyperintense lesions.

Keywords: *magnetic resonance imaging, brain, leukoaraiosis, retrospective cohort study*

Introduction

Currently, magnetic resonance imaging (MRI) is widely used to detect various brain disorders in elderly patients. Asymptomatic hyperintense lesions are frequently detected in the deep and subcortical white matter on T_2-weighted and fluid attenuated inversion recovery (FLAIR) images. These patchy and confluent hyperintense lesions are referred to as leukoaraiosis, hyperintense white matter foci, deep white matter hyperintensities, deep white matter infarctions, unidentified bright objects, or deep and subcortical white matter hyperintensities (DSWMH).[1–9]

Studies on DSWMH lesions, a type of leukoaraiosis, suggest that these changes in the white mater are likely to be associated with aging, hypertension, diabetes, and other stroke risk factors.[1,3,6,8,9–12] Pathological studies have reported reduction in myelination with atrophy of the neuropil around fibrohyalinotic arteries, and myelin pallor and dilation of the perivascular spaces in patchy areas consisting of DSWMH lesions.[1,3–5,7,9] It is generally believed that these lesions result from ischemic injury involving transient and repeated events, characterized by moderate drops in the regional cerebral blood flow, which induces an incomplete form of infarction.[5,6] However, the complete etiology of DSWMH lesions is still unclear.[3,4]

In order to elucidate the radiological characteristics of DSWMH lesions and their etiology, we analyzed the growth of DSWMH lesions using MRI in a retrospective cohort study.

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Materials and Methods

Subjects

The institutional review board approved the study protocol and waived the need for patients' informed consent because the study was designed based on existing data.

In this retrospective cohort study, we enrolled 103 patients who had undergone more than two MRI examinations in a three or more year interval for the observation of DSWMH lesions at our institute from January 2009 to May 2015. Patients with one or more of the following symptoms: headache (n = 43), vertigo (n = 45), cognitive impairment (n = 28), or insomnia (n = 58) were included in the present study. According to their clinical records, the subjects with one or more of the following diagnoses: hypertension (n = 67), diabetes (n = 20), liver dysfunction (n = 14) or hyperlipidemia (n = 37) were included. Patient records were reviewed in order to exclude patients with an organic brain disease (e.g. infarct with neurological deficits, tumor, demyelinating disease, and encephalitis). The patients in the present study consisted of 27 men and 76 women (ages, 51–93 years; mean 73.4 ± 8.1 years).

Prior to DSWMH lesion area measurements, two observers, by their mutual consent, enrolled 1610 DSWMH lesions with demarcated contours including 1160 frontal lobe lesions, 418 parietal lobe lesions, and 32 temporal and occipital lobes lesion, on FLAIR images in the first MRI examination. We excluded hyperintense lesions continuous to the periventricular hyperintensity, lesions in the putamen and thalamus, and lesions that included low-intensity areas considered to be old infarcts on FLAIR images.[13] We also excluded DSWMH lesions which appeared only in the last MRI examination, because the purpose of this cohort study was to observe the progress of DSWMH lesions.

The mean interval between the first and last MRI examination was 4.36 ± 0.94 years (range, 3.00–6.17 years).

MRI

MRI was performed using a 1.5-Tesla superconducting system (Signa EXCITE; General Electric, Milwaukee, WI, USA) with an 8-channel neurovascular phased-array coil.

