Characteristics of Cerebral White Matter Lesions on MRI in Juvenile Patients with Migraine

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Objective: Cerebral white matter lesions (WMLs) have been frequently observed on MRI in patients with migraine. We investigated characteristics of WMLs in migraine and tried to determine the relationship between its causal mechanism and arteriosclerosis.
Methods: A head MRI was performed in juvenile migraine patients. The distributions of deep and periventricular WMLs were separately studied in the anterior and posterior circulation. Grading was conducted according to the Fazekas classification. Arteriosclerotic risk factors were identified, and their effects on WMLs were investigated.
Results: WMLs were observed in 85 (40.5%) of 210 patients in our hospital. This is significantly higher than the 10 (19.2%) of 63 patients in the control group ($p < 0.01$). WMLs were significantly observed on the anterior territory of the deep white matter ($p < 0.01$) and the posterior territory of the periventricular white matter ($p < 0.05$). Multivariable analysis revealed that the occurrence of WMLs was not related to arteriosclerotic risk factors, while migraine ($p < 0.01$) and aging ($p < 0.05$) were significant risk factors.
Conclusion: While migraine was a risk factor of WMLs, its relationship with arteriosclerotic factors was weak. Accordingly, a mechanism other than arteriosclerosis may be involved.

Key words: white matter lesion, migraine, MRI, arteriosclerosis, risk factor

INTRODUCTION

Migraine, mainly characterized by repetitive intense headache attacks, is highly prevalent especially in young people. Upon the onset of headache, daily activities are substantially affected by intense pain. The duration of the headache attack ranges from a few hours to several days, greatly disturbing social living. Several hypotheses have been cited in the past to explain the causes of migraine, including vascular, neural, and neurovascular [1]. Various neuropeptides and endothelial factors have presumably been involved, although no definite consensus has been achieved regarding the causal mechanism. Meanwhile, migraine attack is considered to be closely related to cerebral blood flow (CBF). It is well known that patients with migraine, especially familial hemiplegic migraine, are susceptible to ischemic stroke ('migrainous infarction') [2]. Furthermore, scintillating scotoma that precedes the onset of headache is considered to be caused by decreased CBF around the occipital lobe due to cortical spreading depression (CSD) in migraine [3].

Cerebral white matter lesions (WMLs) are observed in the form of abnormal signals under the cerebral cortex or around the lateral ventricle, often appearing in chronic ischemia, autoimmune demyelinating disease, and metabolic aberration. WMLs are frequently observed in middle-aged and older people, as well as in the patients with arteriosclerotic risks in particular. Multiple WMLs are considered a risk factor of ischemic cerebrovascular disorder. However, relatively young patients with migraine sometimes have WMLs. WMLs are often found in women with migraine aura, in the posterior circulation according to some reports or in other areas according to other reports. In the present study, we examined WMLs and their location in migraine patients, as well as their relationship with arteriosclerotic risk factors.

PATIENTS AND METHODS

Subjects

The subjects were juvenile patients younger than 45 years who visited our outpatient clinic from March 2002 to September 2014, with headache as the main complaint. Of these patients, 210 who satisfied the diagnostic criteria of the *International Classification of Headache Disorders, Second Edition* (*ICHD-II*; male: 53, female: 157; mean age: 32.9 ± 8.4 years) were selected as the "migraine group" and underwent a head MRI. Among the subjects, 77 had migraine with aura and 133 had migraine without aura. Individuals with cerebrovascular diseases, or demyelinating or metabolic disease were excluded, even if they had migraine. The "control group" consisted of 63 patients who visited our hospital because of some neurological conditions except for headache, cerebrovascular disorders, demyelinating diseases, and metabolic diseases, and underwent head MRI (male: 25, female: 38, mean age: 30.9 ± 8.3 years). Informed consent for participation in this study was obtained from all the patients.

