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Clinical significance of centripetal propagation of vasoconstriction in patients with reversible cerebral vasoconstriction syndrome: A retrospective case-control study

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Abstract

Introduction: We previously reported centripetal propagation of vasoconstriction at the time of thunderclap headache remission in patients with reversible cerebral vasoconstriction syndrome. Here we examine the clinical significance of centripetal propagation of vasoconstriction.

Methods: Participants comprised 48 patients who underwent magnetic resonance angiography within 72 h of reversible cerebral vasoconstriction syndrome onset and within 48 h of thunderclap headache remission.

Results: In 24 of the 48 patients (50%), centripetal propagation of vasoconstriction occurred on magnetic resonance angiography at the time of thunderclap headache remission. The interval from first to last thunderclap headache in patients with centripetal propagation of vasoconstriction (14 ± 10 days) was significantly longer than that of patients without centripetal propagation of vasoconstriction (4 ± 2 days). In the patients with centripetal propagation of vasoconstriction at the time of thunderclap headache remission, the incidence of another cerebral lesion (38%, 9 of 24 cases) was significantly higher than in patients without centripetal propagation of vasoconstriction (0%). From findings of sequential magnetic resonance angiography before and after thunderclap headache remission, we observed tendencies in which centripetal propagation of vasoconstriction gradually progressed after the onset of reversible cerebral vasoconstriction syndrome and peaked at the time of thunderclap headache remission. The progress of centripetal propagation of vasoconstriction concluded with thunderclap headache remission.

Conclusions: Centripetal propagation of vasoconstriction has clinical significance as an indicator of the severity of reversible cerebral vasoconstriction syndrome. The presence of centripetal propagation of vasoconstriction is associated with an increased risk of brain lesions and a longer interval from first to last thunderclap headache. Moreover, repeat magnetic resonance angiography to assess centripetal propagation of vasoconstriction during the time from onset to thunderclap headache remission can help diagnose reversible cerebral vasoconstriction syndrome.

Keywords

Headache remission, magnetic resonance angiography, neuroradiological diagnosis, thunderclap headache

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Abbreviations
RCVS: reversible cerebral vasoconstriction syndrome; TCH: thunderclap headache, CPV: centripetal propagation of vasoconstriction; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; FLAIR: fluid-attenuated inversion recovery; SAH: subarachnoid hemorrhage; PRES: posterior reversible encephalopathy syndrome; ICH: intracerebral hemorrhage; WMH: white matter hyperintensity; DSWMH: deep and subcortical white matter hyperintensity; MCA: middle cerebral artery.

Introduction

Features of reversible cerebral vasoconstriction syndrome (RCVS) include thunderclap headache (TCH) and diffuse segmental constriction of cerebral arteries. Vasoconstriction improves on its own in about 3 months (1–6). However, the exact pathophysiology of RCVS remains speculative. In RCVS patients, TCH peaks during the first week after onset, and vasoconstriction of large and medium-sized vessels can persist for weeks after resolution of TCH (3). Therefore, TCH is probably not caused by vasoconstriction of large and medium-sized arteries (2,3). The first purpose of our study was to test this hypothesis by evaluating magnetic resonance angiography (MRA) at the time of TCH remission. In particular, we investigated whether vasoconstriction of distal arteries (such as the M2 or M3 portion, etc.), which are depicted on MRA, is improved at the time of TCH remission, and whether this vasoconstriction is associated with the occurrence of TCH.

On the other hand, typical segmental vasoconstriction of major vessels is not seen in approximately 30% of RCVS patients who first undergo MRA within 10 days of TCH onset (3,7,8). A recently proposed hypothesis is that small distal arteries initially develop abnormalities, followed by aberrations in major vessels (7,9). Based on this hypothesis, we previously demonstrated the presence of centripetal propagation of vasoconstriction (CPV) by comparing MRA at the time of RCVS onset and MRA obtained at the time of TCH remission (10). After that, we experienced additional cases of RCVS, and have unexpectedly experienced many patients with RCVS without CPV. Therefore, we investigated the clinical significance of CPV in patients with RCVS. In addition, we examined RCVS patients with CPV at the time of TCH remission to examine whether CPV occurs before TCH remission, and whether CPV continues to progress after TCH remission. Furthermore, in RCVS patients without CPV at the time of TCH remission, we also examined whether CPV occurs after TCH remission.