Axial T_1-weighted, T_2-weighted, FLAIR, and diffusion-weighted whole brain images were acquired from all patients. All images were obtained parallel to the plane containing the pontomedullary junction and the nasion. The parameters of the T_1-weighted imaging were as follows: repetition time/echo time (TR/TE), 560/13 ms; field of view (FOV), 24 × 18 cm; slice thickness, 6 mm; slice gap, 1.5 mm; matrix, 320 × 224; number of excitations (NEX), 2; and scan time, 3 min 12 s. The parameters of the T_2-weighted imaging using a fast spin-echo sequence were as follows: TR/TE, 4000/97.1 ms; FOV, 24 × 18 cm; slice thickness, 6 mm; slice gap, 1.5 mm; matrix, 384 × 256; 2 NEX; echo train length, 12; and scan time, 2 min 16 s. The parameters of the FLAIR imaging were as follows: TR/TE/inversion time, 8004/130/2000 ms; FOV, 24 × 24 cm; slice thickness, 6 mm; slice gap, 1.5mm; matrix, 320 × 256; 1 NEX; and scan time, 3 min 44 s. The parameters of the single-shot spin-echo echo-planar diffusion-weighted imaging were as follows: TR/TE, 6000/85.6 ms, FOV, 24 × 24 cm; slice thickness, 6 mm; slice gap, 1.5 mm; matrix, 160 × 160; 2 NEX; diffusion sensitivity of P-value, 1000 s/mm^2; and scan time, 48 s.

Measurement of DSWMH Area

Using a computer monitor (RadiForce G20; Eizo Nanao Corporation, Ishikawa, Japan), two observers, one radiologist with 31 years of experience in MRI analysis and one radiological technologist with 20 years of experience, independently measured the area of each DSWMH lesion on FLAIR images from the first and last MRI examinations by tracing the contours of each lesion (Fig. 1). The measurements were completed over a period of 6 months.

Data analysis

In order to evaluate the inter-observer reproducibility of area measurements, we calculated the mean DSWMH lesion area in each of the first and last MRI examinations determined by the two observers, and the Pearson product-moment correlation coefficient of the DSWMH lesion area in each of the first and last MRI examinations between the two observers.

For the following statistical analyses, we used the mean value of each lesion determined by the two observers. In order to evaluate the growth of DSWMH lesions, we compared the mean DSWMH lesion area between the first and last MRI examinations using the paired t-test. Furthermore, in order to evaluate the growth process of DSWMH lesions, the annual rate of increase in the area of each lesion was calculated using the following formula: (area in the last MRI – area in the first MRI) / interval between the first and last MRI examinations. Using the Pearson product-moment correlation coefficient, the correlation between the annual rate of increase in area and the interval between MRI examinations was analyzed. A P value of < 0.05 was considered statistically significant.

Results

Inter-observer reproducibility of area measurements

Observer 1 reported the mean DSWMH lesion area of 0.139 ± 0.142 cm^2 in the first MRI examination, and 0.190 ± 0.189 cm^2 in the last MRI examination. Observer 2 reported the mean lesion area of 0.141 ± 0.142 cm^2 in the first MRI examination, and 0.193 ± 0.188 cm^2 in the last MRI examination. The Pearson product-moment correlation coefficient in the DSWMH lesion area between the two observers was 0.991 in the first MRI examination (Fig. 2a) and 0.993 in the last MRI examination (Fig. 2b).

Evaluation of the DSWMH lesion growth

The mean DSWMH lesion area was 0.140 ± 0.142 cm^2 (range, 0.015–1.595 cm^2) in the first MRI examination and

