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【 ORIGINAL ARTICLE 】

# Reversible Cerebral Vasoconstriction Syndrome Patients with a History of Migraine: A Retrospective Case-control Study

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**Abstract:**

**Objective** We investigated the clinical characteristics of patients with reversible cerebral vasoconstrictor syndrome who had a history of migraine before the onset and considered the relationship between these two pathologies.

**Methods** We investigated 98 patients who underwent magnetic resonance angiography within 14 days of the onset of reversible cerebral vasoconstriction syndrome at our hospital. Of these, 11 cases involved recurrences, so data from 87 patients were analyzed.

**Materials** All consecutive patients diagnosed with reversible cerebral vasoconstrictor syndrome at our institution between October 2010 and July 2021.

**Results** Fifty of the 87 patients (57%) had a history of migraine. A multivariate analysis revealed that the following clinical factors were significantly more frequent in patients with a history of migraine than in those without such a history: female sex; emotional situations as a trigger of the onset; presence of deep and subcortical white matter hyperintensity, absence of vasoconstriction in the M1 portion of the middle cerebral artery, and absence of other cerebral lesions on initial magnetic resonance imaging; absence of vasoconstriction of the basilar artery on follow-up magnetic resonance imaging; and progression of deep and subcortical white matter hyperintensity in the chronic stage.

**Conclusion** Reversible cerebral vasoconstrictor syndrome patients with a history of migraine showed clinical features of migraine, including one aspect of cerebral small-vessel disease due to endothelial dysfunction, as a common causative condition.

**Key words:** cerebral small vessel disease, migraine, reversible cerebral vasoconstriction syndrome, white matter lesion

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## Introduction

A review by Mawet et al. presented clinical and genetic data suggesting that the medical conditions of migraine, reversible cerebral vasoconstriction syndrome (RCVS), and cervical artery dissection share common features and are, at least partially, linked (1). In fact, the frequency of migraine history among RCVS patients is known to be as high as 17-40% (2-5).

In contrast, the prevalence of cerebral white matter lesions on magnetic resonance imaging (MRI) in adult migraine is 14-39% (6-8), and migraine is being increasingly recognized as a risk factor for white matter lesions. However, the mechanism by which migraine patients develop white matter lesions remains unclear. Another brain lesion associated with RCVS has recently been reported to be progression of white matter lesions in the chronic phase (9). However, no studies have clarified the role of RCVS as a potentially exacerbating factor for white matter lesions in migraineurs.

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This study investigated the clinical characteristics of RCVS patients with a history of migraine prior to the onset, and we discussed how being a migraineur may modify the clinical expression of RCVS. In particular, we investigated the characteristics of white matter lesions in RCVS patients with a history of migraine.

## Materials and Methods

### Patient population

The diagnosis of migraine was made in accordance with the third edition of the International Classification of Headache Disorders (10). Patients diagnosed with RCVS in our institution according to our previously reported criteria for RCVS were included in our database (9, 11). The distinction between RCVS and primary angiitis of the central nervous system was diagnosed with reference to the RCVS2 score (12). Our database included 120 RCVS patients between October 2010 and July 2021. We excluded 22 RCVS patients who visited our hospital in the subacute phase and who therefore did not undergo magnetic resonance angiography (MRA) or MRI within 14 days after the RCVS onset. Of the remaining 98 cases, 11 involved multiple recurrence, so data from 87 patients were investigated by a patient-wise analysis.

As much as possible, we performed sequential MRA during the period from the onset of thunderclap headache (TCH) to remission and within 14 days after TCH remission. No significant differences in demographic variables were identified between the 99 enrolled cases and 22 excluded cases.

### Imaging protocol

All MRI examinations were completed within 13-15 min and included conventional axial T1-weighted imaging, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging, and MRA. A 1.5-T superconducting magnet (Signa EXCITE or HDX; GE Medical Systems, Milwaukee, USA) and a quadrature head coil were used for all MRI examinations. We used the pulse sequences reported in previous studies (9, 11).

Follow-up MRI was routinely performed at one, two, and three months after the onset until improvement of vasoconstriction was identified. For patients who did not show improved vasoconstriction on MRI by three months after the onset, additional MRI was performed monthly until improvement was identified.