Methods

Patient population

RCVS was diagnosed in our hospital if patients in our database met the following five criteria: i) acute onset, severe headache (often TCH) in the presence or absence of focal deficits or seizures; ii) a uniphasic course and no new symptoms >1 month after initial symptoms; iii) segmental, multifocal vasoconstriction of cerebral arteries on digital subtraction angiography or indirect angiography (e.g. MRA or three-dimensional computed tomography angiography); iv) aneurysmal subarachnoid hemorrhage (SAH) was excluded; and v) completely normal or almost normal arteries within 12 weeks of initial symptoms, as seen with digital subtraction angiography or indirect angiography such as MRA at the time of follow-up (1,2,7).

Our database included 74 RCVS patients between October 2010 and April 2017. We excluded 12 RCVS patients who visited our hospital in the subacute phase ($\geq$3 days after onset) and who were therefore not initially examined with MRA or magnetic resonance imaging (MRI) within 72 h of RCVS onset. We also excluded 14 RCVS patients who were not examined with MRA/MRI within 48 h of TCH remission; because their TCH resolved in the subacute phase, these patients did not visit an outpatient clinic for additional imaging. In this study, we retrospectively evaluated the clinical and imaging records of the remaining 48 RCVS patients who underwent MRI within 72 h of RCVS onset, within 48 h of remission of TCH, and 3 months after RCVS onset. As much as possible, we performed sequential MRA during the period from onset to TCH remission and within 14 days after TCH remission. No significant differences in demographic variables were present between the enrolled and excluded patients.

Imaging protocol

Insidious onset, low incidence of TCH, and mostly irreversible abnormalities on angiography were considered primary angiitis of the central nervous system and not RCVS. When primary angiitis of the central nervous system was suspected, cerebrospinal fluid analysis was performed for inflammatory reactions evident in the cerebrospinal fluid (2,11). All MRI examinations, which were completed within 13–15 min, 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, WI) and a quadrature head coil were

used for all MRI examinations. We used the pulse sequences reported in a previous study (10).

Definition of variables

We defined TCH as severe pain that peaked rapidly (within seconds) and was diagnosed by a thorough interview of the patient. When a TCH had disappeared for at least 12 h, we requested the patient to report it, and carried out MRI as soon as possible before taking any other steps. When a TCH did not recur, we judged this timing to indicate remission of TCH, which was defined as "the time at which the last TCH improved". Systolic blood pressure >180 mmHg or diastolic blood pressure >120 mmHg was considered a hypertensive emergency.

SAH not caused by trauma or an aneurysm with clots that were present over the cerebral convexity, but which did not involve the basal cistern, was defined as cortical SAH (12). A characteristic pattern of vasogenic edema and hemispheric boundary zones of hyperintensities on FLAIR, plus increased but variable apparent diffusion coefficient values in the cortex and subcortical and deep white matter, was defined as posterior reversible encephalopathy syndrome (PRES) (2,13). Some RCVS patients had cerebral lesions including PRES and any variety of stroke (SAH, intracerebral hemorrhage (ICH), and infarction), and other patients did not have cerebral lesions (they had a normal brain MRI, both initial MRI and MRI at the time of TCH remission).

White matter hyperintensity (WMH) was defined as hyperintensity on FLAIR without hyperintensity on T1-weighted imaging. Progression of WMH after RCVS was assessed by comparison of MRI at onset and 3 months after onset. We assessed progression of periventricular WMH with the Fazekas scale (14), and WMH progression was considered to be present if visual rating increased by at least 1 grade. Progression of deep and subcortical white matter hyperintensity (DSWMH) after RCVS was defined as the occurrence of new WMH in four subcortical white matter regions (frontal, parietal, occipital, temporal), the basal ganglia, and the infratentorial region.