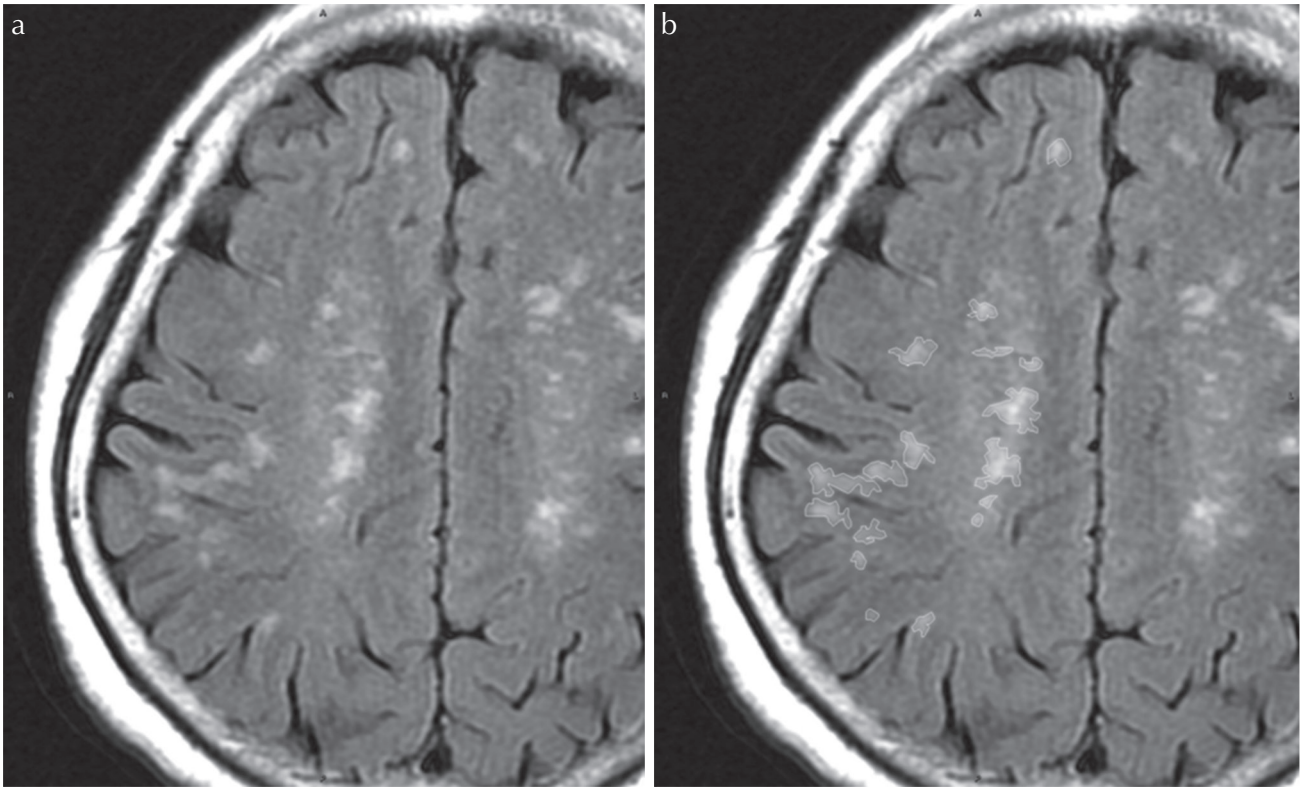

Fig 1. (**a**) Axial FLAIR images showing examples of DSWMH lesions and (**b**) tracing some of these lesions. Please note that these are the same images as shown in Fig 5a.