### Definition of variables

Definitions of the variables examined were the same as in the previous reports, as shown below (9, 11). We defined TCH as severe pain that peaked rapidly (within seconds) and was diagnosed by a thorough interview of the patient. When TCH had disappeared for at least 12 h and did not recur, we judged this timing to indicate remission of TCH, representing the ''last TCH''. We defined the interval from the first TCH at the onset to the last TCH as the ''interval from first to last TCH''. An emotional situation as a trigger of RCVS was defined in cases with acute stress or panic attacks. Systolic blood pressure >180 mmHg or diastolic blood pressure >120 mmHg was considered indicative of hypertensive emergency.

Deep and subcortical white matter hyperintensity (DSWMH) was defined as hyperintensity on FLAIR without hypointensity on T1-weighted imaging. Progression of DSWMH after RCVS was assessed by comparing findings from MRI at the onset and three months after the onset. We assessed the progression of DSWMH using the Fazekas scale (13), and DSWMH progression was considered present if the visual rating increased by at least one grade. Progression of DSWMH after RCVS was defined as the occurrence of new DSWMH in four regions of subcortical white matter (frontal, parietal, occipital, temporal) and the infratentorial region.

MRA was used to assess localized vasoconstriction of cerebral arteries. We defined centripetal propagation of vasoconstriction (CPV) (9, 11) as vasoconstriction that began in the distal arteries (observed on MRA performed within 72 h of the start of RCVS) and spread to the major cerebral arteries in the circle of Willis [defined as the internal cerebral artery, A1 portion of the anterior cerebral artery (ACA), and/or P1 portion of the posterior cerebral artery (PCA)] as well as the M1 portion of the middle cerebral artery (MCA), basilar artery, and vertebral artery on MRA performed multiple times after the first MRA scan.

MRI findings were interpreted by at least 2 senior stroke neurosurgeons (M.S. and S.O., with 39 and 34 years of experience, respectively). When the neurosurgeons disagreed about findings, they consulted with each other to reach a consensus. Outcomes were assessed at three to six months after the onset using the modified Rankin Scale.

### Treatment protocol

Vasoactive medications, such as triptans, were stopped in all patients. Symptomatic analgesic treatment was used in all patients without a standard protocol. Oral cilostazol or lomerizine hydrochloride was administered to prevent cerebral vasoconstriction. Administration of steroids was avoided. For patients with severe TCH, a low dose of propofol (30-50 mg/h) was infused intravenously. For 9 of the 17 patients who experienced a hypertensive emergency, nicardipine was used with intravenous infusion of the dose adapted to normalize blood pressure levels.

### Institutional review board approval

Study approval was obtained from the Institutional Review Board for Clinical Research (approval no. 21R-223) and the Conflict of Interest Management Committee (approval no. 21-364) at our university. We performed MRI after obtaining verbal informed consent from each patient.

**Table 1. Comparison of Clinical Features between RCVS Patients with and without a History of Migraine.**

| | RCVS with history of migraine n=50 (57%) | RCVS without history of migraine n=37 (43%) | p value |
|---|---|---|---|
| Age (years) | | | |
| Mean±SD | 40±13 | 38±14 | 0.507 |
| Range | 13-67 | 14-70 | |
| Sex (M/F) | 5 (10%)/45 (90%) | 10 (27%)/27 (73%) | 0.047 |
| Past history | | | |
| Migraine with aura | 11 (22%) | - | - |
| RCVS | 8 (16%) | 3 (8%) | 0.341 |
| Hypertension | 3 (6%) | 2 (5%) | 1.000 |
| Diabetes mellitus | 4 (8%) | 2 (5%) | 1.000 |
| Hyperlipidemia | 2 (4%) | 0 | 0.505 |
| Smoking | 6 (12%) | 3 (8%) | 0.727 |
| Trigger | | | |
| Sexual activity | 1 (2%) | 0 | 1.000 |
| Pregnancy or postpartum | 11 (22%) | 15 (41%) | 0.096 |
| Emotional situations | 30 (60%) | 6 (16%) | <0.001 |
| Bathing-related | 6 (12%) | 3 (8%) | 0.727 |
| Illicit drug use | 0 | 0 | - |
| SSRI use | 8 (16%) | 1 (3%) | 0.072 |
| Symptom | | | |
| Multiple episodes of TCH | 47 (94%) | 29 (78%) | 0.048 |
| TCH-associated symptom | | | |
| Transient visual disturbance | 10 (20%) | 6 (16%) | 0.782 |
| Disturbance of consciousness | 1 (2%) | 6 (16%) | 0.039 |
| Weakness | 0 | 3 (8%) | 0.073 |
| Epilepsy | 3 (6%) | 6 (16%) | 0.161 |
| Hypertensive emergency | 7 (14%) | 10 (27%) | 0.173 |