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Table 1 Demographic features and incidence of cerebral white matter lesions in the migraine and control groups

	Migraine (n = 210)	Control (n = 63)	p value
Age (year)	32.9 ± 8.4	30.9 ± 8.3	NS#
Female (n)	74.8% (157)	60.3% (38)	NS*
Atherosclerotic risk factors			
Hypertention (n)	12.3% (26)	7.9% (5)	NS*
Hyperlipidemia (n)	22.9% (48)	27.0% (17)	NS*
Diabates (n)	5.2% (11)	7.9% (5)	NS*
Aura (n)	36.7% (77)	-	-
WML (n)	40.5% (85)	15.9% (10)	< 0.001*

NS: not significant, WML: white matter lesion. # Mann-Whitney U test, * χ^2 test

Image assessment

For image assessment, MRI (1.5 Tesla, Signa HDX, GE) was used at our hospital, and T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging were used for detection of WMLs. The distribution and severity of WMLs were examined separately for the anterior and posterior circulation territories by using the central sulcus as boundary. By using the Fazekas classification [4], grading was conducted in a blind manner by 3 neurologists who did not know background information of the subjects: Deep white matter hyperintensity (DWMH) was graded as grade 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent areas and periventricular hyperintensity (PVH) was rated as grade 0 = absence, 1 = "caps" or pencil-thin lining, 2 = smooth "halo", 3 = irregular PVH extending into the deep white matter.

Patient background

Age, sex, and arteriosclerotic risk factors (hypertension, diabetes, and hyperlipidemia) were retrospectively examined by using patient records, and their relationships with the occurrence of WMLs were analyzed. Arteriosclerotic risk factors were identified based on medical history obtained through medical interview, use of medication, blood pressure, and blood test data taken during examination by a physician. A patient was judged hypertensive when systolic blood pressure was > 140 mmHg and diastolic blood pressure was > 90 mmHg, although definite white coat hypertension was excluded. A patient was judged diabetic or glucose intolerant when casual blood glucose level was > 200 mg/dL or HbA1c level was > 6.2%. A patient was diagnosed with hyperlipidemia when total serum cholesterol was > 240 mg/dL, triglyceride level was > 150 mg/dL, and low-density lipoprotein-cholesterol was > 140 mg/dL. The presence/absence of aura was determined based on the physician's inquiry about scintillating scotoma and visual abnormality.

Protocol approval

The protocol was approved by Tokai University ethical standards committee on clinical experimentation (12-205: Localization of cerebral WMLs on MRI and associated arteriosclerotic risk factors in juvenile patients with migraine).

Statistical analysis

The Mann-Whitney's U test was used to confirm that age distribution did not significantly differ between the two groups. Multivariable analysis (multiple stepwise regression analysis, SPSS21.0 for Windows, SPSS Inc., Chicago, IL) was used to examine the relationships between the occurrence of WMLs and age, sex, arteriosclerotic factors, and aura (scintillating scotoma) in the two groups. The distribution of WMLs was examined respectively for subcortical deep white matter lesions (anterior and posterior) and periventricular WMLs (anterior and posterior). The difference was analyzed by using the χ^2 test.

RESULTS

1) Analysis of patient background

No significant difference was observed in age distribution between the migraine and control groups (Table 1). Although the number of female patients was slightly larger in the migraine group, the difference was not statistically significant. Moreover, in both groups, no significant difference was observed in the frequency of WMLs between the subjects with and those without risk factors of arteriosclerosis (hypertension, diabetes, and hyperlipidemia; χ^2 test). Aura was present in 35% of the patients in the migraine group.

2) Difference in the frequency of cerebral WMLs between subjects with and those without migraine

In the migraine group, the frequency of cerebral white matter lesions (Fazekas classification grade 1-3 or PVH grade 1-3) was 40.5% (85 of 210 subjects; Table 2). On the other hand, the frequency of cerebral WMLs was 15.9% (63 of 10 patients) in the control group. This indicates that the frequency of WMLs was significantly higher in the migraine group than in the control group (Table 1, $p < 0.001$, χ^2 test).

3) Distribution of cerebral WMLs in migraine patients

The distribution of cerebral WMLs was analyzed (Fig. 1). DWMH lesions in the anterior circulation were more frequently observed, with statistical significance, in the migraine group than in the control group ($p < 0.01$, χ^2 test). However, the frequency of DWMH in the posterior circulation did not differ significantly between the groups. The frequency of PVH lesions was significantly higher in the posterior circulation ($p < 0.05$, χ^2 test). Moreover, no clear trend was observed in the relationship between the presence/absence of scintillating scotoma and the distribution of WMLs (Table 3).

As stated earlier, most of these WMLs were either

Table 2 Fazekas grading of cerebral white matter lesions in the migraine group (n = 85)

	grade 1	grade 2	grade 3
DWMH			
anterior	50	6	2
posterior	17	1	0
PVH			
anterior	13	1	0
posterior	25	2	1

DWMH: deep white matter hyperintensity. PVH: periventricular hyperintensity.