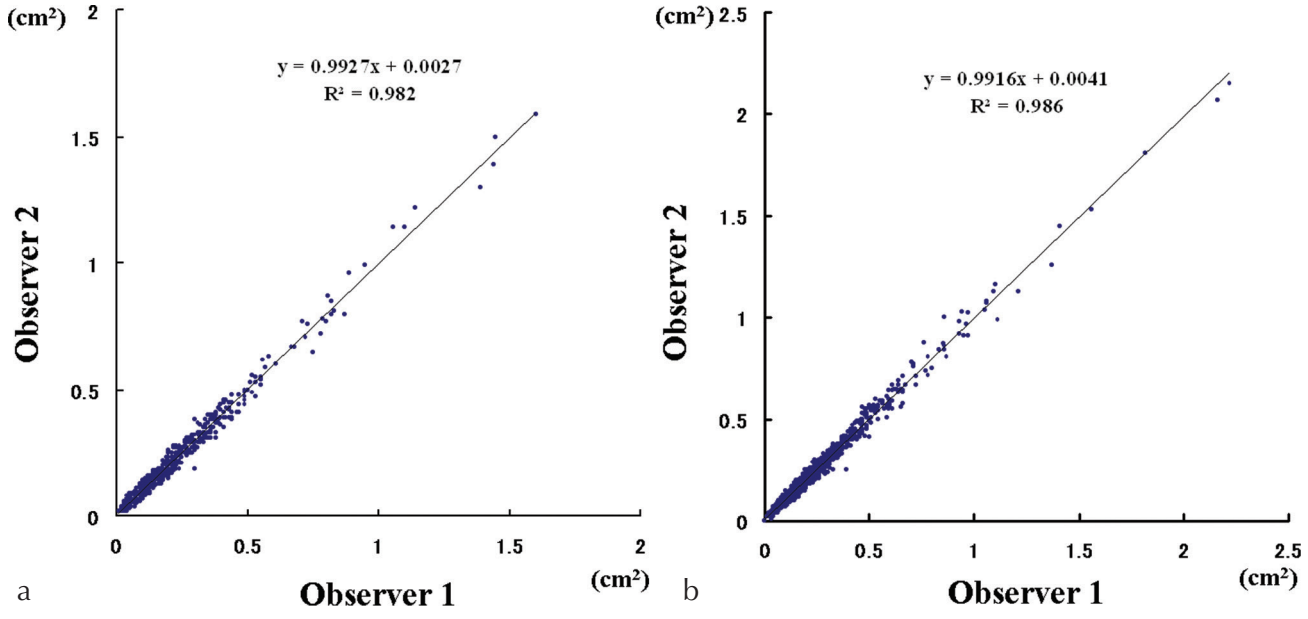

Fig 2. (**a**) A scatter plot showing the correlation in the DSWMH lesion area between observer 1 and 2 in the first MRI, (**b**) a scatter plot showing the correlation between the observers in the last MRI.

0.192 ± 0.188 cm^2 (range, 0–2.185 cm^2) in the last MRI examination. The paired *t*-test showed a significant difference in the mean DSWMH lesion area between the first and last MRI examinations ($P < 0.001$).

Growth process of DSWMH lesion

The mean annual rate of increase in the DSWMH lesion area was 0.013 ± 0.021 cm^2 per year. The Pearson product-moment correlation coefficient between the annual rate of

increase in area and the interval between MRI examinations was −0.121 ($P < 0.01$). Therefore, there was a small but significant negative correlation between the annual rate of increase in area and the interval between MRI examinations (Fig. 3).

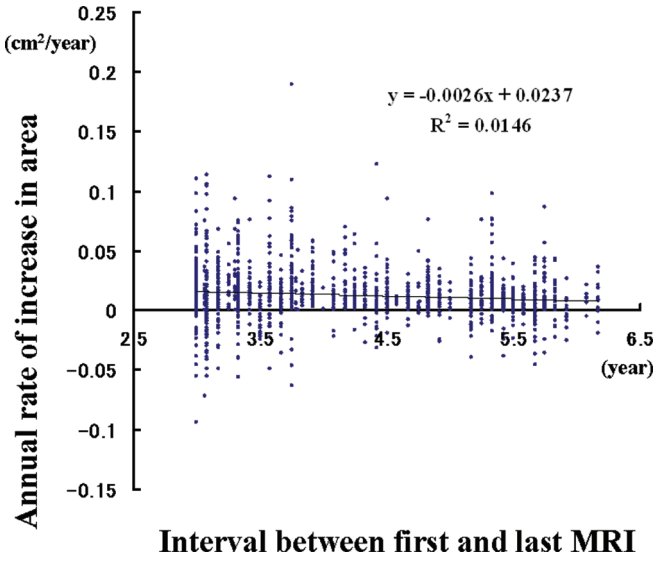

Fig 3. A scatter plot showing the correlation between the annual rate of increase in the DSWMH lesion area and the interval between the first and last MRI examinations.

Decreasing or vanishing DSWMH lesions

Of all DSWMH lesions examined, 227 lesions (14.1%) decreased in the area or disappeared in the last MRI examination (Figs. 4 and 5). Of the 227 lesions, 156 (13.4%) were in the frontal lobe, 67 (16.0%) were in the parietal lobe, and 4 (12.5%) were in the temporal and occipital lobes. The *F*-test did not show any significant differences in the frequency of decreasing or vanishing lesions among the lobes.