RCVS: reversible cerebral vasoconstriction syndrome, SD: standard deviation, M: male, F: female, SSRI: selective serotonin reuptake inhibitor, TCH: thunderclap headache

### *Statistical analyses*

Due to the presence of recurrent cases in this study, statistical comparisons were made by a patient-wise analysis. The significance of clinical factors potentially associated with RCVS patients with a history of migraine was determined by the two-tailed Fisher's exact test. Continuous variables (age, interval from first to last TCH, and timing of initial MRI after the onset) were tested using an independent sample two-tailed Student's *t*-test. Clinical factors with a significance level of $p<0.10$ were subjected to a multivariate logistic regression analysis with the presence of a history of migraine as the dependent variable.

All statistical analyses were performed using a commercially available software program (IBM SPSS Statistics for Windows, version 22.0; IBM, Armonk, USA).

## Results

### *The comparison of the clinical features of patients with and without a history of migraine before the onset*

The frequency of RCVS with a history of migraine before the onset was 57% (50/87 patients). Of the 21 RCVS patients who visited our facility more than 14 days after the onset and were excluded from this study, 76% (16 patients) had no history of migraine. In RCVS patients with a history of migraine, migraine with aura was seen in 11 of 50 patients (22%). The sex ratio of all RCVS patients was 72:15 (4.8:1), with a female predominance.

Among cases of RCVS with a history of migraine, the clinical factors that were significantly more frequent according to a chi-square test than in cases of RCVS without a history of migraine were: female preponderance as a presymptomatic clinical factor, emotional situations as a trigger of the onset, and multiple episodes of TCH (Table 1). The frequency of disturbance of consciousness was significantly lower in RCVS patients with a history of migraine than in

**Table 2. Comparison of Interval from First to Last TCH, and Timing of Initial MRI between RCVS Patients with and without a History of Migraine.**

| | RCVS with history of migraine n=50 (57%) | RCVS without history of migraine n=37 (43%) | p value |
|---|---|---|---|
| Interval from first to last TCH | | | |
| Mean±SD (days) | 10±8 | 10±7 | 0.267 |
| Range (days) | 2-36 | 2-30 | |
| Timing of initial MRI after onset (days) | | | |
| Mean±SD (days) | 3±3 | 3±2 | 0.291 |
| Range (days) | 1-14 | 1-7 | |

RCVS: reversible cerebral vasoconstriction syndrome, TCH: thunderclap headache, SD: standard deviation, MRI: magnetic resonance imaging

**Table 3. Comparison of Vasoconstricted Vessels on Initial and Follow-up MRI between RCVS Patients with and without a History of Migraine.**

| | RCVS with history of migraine n=50 (57%) | RCVS without history of migraine n=37 (43%) | p value |
|---|---|---|---|
| Associated lesions on MRI | | | |
| other cerebral lesion (SAH, PRES, infarction, ICH) | 5 (10%) | 12 (32%) | 0.013 |
| cortical SAH | 4 (8%) | 6 (16%) | 0.313 |
| PRES | 0 | 4 (11%) | 0.030 |
| infarction | 2 (4%) | 1 (3%) | 1.000 |
| ICH | 0 | 1 (3%) | 0.425 |
| DSWMH | | | |
| on initial MRI | 23 (46%) | 9 (22%) | 0.045 |
| deterioration in chronic stage | 25 (50%) | 8 (22%) | 0.008 |
| Drug administered as treatment for RCVS | | | |
| lomerizine | 20 (40%) | 2 (5%) | 1.000 |
| cilostazol | 3 (6%) | 4 (6%) | 0.477 |
| nicardipine | 0 | 10 (15%) | 0.597 |
| Drug administered as treatment for analgesia of TCH | | | |
| propofol | 10 (20%) | 10 (27%) | 0.453 |
| Period from onset to improvement of vasoconstriction | | | |
| within 45 days | 14 (28%) | 3 (8%) | 0.029 |

RCVS: reversible cerebral vasoconstriction syndrome, MRI: magnetic resonance imaging, SAH: subarachnoid hemorrhage, PRES: posterior reversible encephalopathy syndrome, ICH: intracerebral hemorrhage, DSWMH: deep and subcortical white matter hyperintensity, TCH: thunderclap headache

those without a migraine history (Table 1). No significant differences between groups were seen in histories of hypertension, hyperlipidemia, diabetes, or smoking, all of which are arteriosclerotic factors associated with progression of white matter lesions (Table 1).

On comparing the groups with and without a history of migraine before the RCVS onset, no significant differences were seen in the interval from first to last TCH or timing of initial MRI after the onset (Table 2).