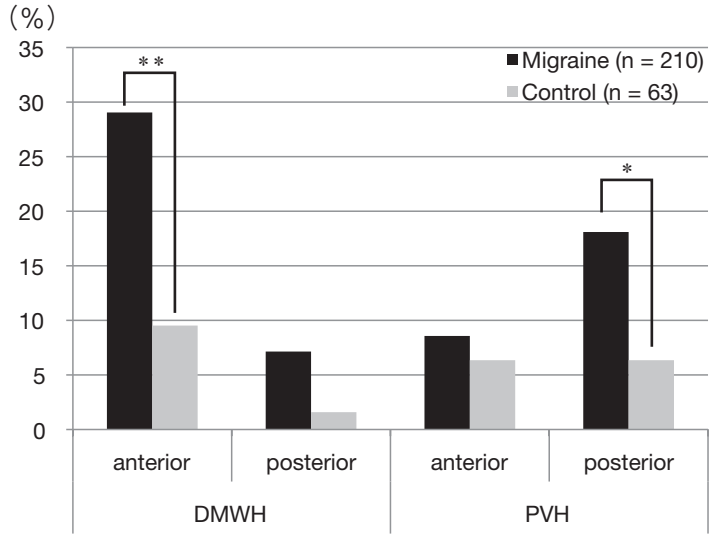

Fig. 1 Incidence of cerebral white matter lesions in each area in the migraine and control groups.
Deep white matter hyperintensity (DWMH) lesions on MRI were significantly more abundant in the anterior circulation territory in the migraine group than in the control group (**$p < 0.01$, χ^2 test). Periventricular hyperintensity (PVH) lesions were also found significantly more frequently in the posterior circulation territory in the migraine group than in the control group (*$p < 0.05$, χ^2 test).

DWMH or PVH grade 1, which are considered to be mild changes according to the Fazekas classification. However, severe WMLs were also observed in some subjects. The typical cases are presented in Fig. 2.

4) Multiple stepwise regression analysis of the risk factors for cerebral WMLs

The relationship between the frequency of cerebral WMLs and each of the following factors was analyzed using multiple stepwise regression analysis: migraine, age group (stratified by 1-year age), female sex, and the risk factors for arteriosclerosis, such as hypertension, diabetes, and hyperlipidemia (Table 4). The analysis population included all the subjects, who were younger than 45 years.

The result indicates that migraine is a significant risk factor for WMLs ($p < 0.01$), and the odds ratio of WMLs was 2.87. The result of the age-group analysis suggests that the frequency of WMLs increased with age ($p < 0.05$). No significant difference was observed in the frequency of WMLs between the male and female subjects. Moreover, the analysis of risk factors for arteriosclerosis revealed that the frequency of WMLs is not related with the presence/absence of hypertension, diabetes, or hyperlipidemia. In other words, the result of the multiple stepwise regression analysis indicates that only "aging" and "migraine" are the independent risk factors for cerebral WMLs in the young patients.

DISCUSSION

Changes in MRI imaging findings in migraine patients have been reported. In 2004, Kruit *et al.* [5] conducted a large-scale imaging evaluation in migraine patients and reported that infarcted changes were prevalent in the posterior circulation area, including the infratentorial region and occipital lobe. Other reports indicated that lesions were frequently found in the posterior circulation territories [6], while migraine itself was reported to be a risk factor of cerebral infarction [7]. However, no consensus has been reached on WMLs [8]. Palm-Meinders *et al.* [9] reported that WMLs were frequently found in women with aura, although no significant difference in distribution was observed. In studies in younger migraine patients, WMLs were frequently found in the frontal, parietal, and temporal lobes [10, 11].

In general, cerebral WMLs, often associated with chronic ischemia, develop with aging and become more prevalent in patients with arteriosclerotic risk factors [12]. Advanced WML is considered as a risk factor of ischemic stroke. Edema or tissue damage induced by leakage of water or protein from impaired blood-brain

Table 3 Incidence of cerarebral white matter lesions on each area in the migraine group with or without aura

	Aura (+) (n = 77)	Aura (-) (n = 133)	p value (χ^2 test)
DWMH grade 1–3			
anterior (n)	22.1% (17)	33.1% (41)	NS
posterior (n)	6.5% (5)	9.8% (13)	NS
PVH grade 1–3			
anterior (n)	2.6% (2)	9.8% (12)	NS
posterior (n)	14.3% (11)	20.3% (17)	NS

DWMH: deep white matter hyperintensity. PVH: periventricular hyperintensity.