The mean area of the decreasing or vanishing DSWMH lesions in the first MRI examination was 0.141 ± 0.122 cm^2 (range, 0.020–1.120 cm^2). The mean area of the other 1383 lesions that increased in the area was 0.140 ± 0.145 cm^2 (range, 0.015–1.595 cm^2) in the first MRI examination. The unpaired *t*-test indicated that there was no significant difference in the mean area between those lesions that increased, and those that decreased in area or vanished, in the first MRI ($P = 0.914$). However, in limited 54 (3.4%) vanishing lesions, the mean area in the first MRI examination was 0.096 ± 0.059 (range, 0.020–0.280 cm^2). The unpaired *t*-test showed that the mean area of vanishing lesions was significantly smaller than that of increasing lesions in the first MRI examination ($P < 0.001$).

Besides, the mean annual rate of increase in area of decreasing or vanishing DSWMH lesions was −0.016 ± 0.014 cm^2 per year, and that of increasing lesions was 0.017 ± 0.018 cm^2 per year.

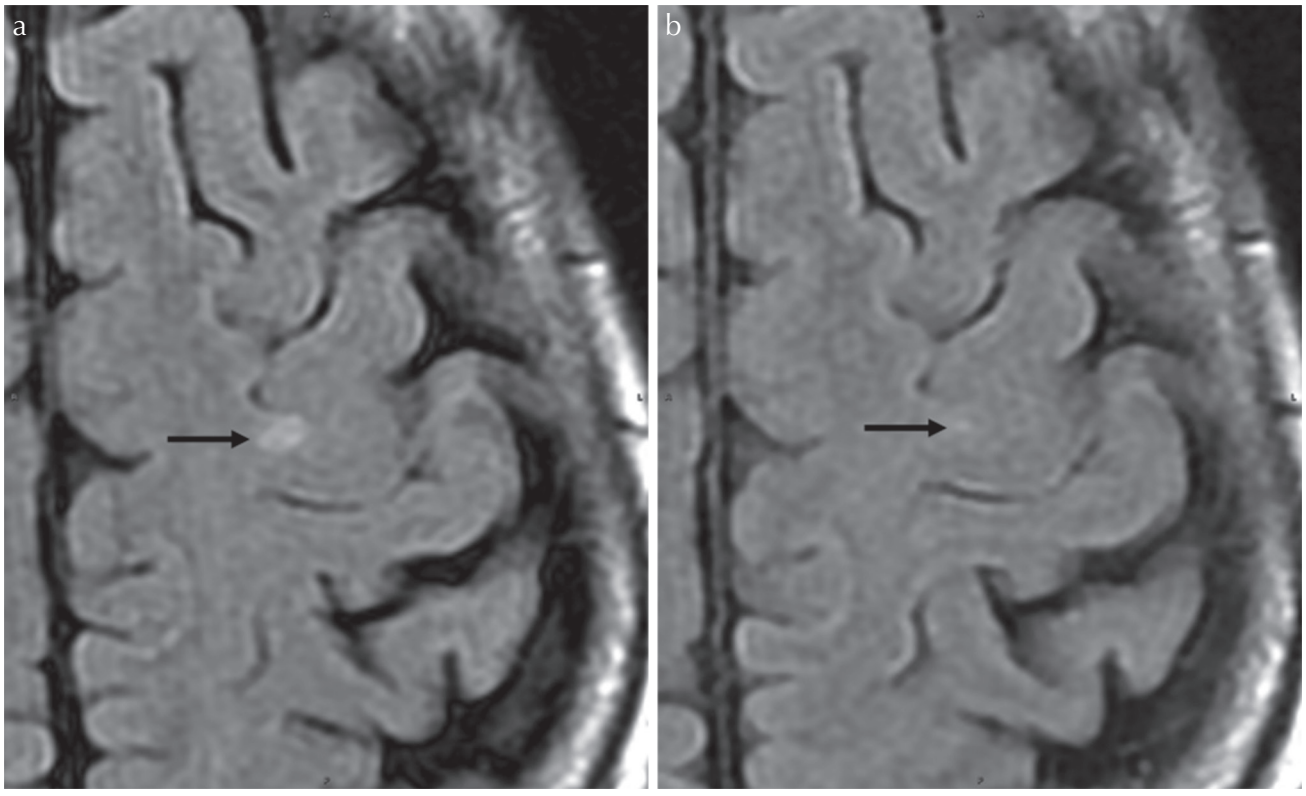

Fig 4. (**a**) An axial FLAIR image of the first MRI examination obtained from a 68-year-old woman with hypertension, diabetes, liver dysfunction, hyperlipidemia and insomnia, (**b**) an axial FLAIR image performed 5.42 years after the first MRI examination. A patchy hyperintensity (arrow) in the left frontal lobe in (**a**) is remarkably decreased in (**b**) (arrow).