MRA was used to assess localized vasoconstriction of cerebral arteries. We defined CPV as vasoconstriction that began in distal arteries (observed with MRA performed within 72 h of initiation of RCVS) and spread to the major cerebral arteries in the circle of Willis (defined as the internal cerebral artery, the A1 portion of the anterior cerebral artery, and/or the P1 portion of the posterior cerebral artery), as well as the M1 portion of the middle cerebral artery (MCA), basilar artery, and vertebral artery, on repeated MRA performed multiple times after the first MRA. We assessed CPV by analyzing serial MRA examinations performed at different time points after headache onset, namely within 72 h of RCVS onset, from 72 h of RCVS onset to TCH remission, within 48 h of TCH remission, within 14 days after TCH remission, and finally, 2–3 months after the onset. Even if the initial MRA was normal, patients with vasoconstriction of distal arteries on MRA a few days after onset were defined as patients with RCVS, and we assessed CPV on follow-up MRA. We divided RCVS patients into two groups depending on the presence or absence of CPV on MRA at the time of TCH remission and examined differences in clinical features and time-dependent changes in MRA.

Two senior stroke neurosurgeons (M.S. and S.O.) with 34 and 29 years of experience, respectively, evaluated all MRIs. When the neurosurgeons disagreed about the findings, they consulted with each other to reach a consensus. The modified Rankin scale was used to assess patient outcomes at 3 months after onset.

Treatment protocol

Vasoactive drugs were discontinued in all patients. Medication was used to alleviate pain in all patients as needed. For prophylaxis of cerebral vasoconstriction, we prescribed oral lomerizine hydrochloride. No steroids were prescribed. A low dose of propofol (30–50 mg/h) was administered intravenously in patients with severe TCH. For two of five patients who experienced a hypertensive emergency, a small amount of nicardipine (0.5–2 mg) was administered with one-shot intravenous infusion of a dose adapted to normalize blood pressure levels.

Institutional Review Board approval

Study approval was obtained from the Institutional Review Board for Clinical Research (16R-224) and Conflict of Interest management committee (16-365) at our university. We performed MRI after obtaining oral informed consent from each patient.

Statistical analysis

The significance of clinical factors potentially associated with CPV at the time of TCH remission was determined by the two-tailed Fisher's exact test. Continuous variables (age and duration of TCH) were tested using an independent sample two-tailed Student's t test. A p value < 0.05 was considered significant. All statistical analyses were performed using a commercially available software program (SPSS v. 22.0 for Windows, Mehta and Patel/SPSS, Chicago, IL).

Results

Clinical features

The clinical features of the 48 RCVS patients, all of whom underwent MRI within 72 h of RCVS onset and within 48 h of TCH remission, are shown in Table 1. The overall incidence of CPV on MRA obtained at the time of TCH remission, compared with MRA at the time of RCVS onset, was 50% (24 of 48 cases). In RCVS patients without CPV at the time of TCH remission, the frequencies of a history of migraine (71%: 17 of 24 cases) and migraine with aura (29%: 7 of 24 cases) were higher, but the difference was not statistically significant. No other significant

Table 1. Clinical features in patients with reversible cerebral vasoconstriction syndrome with and without centripetal propagation of vasoconstriction at the time of thunderclap headache remission.

	RCVS with CPV at the time of TCH remission	RCVS without CPV at the time of TCH remission	*p* value	All patients
No. of patients	24 (50%)	24 (50%)		48
Age (years)				
Mean ± SD	42 ± 13	37 ± 12	0.219	40 ± 13
Range	13–70	25–61		13–70
Gender (M/F)	6:18	7:17	1.000	8:30
History of migraine (aura)	13 (54%)	17 (71%)	0.371	30 (63%)
	3 (13%)	7 (29%)	0.286	10 (21%)
History of hypertension	2 (8%)	1 (4%)	1.000	3 (6%)
History of smoking	2 (8%)	5 (21%)	0.416	7 (15%)
Trigger				
Sexual activity	0	0	–	0
Pregnancy or postpartum	3 (13%)	5 (21%)	0.701	8 (17%)
Emotional situations	11 (46%)	13 (54%)	0.773	24 (50%)
Bathing-related	2 (8%)	1 (4%)	1.000	3 (6%)
Overuse of triptan	0	2 (8%)	0.489	2 (4%)
Illicit drug use	0	0	–	0
SSRI use	5 (21%)	1 (4%)	0.188	6 (13%)
Symptom				
Multiple episodes of TCH	22 (92%)	23 (96%)	1.00	45 (94%)
TCH-associated symptom				
Nausea	16 (67%)	14 (58%)	0.766	30 (63%)
Vomiting	7 (29%)	5 (21%)	0.740	12 (25%)
Photophobia	5 (21%)	1 (4%)	0.188	6 (13%)
Phonophobia	4 (17%)	2 (8%)	0.666	6 (13%)
Transient visual disturbance	2 (8%)	6 (25%)	0.245	8 (33%)
Consciousness disturbance	2 (8%)	1 (4%)	1.000	3 (6%)
Weakness	3 (13%)	0	0.234	3 (6%)
Epilepsy	1 (4%)	1 (4%)	1.000	2 (4%)
Hypertensive emergency	4 (17%)	1 (4%)	0.348	5 (10%)
Drug administered as a treatment for RCVS				
Lomerizine	7 (29%)	4 (17%)	0.494	11 (23%)
Propofol	5 (21%)	7 (29%)	0.740	12 (25%)
Nicardipine	4 (17%)	1 (4%)	0.348	5 (10%)