### *The comparison of neuroradiological findings in patients with and without a history of migraine before the onset*

Among cases of RCVS with a history of migraine, neuroradiological findings that were significantly more infrequent according to a chi-square test than in cases of RCVS without a history of migraine were cerebral lesion and posterior reversible encephalopathy syndrome (PRES) on initial MRI, vasoconstriction of the M1 portion of the MCA on initial MRA, and vasoconstriction of the basilar artery on follow-up MRA (Table 3, 4). The neuroradiological findings that were significantly more frequent than in cases of RCVS

**Table 4. Comparison of Location of Vasoconstriction on Initial and Follow-up MRA between RCVS Patients with and without a History of Migraine.**

| Location of vasoconstriction on MRA | | RCVS with history of migraine n=50 (57%) | RCVS without history of migraine n=37 (43%) | p value |
|---|---|---|---|---|
| MCA | | | | |
| M1 portion | initial MRA | 3 (6%) | 11 (30%) | 0.006 |
| | follow-up MRA | 18 (36%) | 18 (49%) | 0.269 |
| M2/3 portion | initial MRA | 46 (92%) | 33 (89%) | 0.718 |
| | follow-up MRA | 39 (78%) | 26 (70%) | 1.000 |
| PCA | | | | |
| P1 portion | initial MRA | 4 (8%) | 4 (11%) | 0.718 |
| | follow-up MRA | 16 (32%) | 17 (46%) | 0.186 |
| P2/3 portion | initial MRA | 47 (94%) | 32 (86%) | 0.277 |
| | follow-up MRA | 40 (80%) | 29 (78%) | 1.000 |
| ACA | | | | |
| A1 portion | initial MRA | 3 (6%) | 6 (16%) | 0.161 |
| | follow-up MRA | 12 (24%) | 15 (41%) | 0.105 |
| A2/3 portion | initial MRA | 14 (28%) | 7 (19%) | 0.448 |
| | follow-up MRA | 12 (24%) | 11 (30%) | 0.620 |
| Basilar artery | initial MRA | 0 | 2 (5%) | 0.178 |
| | follow-up MRA | 1 (2%) | 7 (19%) | 0.009 |
| VA | initial MRA | 4 (8%) | 3 (8%) | 1.000 |
| | follow-up MRA | 3 (6%) | 7 (19%) | 0.088 |
| IC | initial MRA | 0 | 0 | - |
| | follow up MRA | 4 (8%) | 1 (2%) | 0.390 |
| Hyperintense vessel sign | | | | |
| | initial MRA | 29 (58%) | 15 (41%) | 0.098 |
| | follow-up MRA | 31 (62%) | 19 (51%) | 0.383 |
| CPV on follow-up MRI | | 25 (50%) | 23 (62%) | 0.072 |

MRA: magnetic resonance angiography, RCVS: reversible cerebral vasoconstriction syndrome, MCA: middle cerebral artery, PCA: posterior cerebral artery, ACA: anterior cerebral artery, VA: vertebral artery, IC: internal cerebral artery, CPV: centripetal propagation of vasoconstriction

without a history of migraine were DSWMH on initial MRI, progress of DSWMH in the chronic stage, and improved vasoconstriction on MRA within 45 days after the onset (Table 3). No significant difference in the incidence of CPV was seen between groups (Table 4). However, all 10 RCVS patients with cortical subarachnoid hemorrhage (SAH) were women, with or without a history of migraine.

The localization of DSWMH is shown in Fig. 1. DSWMH, which is more common in RCVS with a history of migraine than in that without such a history, tended to be more common in the watershed area of ACA/MCA and MCA/PCA and in the subcortical area of the MCA on both initial MRI and MRI in the chronic phase. In addition, few instances of DSWMH tended be present in the PCA area.

Three months later, the modified Rankin Scale score was 0 in all 87 RCVS patients, and all had been able to resume their prior daily activities.

### Clinical factors associated with RCVS with a history of migraine according to a multivariate analysis

According to a multivariate logistic regression analysis, the clinical factors significantly associated with RCVS patients with a history of migraine were: female sex (p=0.045) as a presymptomatic clinical factor; emotion as a trigger of the onset (p<0.001) as a clinical factor at the time of the onset; presence of DSWMH (p=0.016), absence of vasoconstriction in the M1 portion of the MCA (p=0.009) (Fig. 2A, B), and absence of other cerebral lesions (p=0.023) as a finding on initial MRI; absence of vasoconstriction of the basilar artery (p=0.025) as a finding on follow-up MRI; and progression of DSWMH (p=0.010) as a clinical factor in the chronic stage (Table 5).