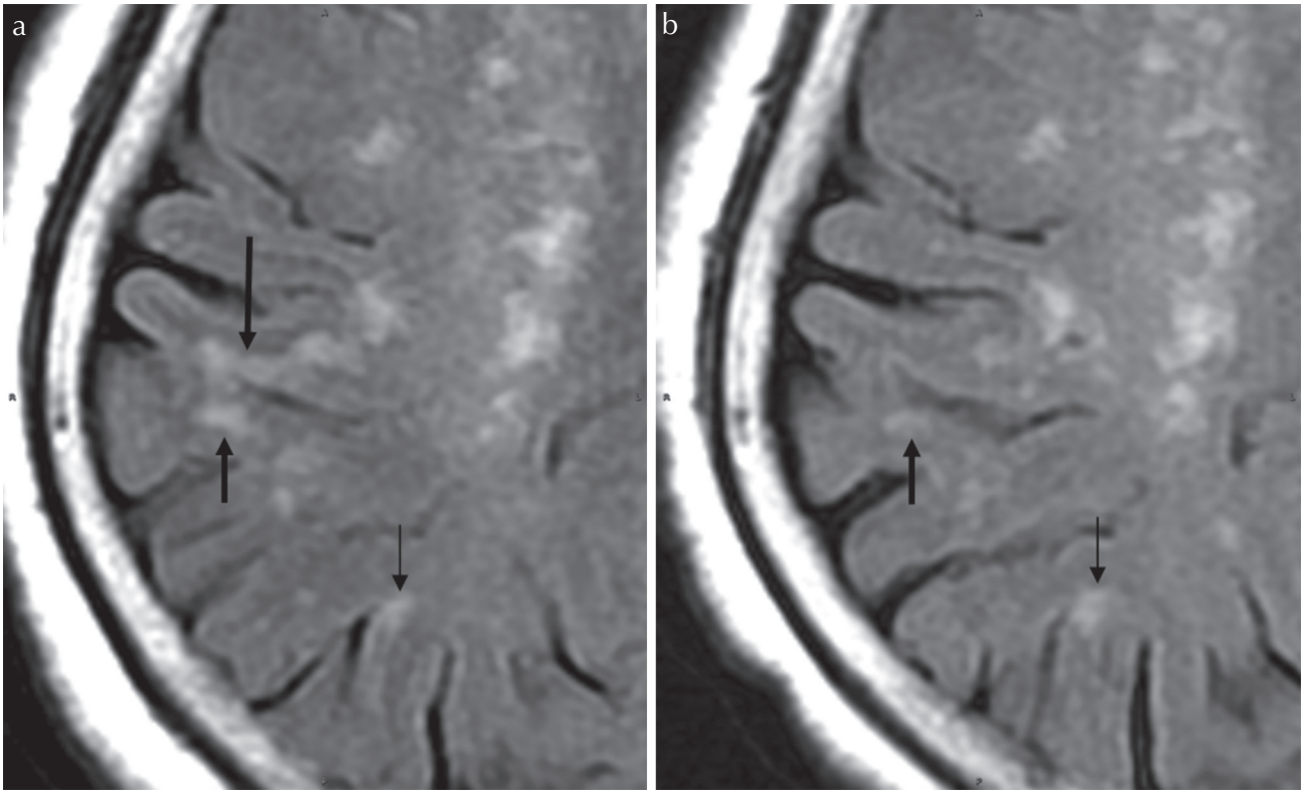

Fig 5. (**a**) An axial FLAIR image of the first MRI examination obtained from a 68-year-old woman with hypertension, headache and vertigo, (**b**) an axial FLAIR image performed 3 years after the first MRI examination. A patchy hyperintense lesion (long arrow) in (**a**) is not present in (**b**) and another hyperintense lesion (short arrow) has decreased in area. A patchy hyperintense lesion (thin arrow) has increased in area.