RCVS: reversible cerebral vasoconstriction syndrome; CPV: centripetal propagation of vasoconstriction; SD: standard deviation; M: male; F: female; TCH: thunderclap headache; SSRI: selective serotonin reuptake inhibitor.

Values represent n (%) unless otherwise stated.

Percentages in the "Number of patients" row show the percentages of the total number of patients, whereas percentages in the "with CPV" and "without CPV" columns indicate the percentages of patients with and without CPV, respectively.

differences were noted between the patient groups for any other clinical features including drugs administered to treat RCVS such as lomerizine, propofol, and nicardipine.

The interval from first to last TCH

The interval from first to last TCH in both groups is summarized in Table 2. The interval from first to last TCH in the RCVS patients with CPV at the time of TCH remission (14 ± 10 days) was significantly longer than that of RCVS patients without CPV (4 ± 2 days) (two-tailed Student's t test: $p < 0.001$). Moreover, the frequency of an interval from first to last TCH of more than 7 days after onset was significantly higher in the RCVS patients with CPV at the time of TCH remission (79%) (Fisher's exact test: $p < 0.001$).

Timing of MRI

The timing of MRI in both groups (RCVS patients with or without CPV) is summarized in Table 2. In all patients, a mean delay of 24 h (range, 1–71 h) was seen between RCVS onset and initial MRI. No significant difference was found between the groups in the mean delay from onset to initial MRI. In 58% or more of patients in both groups, initial MRI was performed on day 0 (i.e. within 24 h of onset). On the other hand, the mean delay from onset to MRI at the time of TCH remission in the RCVS patients with CPV (12 ± 7 days) was significantly longer than that of RCVS patients without CPV (4 ± 2 days) (two-tailed Student's t test: $p < 0.001$).

In the RCVS patients with CPV at the time of TCH remission, sequential MRI that was obtained from 72 h after onset to TCH remission was performed in 12 patients (50%). Among these 12 patients, the MRI of 11 patients showed findings of CPV before TCH remission, and the findings of CPV progressed and became clear on MRI at the time of TCH remission (Figure 1(a)–(c)). On the other hand, in the RCVS patients with CPV at the time of TCH remission, sequential MRA that was obtained within 14 days after TCH remission was performed in 15 patients (63%). However, the findings of CPV did not

Table 2. Interval from first to last thunderclap headache and centripetal propagation of vasoconstriction, and timing of initial MRA and MRA obtained at the time of TCH remission.

	RCVS with CPV at the time of TCH remission	RCVS without CPV at the time of TCH remission	p value	All patients
No. of patients	24 (50%)	24 (50%)		48
Interval from first to last TCH				
Mean ± SD (days)	14 ± 10	4 ± 2	<0.001	9 ± 9
Range (days)	4–49	2–9		2–49
Interval from first to last TCH of more than 7 days after onset	19 (79%)	1 (4%)	<0.001	20 (42%)
Timing of MRI				
Sequential MRI that was obtained from 72 h after onset to TCH remission	12 (50%)	0	–	12 (25%)
MRI at the time of TCH remission (days after onset) Mean ± SD (range)	12 ± 7 (4–30)	4 ± 2 (2–10)	<0.001	8 ± 6 (2–30)
More than 7 days after onset	18 (75%)	3 (12%)	< 0.001	21 (43%)
Sequential MRA that was obtained within 14 days after TCH remission	15 (63%)	9 (38%)	–	24 (50%)
Final MRI that was obtained 2–3 months after onset	24 (100%)	24 (100%)	–	48 (100%)

RCVS: reversible cerebral vasoconstriction syndrome; TCH: thunderclap headache; CPV: centripetal propagation of vasoconstriction; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography.