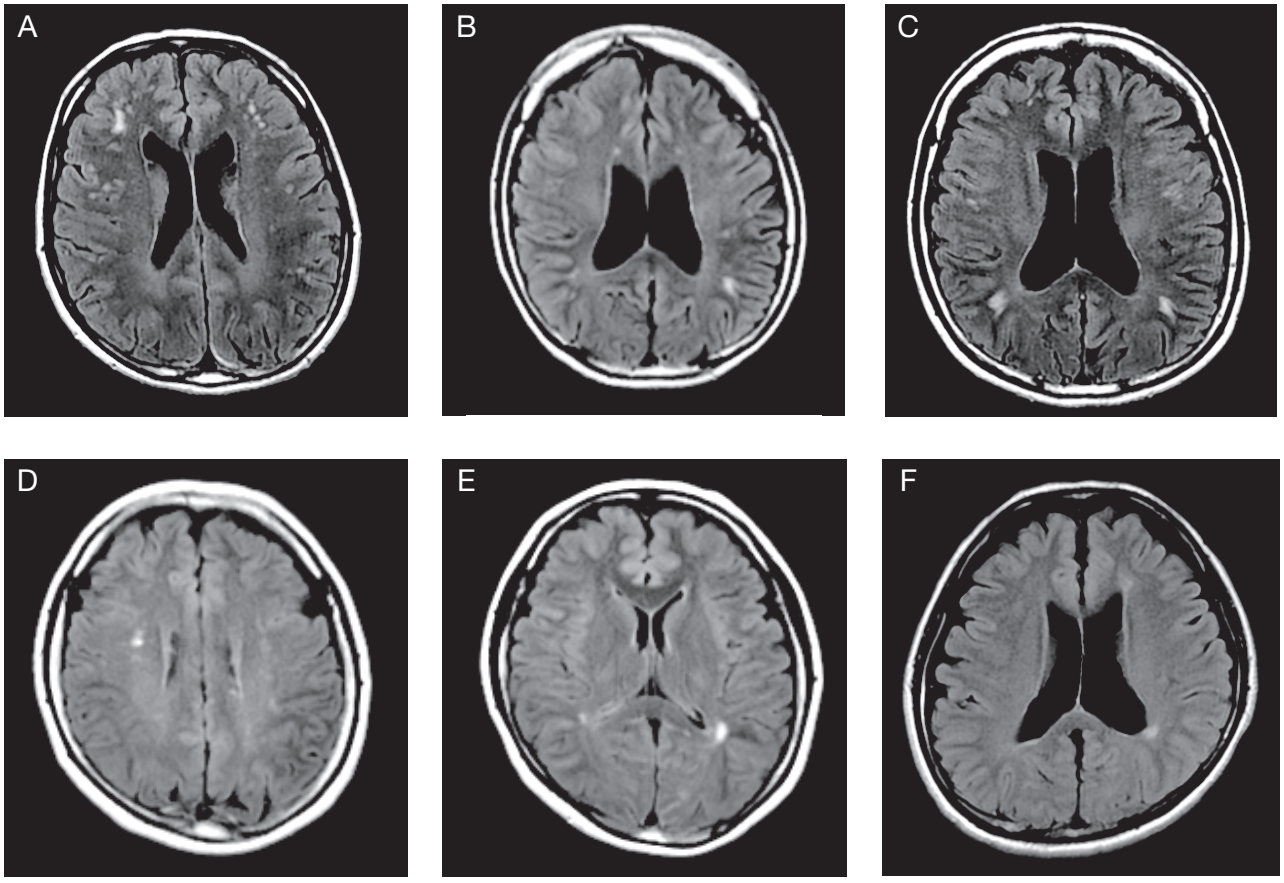

Fig. 2 MRI FLAIR images of migraine patients with cerebral white matter lesions (1.5 Tesla, TR: 2000 ms, TE: 125 ms, TI: 2000 ms).
A: A 35-year-old female migraine patient with scintillating scotoma had a large confluent deep white matter hyper intensity lesion (DWMH) grade 3 in the right anterior circulation territory and small confluence of loci (DWMH grade 2) in the left anterior territory. B, C: A 28-year-old female complained of headache without aura during the premenstrual period. MRI images obtained at the first visit revealed DWMH grade 2 in the posterior area mainly on left side (C). Longitudinal follow-up of MRI performed 5 years later clearly demonstrated progression of DWMH (grade 3) in the bilateral posterior areas. Note the expansion of the bilateral posterior horn of the lateral ventricle. D, E: A 35-year-old female experienced triptan-responsive episodic headache without aura. MRI images showed a periventricular smooth halo [periventricular hyperintensity (PVH) grade 2] and DWMH (grade 2) in the right anterior territory at the centrum semiovale level (D) and irregular PVH extending into the deep white matter (grade 3) in the left posterior territory at the basal ganglia level (E). F: PVH (grade 2) around the left posterior horn of the lateral ventricle was detected on an MRI image of a 31-year-old female patient with menstruation-related migraine without aura.