In contrast, according to multivariate logistic regression analysis, the clinical factors significantly associated with RCVS with progression of DSWMH on chronic-phase MRI were a history of migraine (OR 3.623, p=0.008) as a presymptomatic clinical factor and the presence of DSWMH (OR 128.628, p<0.001) as a finding on initial MRI (Fig. 3A, B).

### Clinical features in RCVS patients with a history of migraine with aura

According to chi-square testing, among 50 RCVS patients with a history of migraine, a significantly more frequent clinical factor in 11 RCVS patients with a history of migraine with aura was visual impairment at onset (6 of 11 pa-

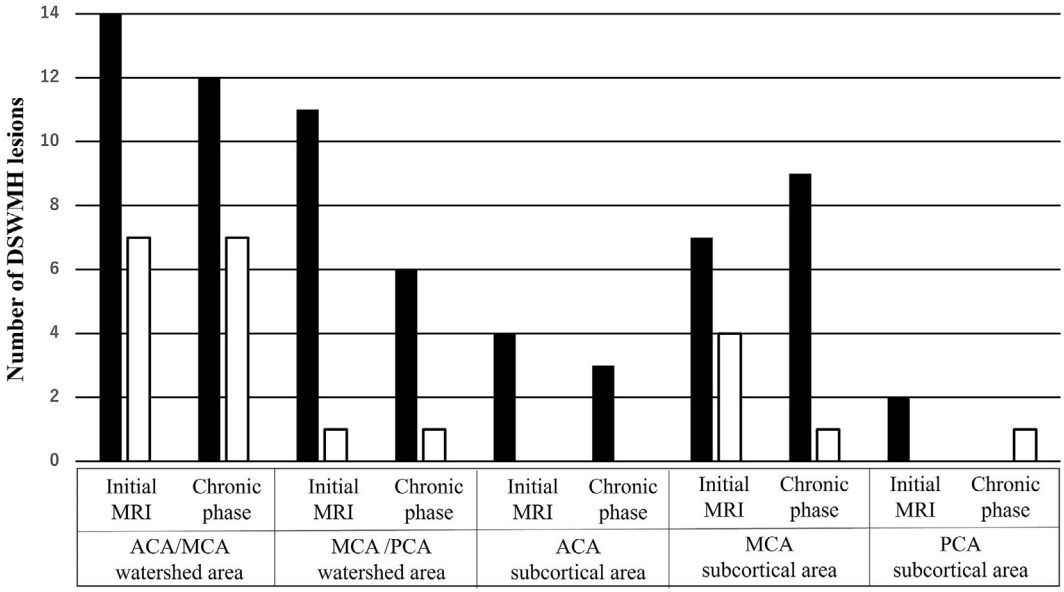


**Figure 1.** **Bar graphs show the total number of patients with reversible cerebral vasoconstrictor syndrome [with a history of migraine (black bar) and without a history of migraine (white bar)] with deep and subcortical white matter hyperintensity (DSWMH) lesions in each region.**