The investigation of the impact of the patients' background on lesion growth, by the unpaired *t*-test, indicated that there was no significant difference in age between the 66 patients with decreasing and/or vanishing DSWMH lesions (73.2 ± 6.6 years) and the other 37 patients with increasing lesions (73.8 ± 10.5 years) ($P = 0.736$).

Further, in the 66 patients with decreasing and/or vanishing DSWMH lesions, 65% ($n = 43$) had hypertension; 24% ($n = 16$) had diabetes; 15% ($n = 10$) had liver dysfunction; 38% ($n = 25$) had hyperlipidemia; 30% ($n = 20$) had cognitive impairment; 42% ($n = 28$) had headache; 38% ($n = 25$) had vertigo; and 56% ($n = 37$) had insomnia. On the other hand, in the 37 patients with increasing lesions, 65% ($n = 24$) had hypertension; 11% ($n = 4$) had diabetes; 11% ($n = 4$) had liver dysfunction; 32% ($n = 12$) had hyperlipidemia; 24% ($n = 9$) had cognitive impairment; 41% ($n = 15$) had headache; 54% ($n = 20$) had vertigo; and 57% ($n = 21$) had insomnia. The *F*-test indicated that there were no significant differences in the number of patients with hypertension ($P = 0.935$), liver dysfunction ($P = 0.373$), hyperlipidemia ($P = 0.864$), cognitive impairment ($P = 0.694$), headache ($P = 0.980$), vertigo ($P = 0.800$), and insomnia ($P = 0.955$) between the two groups. However, there was a significant difference in the number of patients with diabetes between groups ($P = 0.042$).

Of the 20 patients with diabetes in the present study, hemoglobin A1c (HbA1c) as one of indicators of diabetes had been followed up at the same time as the first and last MRI examinations in 10 patients with decreasing and/or vanishing DSWMH lesions and in 3 patients with increasing lesions. Of the 10 patients with decreasing and/or vanishing lesions, the value of HbA1c decreased in three patients and remained within the normal range (< 6%) in two patients; however, in five patients, the value increased. On the other hand, of the three patients with increasing lesions, the value of HbA1c remained within the normal range in one patient and increased in the other two patients.

Discussion

Asymptomatic patchy hyperintense lesions are frequently encountered in T_2-weighted and FLAIR images of elderly patients. In general, asymptomatic hyperintense lesions, termed leukoaraiosis, include periventricular hyperintensity and DSWMH.[1,3,5,7,8] DSWMH lesions are associated with risk factors for stroke including aging, hypertension, and diabetes.[1,3,6,8,9–12] However, the etiology of DSWMH lesions has not been fully elucidated. In this retrospective cohort study, we analyzed the growth of DSWMH lesions, which are relatively easy to measure, in order to understand the radiological

characteristics of leukoaraiosis and to further understand the etiology of these lesions.

Pathological features of DSWMH lesions consisted of varying degrees of diffuse white matter pallor, reduced myelination with atrophy of the neuropil around fibrohyalinotic arteries and dilated perivascular spaces.[3–5,7,9] Although necrotic debris, foamy cells, and reactive gliosis associated with cerebral infarcts are not observed in DSWMH lesions, DSWMH is currently believed to be a minor perivascular damage. It is considered to be an ischemic tissue damage and a type of ischemic injury that is most likely responsible for these white matter changes involving transient and repeated events characterized by a moderate decrease in the regional cerebral blood flow that induces an incomplete form of infarction.[3–6]

DSWMH lesions are an age-related subcortical occlusive small-vessel disease secondary to arteriosclerosis and are considered to be a progressive process. However, in the present study, a small number of DSWMH lesions decreased in the area or disappeared. Furthermore, despite the fact that most of the DSWMH lesions grew over time, the annual rate of growth of DSWMH lesions declined as the interval between MRI examinations stretched. These phenomena suggest that the growth characteristics of DSWMH lesions include expansion following some manner of growing, but also reversible changes.