Table 4 Odd ratios of migraine, age, female, and atherosclerotic risk factors for cerebral white matter lesions on MRI

Variables	Odd ratio	95% CI	p value*
Migraine	2.87	1.35–6.08	< 0.01
Age	1.06	1.02–1.09	< 0.05
Female	1.02	0.52–2.01	0.95
Hypertention	1.74	0.72–4.20	0.22
Diabates	1.44	0.76–2.69	0.25
Hyperlipidemia	0.40	0.10–1.63	0.20

CI: confidence interval. * multivariate stepwise regression analysis.

barrier is also associated with deep WMLs [13], while periventricular WMLs might be caused by cerebrospinal fluid leakage as well as ischemia and edema [14]. Furthermore, WMLs are sometimes found in metabolic abnormality, demyelinating disease, and vasculitis. Edematous changes, induced by failure of the blood-brain barrier, frequently occur in the periventricular region in multiple sclerosis [15].

WMLs, which are often observed in migraine patients with very mild arteriosclerotic risk factors, may be progressive over time [9, 11], indicating a high possibility of direct involvement of migraine in the occurrence of WMLs. We summarized possible causal mechanisms of cerebral WMLs in the patients with migraine in Fig. 3.

According to the previous theory on migraine mechanism, aura may develop upon vasoconstriction, followed by onset of headache due to the subsequent vasodilatation. Such vascular theory used to be a mainstream explanation. However, the trigeminovascular hypothesis [9, 16] has now become a main concept. According to this theory, migraine aura (scintillating scotoma) develops because of CSD and stimulates the region of the first trigeminal branch. Subsequently, the decreased CBF and bold signal change on functional MRI spreads forward from the occipital lobe [17]. Furthermore, neuropeptides such as histamine, calcitonin gene-related peptide (CGRP), and substance P are released, inducing the appearance of brain surface or dural vessel that activates the trigeminal nerve. Then, pain stimulus is considered to be centripetally transmitted to the brainstem site, thalamus, and cerebral cortex, inducing migraine attack [16]. During a migraine attack, release of serotonin from platelets may trigger platelet aggregation [18]. In migraine patients, ischemia in the medullary arteriole could be triggered during a migraine attack. After repetition of these events, WMLs may occur as an irreversible change.

Recent evidence has demonstrated concurrent occurrence of reversible cerebral vasoconstriction syndrome (RCVS) or posterior reversible leukoencephalopathy syndrome (PRES) in migraine patients. A report indicated that 40% of RCVS patients had a history of migraine [19]. Repetitive migraine attacks and continuous usage of medication may induce cerebral vasospasm and increase permeability of brain vessel, causing chronic changes in white matter.

In migraine attacks, pain stimulus from activated trigeminal nerve ascends in the brain and is projected onto the thalamus, primary sensory area of the parietal lobe, cingulated gyrus, frontal lobe, and insular gyrus [20]. According to recent evaluation with voxel-based morphometry in chronic migraine patients, cortical atrophy was observed in the parietal lobe, frontal lobe, and insular gyrus [21]. Therefore, certain organic changes may occur in subcortical deep white matter.

In addition to these acquired factors, genetic factors may be related with WMLs in the patients with migraine [22]. Migraine and WML are major clinical features of certain monogenic disorders such as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Migraine-like headache and stroke attack is well known to often occur in MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) caused by abnormal mitochondrial gene. Accordingly, mitochondrial dysfunction may partially be involved in the occurrence of migraine attack and WML [23]. Its pathology may involve the disorder of CBF-regulating astrocyte [24] and cellular-level metabolic abnormality. The above-mentioned pathology of migraine attack may bring about histological change in the cerebral cortex and white matter, inducing sclerotic change and WML [25].

Many earlier studies demonstrated posterior predominance of WMLs in the migraine patients [5, 6]. In the present study, however, subcortical deep WMLs were prevalent on the anterior side, which concurred with several past reports [10, 11]. Although aging-related white matter changes are often found in the frontal and parietal lobes, our study ruled out the relationship with arteriosclerotic risk factors. A plausible explanation is that spasm-caused hemodynamic change may occur at the border between major cerebral arteries. However, the deep WMLs which observed in this study were located not only in the anterior watershed areas but also in proximity to these areas (Fig. 2A). Therefore, further investigation is necessary.