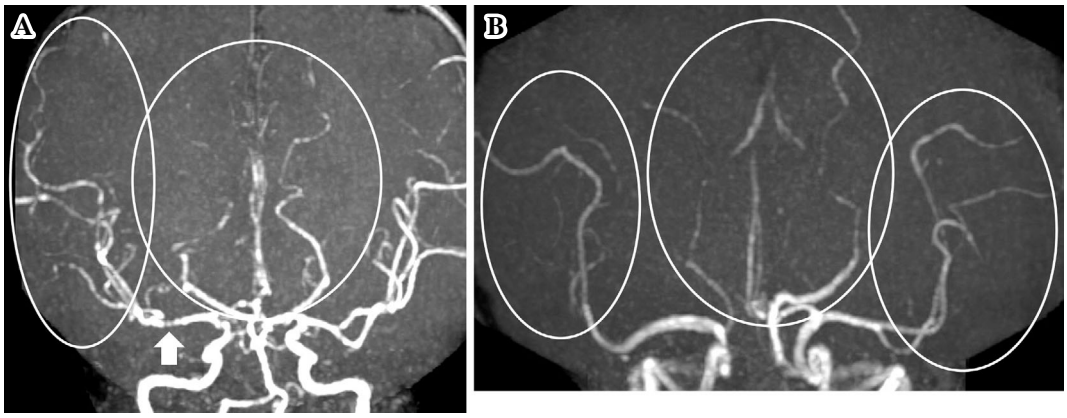


**Figure 2.** **Typical findings of MRA in the RCVS patients with/without history of migraine. A) Image from a 57-year-old woman with bath-related RCVS without a history of migraine. Initial MRA obtained five days after the onset shows vasoconstriction in the right M2-3 portions (circle) and right terminal M1 portion of the MCA (white arrow) and in the right P2-3 and left P3 portions of the PCA (circle). B) Image from a 48-year-old woman with RCVS with a history of migraine. Initial MRA obtained three days after the onset shows diffuse vasoconstriction in the bilateral M2-3 portions of the MCA and P2-3 portions of the PCA (circles). However, no vasoconstriction of the major trunks of cerebral arteries, such as the M1 portion of the MCA, were found on initial MRA.**

tients, 55%, p=0.007). In addition, in the 11 RCVS patients with a history of migraine with aura, no patients showed vasoconstriction of the A2/3 portion of the ACA on initial (p =0.012) or follow-up MRA (p=0.045). Other than these findings, among the clinical factors examined in this study, no significant difference was seen between cases of migraine with and without aura. A multivariate analysis was not performed due to the small number of RCVS patients with migraine aura (n=11).

## Discussion

### *Link between RCVS and migraine*

In this study, a history of migraine was seen in 50 of 87 RCVS patients (57%), which was higher than the previously reported 17-40% (2-5). Chen et al. reported that the rate in Taiwan was as low as 17%, so a history of migraine does not seem to be characteristic in RCVS patients of Asian descent (5). MRI is usually required to identify the cause of headache in pathological conditions that cannot be detected

**Table 5. Results of Multivariate Logistic Regression Analysis for Presence of History of Migraine in RCVS Patients.**

| | Odds ratio | 95%CI | p value |
|---|---|---|---|
| Presymptomatic clinical factors | | | |
| Sex (female) | 3.333 | 1.030-10.791 | 0.045 |
| Clinical factors at time of onset | | | |
| Emotion situation as a trigger of onset | 7.752 | 2.732-21.739 | <0.001 |
| Findings on initial MRI | | | |
| Presence of DSWMH on initial MRI | 3.846 | 1.280-11.494 | 0.016 |
| Absence of vasoconstriction in M1 portion of MCA | 7.203 | 1.645-31.547 | 0.009 |
| Absence of other cerebral lesions | 4.342 | 1.225-15.393 | 0.023 |
| Findings of follow-up MRI | | | |
| Absence of BA vasoconstriction | 11.586 | 1.356-99.009 | 0.025 |
| Clinical factors in chronic stage | | | |
| Progression of DSWMH at time of chronic stage | 3.846 | 1.385-10.638 | 0.010 |

MRI: magnetic resonance imaging, DSWMH: deep and subcortical white matter hyperintensity, MCA: middle cerebral artery, BA: basilar artery

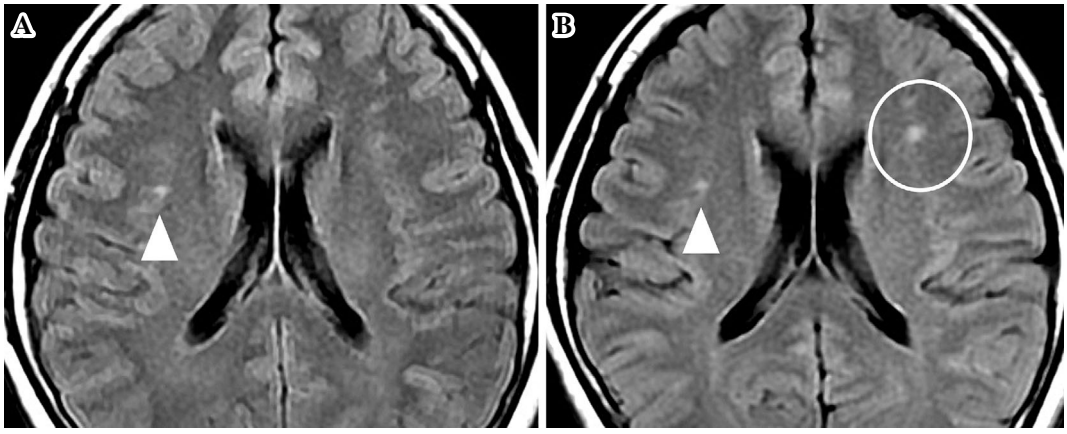


**Figure 3. Images from a 39-year-old woman with RCVS with a history of migraine. A) Initial FLAIR obtained at the time of the RCVS onset shows DSWMH (arrowhead). B) FLAIR obtained three months after the onset shows progression of DSWMH (circle).**

by computed tomography (CT), such as RCVS, PRES, and cerebral vein thrombosis, all of which can cause TCH. In Japan, including at our own center, an increasing number of headache centers are choosing MRI as the first examination to perform for patients who complain of TCH in order to quickly and accurately diagnose the causative condition.