Values represent n (%) unless otherwise stated.

Percentages in the "Number of patients" row show the percentages of the total number of patients, whereas percentages in the "with CPV" and "without CPV" columns indicate the percentages of patients with and without CPV, respectively.

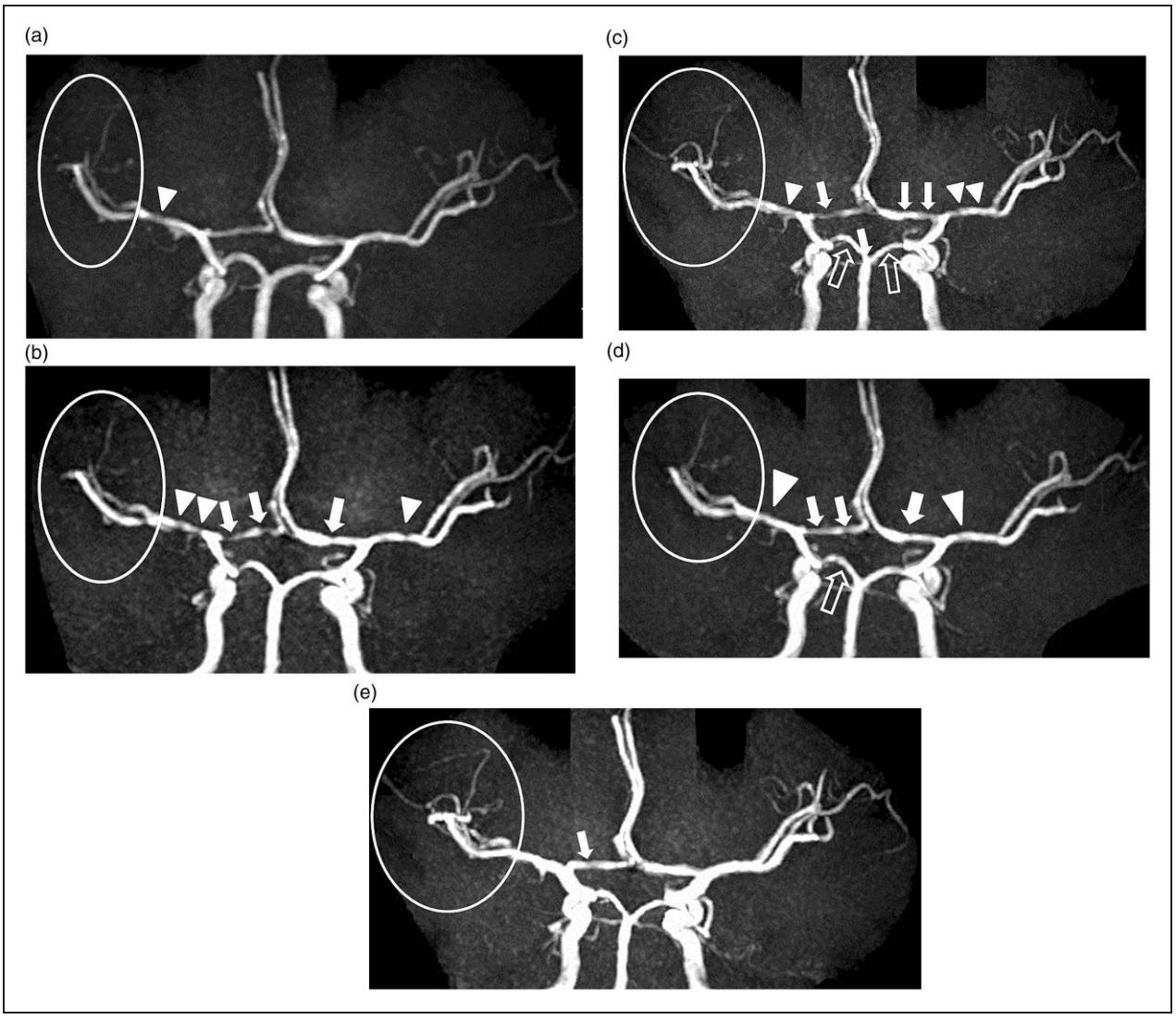

Figure 1. Images from a 28-year-old woman with puerperium-related reversible cerebral vasoconstriction syndrome. The patient was admitted to the hospital 2 h after onset. (a) The initial magnetic resonance angiography (MRA) obtained 3 h after the onset of thunderclap headache (TCH) shows vasoconstriction in the right M2-3 portions (circle) and terminal of the M1 portion of the middle cerebral artery (white arrowhead). (b) MRA obtained 6 days after onset shows centripetal propagation of vasoconstriction (CPV) in the bilateral M1 portions (white arrowheads) and A1 portions of the anterior cerebral arteries (white arrows). Vasoconstriction of the right M2-3 portion remains (circle). (c) MRA obtained at the time of TCH remission (12 days after onset of TCH) shows progress of CPV in the bilateral P1 portions of the posterior cerebral artery (open arrows). Vasoconstriction of the right M2-3 portion remains (circle). (d) MRA obtained 16 days after onset shows conclusion of CPV. Vasoconstriction of the bilateral A1 (white arrows), M1 (white arrowheads), and P1 (open arrow) portions tends to improve. Vasoconstriction of the right M2-3 portion remains (circle). (e) MRA obtained 31 days after onset shows only mild vasoconstriction of the right M1 portion (white arrow). Vasoconstriction of the right M2-3 portion tends to improve (circle).

progress on sequential MRI after TCH remission (Figure 1(d), (e)).

In the RCVS patients without CPV at the time of TCH remission, sequential MRI that was obtained from 72 h after onset to TCH remission was not performed, because intervals between onset and TCH remission were too short in these RCVS patients. In the RCVS patients without CPV at the time of TCH remission, sequential MRA that was obtained within 14 days after TCH remission was performed in nine patients (38%); however, no patient had CPV on sequential MRI after TCH remission (Figure 2(a)–(c)).

Associated lesions

In the RCVS patients with CPV at the time of TCH remission, the incidence of cerebral lesions including PRES and any variety of stroke (SAH, ICH, and