In contrast, periventricular WMLs were predominant in the posterior territories (Fig. 2E, F). In migraine patients, CSD spreads from the occipital lobe, and CBF reduction is likely to occur predominantly in the posterior circulation. Moreover, RCVS or PRES occurs often in the posterior watershed areas. Therefore, WMLs in the periventricular regions may occur frequently on the posterior side in migraine patients.

The present study has several limitations. First, it was a cross-sectional study of patients who visited our outpatient clinic. No considerations were taken regarding the patients' backgrounds, including the length of disease or frequency of headache episodes. Second, use of medications such as triptan or other oral analgesics was not considered. A report mentioned that WMLs

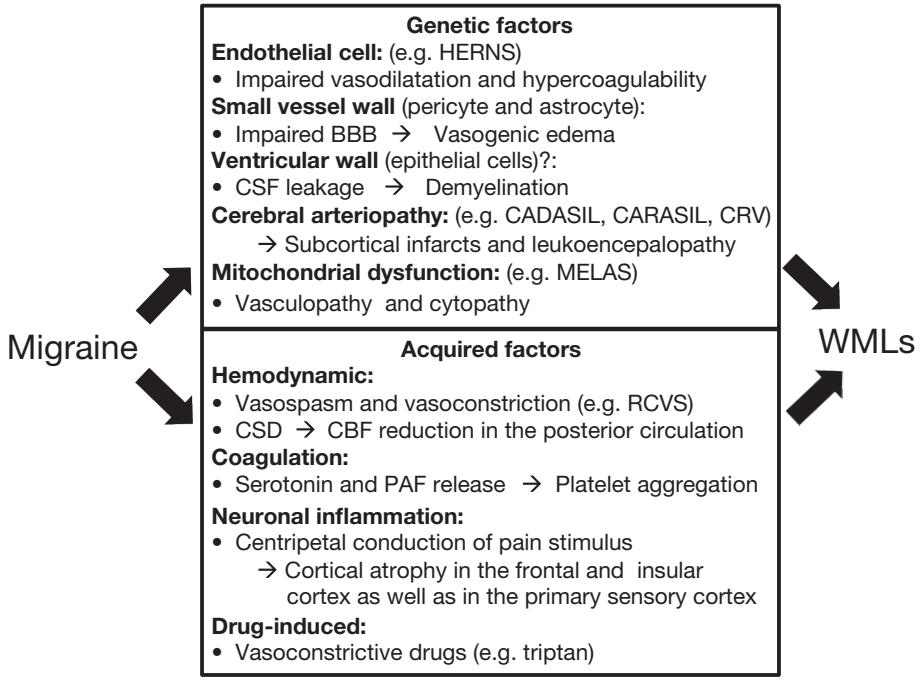

Fig. 3 Multifactorial causal mechanisms of cerebral white matter lesions (WMLs) in patients with migraine.
Both genetic and acquired factors in migraine could cause WMLs. BBB: blood brain barrier, CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CARASIL: cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, CRV: cerebroretinal vasculopathy, CSD: cortical spreading depression, HERNS: hereditary endotheliopathy with retinopathy, nephropathy, and stroke, MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, PAF: platelet activating factor, RCVS: reversible cerebral vasoconstriction syndrome.

were frequently found in patients who were taking oral triptan or having migraine attacks at least once a month [5]. Therefore, more-detailed physician interview is needed regarding patient background. Third, the severity of the arteriosclerotic risk factors was not evaluated in the present study. More detailed examination is needed concerning the data, including the information on the duration of arteriosclerotic risks and medication. Forth, the subjects in the control group might not be completely healthy, although patients with headache and any other neurological conditions which could present WMLs were excluded.

For the future, it will be important to conduct a prospective study by using imaging observations in migraine patients, concerning how arteriosclerotic changes and WMLs appear during repeated migraine attacks and the distribution areas. Thus, we will be able to know the influence of migraine on brain tissue and CBF. The insights will provide a clue for identifying the causal mechanism of migraine. In the present study, the MRI images frequently provided the signs of migraine even in asymptomatic patients. Therefore, MRI should be taken at least once, together with subsequent follow-up observations over time.

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CONFLICTS ON INTEREST DISCLOSURES

None

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