While migraine patients generally clearly identify the TCH of RCVS as differing from their usual headaches, they often complain on admission of the "worst-ever migraine attack" (14). RCVS patients with a history of migraine therefore tend to visit the headache center soon after the onset. However, in the present study, of the 21 RCVS patients excluded from the study because they visited our facility more than 14 days after the onset, 76% had no history of migraine. We therefore speculate that RCVS patients with no history of migraine are more likely to be observed at home without visiting a headache center during the acute phase after the onset. These reasons may be why the frequency of RCVS patients with a history of migraine was high in this study.

Although the frequency of RCVS patients with a history of migraine in this study and previous reports (17-57%) (2-5) was clearly higher than the prevalence of migraine (Asia, 5-10%; the United States and Europe, 10-15%) in the general population (15), the pathophysiological link between the migraine and RCVS remains unclear. However, studies of circulating endothelial progenitor cells (16, 17) and endothelial microparticles in migraine patients (18) have demonstrated endothelial dysfunction in migraineurs (19), and this is therefore considered to represent one of the mechanisms explaining the increased risk of stroke among migraineurs (20). In addition, the endothelial dysfunction reported in studies with these biomarkers has also been demonstrated in RCVS patients (21). RCVS therefore tends to be more common in migraine patients than the general population, and we speculate that RCVS and migraine are linked. To clarify whether or not migraine increases the risk of RCVS, further studies will be needed to assess whether or not the frequency of migraine is significantly higher in RCVS patients than in age- and sex-matched referents in the

general population.

### Clinical features of RCVS with a history of migraine

An overall female dominance among RCVS patients was found in our study (4.8:1), as in previous reports [1.8:1 (22), 4.3:1 (23), 10.2:1 (24)]. In our study, this female preponderance was significantly more pronounced for RCVS patients with a history of migraine (9:1) than for RCVS patients without such a history (2.7:1). Conventionally, migraine sex differences are similar in Japan, Europe, and the United States, with female patients known to be about three times more common than male patients (25, 26). Even with this in mind, the female predominance of RCVS patients with a history of migraine seems noticeable. In migraine patients, particularly in women, accumulating evidence supports the involvement of endothelial activation, which is mediated by oxidative stress and associated with a pro-inflammatory and pro-coagulatory milieu (27). We speculate that this may underscore the female predominance of RCVS patients with a history of migraine.

However, one of the significant clinical factors of RCVS with a history of migraine in this study was emotional stress as a trigger. Similarly, emotional stress is the most frequent trigger for migraine (28, 29). We therefore speculated that in RCVS patients with a history of migraine, emotional stress as a trigger for the onset was significantly more frequent as a result of reflecting the clinical characteristics of migraine itself.

Ducros et al. reported that female sex and a history of migraine were two independent risk factors for hemorrhagic complications of RCVS (30). In our study, all 10 RCVS patients with cortical SAH were women, with or without a history of migraine. The results of cortical SAH in our study were consistent with the findings reported by Ducros et al. (30). However, in our study, a history of migraine did not correlate significantly with hemorrhagic complications of RCVS. Conversely, a history of migraine was significantly associated with the absence of vasoconstriction of the M1 portion of the MCA, absence of other cerebral lesions as findings on initial MRI, and absence of vasoconstriction of the basilar artery as findings from follow-up MRI. That is, RCVS patients with a history of migraine tended to exhibit the clinical features of non-serious-type RCVS. Considering these reasons, first, as mentioned above, migraine patients can clearly identify that the TCH of RCVS differs from the usual migraine headache (14). Patients with a history of migraine therefore often visit our facility during the acute phase after the onset of TCH, and our study may have included a number of cases of mild-type RCVS. In contrast, severe vasoconstrictions in the M1 segment of the MCA and P2 segment of PCA are known to be associated with an increased risk of PRES and ischemic stroke in patients with RCVS (31). The frequencies of M1 vasoconstriction and PRES were also significantly lower in RCVS patients with a history of migraine than in those without a history of migraine in this study, which may be why mild-type RCVS was more common.