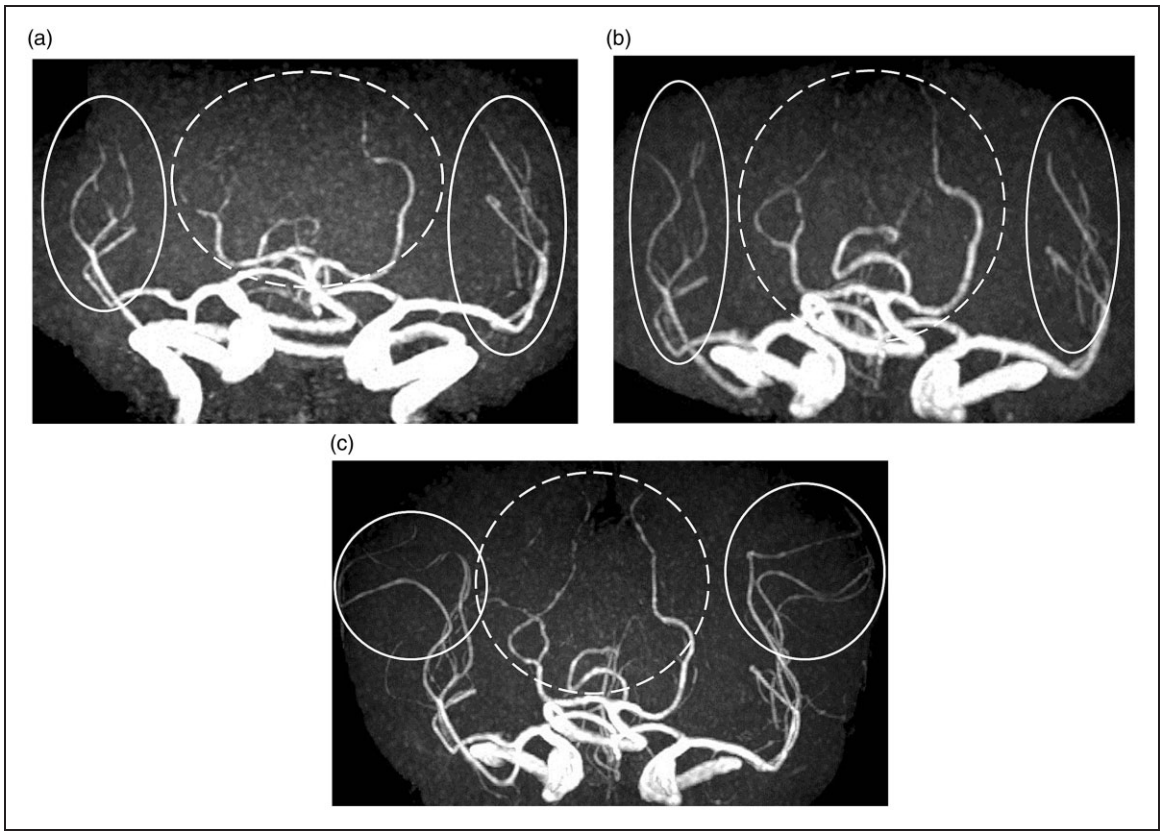

Figure 2. Images from a 50-year-old woman with reversible cerebral vasoconstriction syndrome. The patient was admitted to the hospital 6 h after onset. (a) The initial magnetic resonance angiography (MRA) obtained 7 h after the onset of thunderclap headache (TCH) shows vasoconstriction in the bilateral M2-3 portions of the middle cerebral artery (circles) and the P2-3 portion of the posterior cerebral artery (dotted circle). (b) MRA obtained at the time of TCH remission (5 days after onset of TCH) shows no findings of centripetal propagation of vasoconstriction (CPV) in the major cerebral arteries. Vasoconstriction of the bilateral M2-3 (circles) and P2-3 portion (dotted circle) remains. (c) MRA obtained 12 days after onset (5 days after TCH remission) also shows no findings of CPV in the major cerebral arteries. Vasoconstriction of the bilateral M2-3 (circles) and P2-3 portion (dotted circle) tends to improve.

infarction) as a complication of RCVS (38%, 9 of 24 cases) was significantly higher than in RCVS patients without CPV at the time of TCH remission (0%) (Table 3) (Fisher's exact test: $p = 0.002$). No other significant differences were noted between the patient groups for any other associated lesions.

Regarding a new associated lesion on MRI that developed after CPV, we encountered only one patient with such a lesion that was due to infarction. All other associated lesions were depicted on initial MRI (Table 3).

Location of vasoconstricted vessels on initial MRA and MRA obtained at the time of TCH remission