Recently, regressive white matter hyperintense lesions were reported in stroke patients.[14,15] Cho et al. speculated that a disturbance in cerebrospinal fluid circulation and vasogenic cerebral edema, both of which are reversible conditions, may be interrelated to the ischemic origin of leukoaraisosis.[4] Furthermore Yamada et al. published a case report of partial reversal of white matter lesions shortly after carotid artery stenting, and proposed that increased permeability of the blood–brain barrier (BBB) may be a cause of white matter lesions.[15] From the imaging perspective, the case most closely resembled white matter lesions reversal of patients in liver cirrhosis with hyperammonemia, which causes increased permeability of the BBB, after liver transplantation.[16] However, in the present study, we did not observe a relation between a decrease or disappearance of DSWMH lesions and liver dysfunction; therefore, increased BBB permeability caused by hyperammonemia was not considered to be the reason for the decrease or disappearance of DSWMH lesions.

On the other hand, anatomical studies have suggested a reversible process of interstitial fluid collection in the intercellular spaces around the vascular components.[17,18] The interstitial fluid gathers around the vessels and is drained through the intercellular compartments.[19–21] Therefore, dysfunctional interstitial fluid drainage would cause an accumulation of the interstitial fluid around the small vessels, resulting in increased water content in the intercellular spaces in these regions.

It has been demonstrated that leukoaraiosis is widely associated with diabetes. In the present study, DSWMH lesions that decreased in area or disappeared were relatively small in area and were found in a significantly larger number of patients with diabetes. Due to a small sample size, it was difficult to statistically evaluate the effect of diabetes on the decrease in the area or disappearance of DSWMH lesions. However, at follow-up, decreasing or remaining within the normal range of the value of HbA1c in some patients with diabetes suggested that the improvement in the diabetic status might be associated with shrinking or vanishing of DSWMH lesions. Although, the mechanism responsible for shrinking or vanishing of the lesions in diabetes is not clear, an improvement in the interstitial fluid drainage in diabetes may cause DSWMH lesions to shrink or disappear.

We also observed that the annual rate of increase in the DSWMH lesion area slightly declined as the interval between MRI examinations increased. Assuming that the interstitial fluid is drained at a constant rate in the normal brain to prevent a dysfunction in interstitial fluid drainage, the area around the vessels would grow rapidly in the early stages of interstitial fluid collection, but as these areas expand, the lesion growth rate would decline on sectional MR images. The concern that chronic ischemic events result in DSWMH lesions is undeniable. The results of the present study suggest that the accumulation of interstitial fluid affects the growth rate of DSWMH lesions.

In contrast to the pathological findings on DSWMH lesions using MRI, another report has shown that gliosis and small areas of infarction were not present in all areas with MRI lesions and could not be distinguished by MRI signal alone.[9] If the interstitial fluid accumulation is one of etiologies of DSWMH lesions, it is likely that the structure of brain tissue would be spared, unlike the areas affected by an infarction.

This study has some limitations. First, the study is a retrospective cohort study, and thus, age, gender and the interval between MRI examinations of each patient were not always available for statistical analyses. Second, the information regarding the clinical records of the patients may not have been sufficiently documented. Third, the slice level and the angle of the MRI scans were not necessarily the same in the first and last MRI examinations. Finally, the partial volume effect on the measurement in digital images of MRI scans with thick slices is unavoidable. The mismatch of the slice level and angle, and the partial volume effect may cause an inaccurate measurement of the DSWMH lesions. However, the inter-observer reproducibility for area measurements was sufficient for statistical analyses.

Conclusion

The present study demonstrated two characteristic phenomena of the growth of DSWMH lesions. We observed that the annual rate of increase in the DSWMH lesion area declined with time, and that a small number of DSWMH lesions decreased in the area or vanished on MRI examinations, particularly in patients with diabetes. These phenomena indicate that DSWMH

lesions can increase, decrease, or vanish as the interstitial fluid accumulation, which is associated with dysfunctional drainage, changes around the vessels.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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