The present findings failed to clarify why RCVS with a history of migraine has many non-serious types. However, we speculate that patients with migraine may easily develop RCVS due to cerebrovascular tone dysregulation, since they potentially have endothelial dysfunction that shares pathophysiological factors with RCVS. We believe that the cerebral vasoconstriction seen in cases of RCVS with a history of migraine is mild, as patients with migraine develop RCVS with even a slight deterioration of the endothelial function.

### DSWMH in RCVS and migraine patients

In the present study, DSWMH was seen as a chronic complication of RCVS in 33 of 87 cases (38%), similar to our previous report (9). We speculate that the mechanisms by which DSWMH progression occurs after RCVS involve the following: 1) other organic brain parenchymal complications due to RCVS, such as cerebral infarction and cerebral hemorrhaging; 2) endothelial dysfunction, oxidative stress, blood-brain barrier failure, autoregulation failure, and PRES, as a pathological conditions of RCVS (32); and 3) chronic ischemia due to widespread vasoconstriction over a long period of about three months.

However, the frequency of DSWMH on MRI in adult migraine patients was reported to be 14-39% (6-8). Many causes, such as patent foramen ovale, microembolism, and depression as factors coexisting with migraine, have been proposed as being involved in the mechanism underlying the development of DSWMH in migraine patients (33-35). Relatedly, genetic vasculopathies patients with migraine, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), are known to often present on brain MRI white matter lesions that resemble ischemic infarcts in the territory of a small cerebral vessel (36). Migraine patients have also been shown to have endothelial dysfunction, similar to genetic cerebral small-vessel disease with migraine, such as CADASIL (16-20, 36). In addition, even in normal migraine patients, prolonged and repeated oligemia during migraine attacks may affect the vulnerable small deep penetrating arteries, and local critical hypoperfusion may lead to minor brain injury revealed as white matter lesions (36). We may therefore conclude that migraine itself is a category of cerebral small-vessel disease.

In the present study, a multivariate analysis identified significant clinical features of RCVS patients with a history of migraine as the presence of DSWMH on initial MRI and progression of DSWMH on chronic MRI. Conversely, the clinical features that were significant for the progression of DSWMH on chronic MRI in RCVS patients in this study were a history of migraine and the presence of DSWMH on initial MRI. DSWMH on initial MRI can be interpreted as DSWMH that developed before the onset of RCVS. The results of this study suggest that RCVS patients with a predisposition toward cerebral small-vessel disease are more likely to develop DSWMH in the chronic phase. Our research re-

sults show that a significant clinical factor for the predisposition to cerebral small-vessel disease was "a history of migraine". In addition, although the results of this study did not provide clear evidence, the close link between migraine and RCVS suggests that at least RCVS may be an etiology of DSWMH in migraine patients. The characteristics of DSWMH in RCVS patients with a history of migraine with aura were examined, but no significant findings were obtained. This seems to be an important issue to address in the future.

### Limitations

Several limitations associated with the present study warrant mention. In this study, MRI findings were interpreted by senior stroke neurosurgeons, but blinding to the timing of imaging was not performed. We also did not measure the inter-rater reliability of MRI rating regarding vasoconstriction and progression of WMH. However, in cases of disagreement between raters, the diagnosis was obtained by consensus. Regarding the treatment of RCVS, because nimodipine has not been approved in Japan for use as a calcium channel antagonist for preventing vasospasm after SAH due to ruptured aneurysm, we were unable to administer this drug. Our results thus may not be generalizable to hospital facilities in which nimodipine is used. However, we did not calculate recurrence rates in this study because we were unable to obtain a sufficient observation period from the onset of RCVS in all patients. Furthermore, this was a retrospective study of a small group of patients, and prospective studies with a greater number of cases are necessary in the future. Finally, differences in onset stress scores with or without a history of migraine in RCVS patients are very important. However, we were unable to address this issue, as we did not examine stress scores at the onset, and this study used a retrospective design. This represents an important issue to address in the future.

## Conclusion

RCVS patients with a history of migraine were significantly more often women and more often showed emotional stress as a trigger at the onset. Furthermore, significantly, DSWMH was already present at the initial performance of MRI and often worsened in the chronic phase. Given the above, RCVS patients with a history of migraine displayed a clinical picture similar to that of migraine, including one aspect of cerebral small-vessel disease due to endothelial dysfunction, a common causative condition. Since endothelial dysfunction is a common pathology, we believe that RCVS is a comorbid disorder of migraine and that the two diseases are linked.

**The authors state that they have no Conflict of Interest (COI).**

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