The location of vasoconstricted vessels on initial MRA and MRA obtained at the time of TCH remission is summarized in Table 3. On initial MRA at the time of onset, no statistically significant difference was found between the two groups regarding the frequencies of bilateral vasoconstriction, vasoconstriction of the M2 or M3 portion of the MCA, vasoconstriction of the P2 or P3 portion of the posterior cerebral artery, or vasoconstriction of the A2 or A3 portion of the anterior cerebral artery.

On the other hand, on MRA obtained at the time of TCH remission, in the RCVS patients with CPV at the time of TCH remission, the frequencies of vasoconstriction of the M1 portion of the MCA (75%) (Fisher's exact test: $p < 0.001$), vasoconstriction of the P1 portion of the posterior cerebral artery (71%) (Fisher's exact test: $p < 0.001$), vasoconstriction of the A1 portion of the anterior cerebral artery (50%) (Fisher's exact test: $p < 0.001$), and basilar artery (25%) (Fisher's exact test: $p = 0.022$) were significantly higher than those in RCVS patients without CPV.

In both groups, half or more of the vasoconstricted distal arteries (such as M2 or M3, P2 or P3, A2 or A3

Table 3. Vasoconstricted vessels on initial MRA and MRA obtained at the time of TCH remission.

	RCVS with CPV at the time of TCH remission	RCVS without CPV at the time of TCH remission	*p* value	All patients
No. of patients	24 (50%)	24 (50%)		48
Associated lesions on MRI Total number Initial MRI/ MRI at the time of TCH remission				
Cerebral lesion (SAH, PRES, infarction, ICH)	9 (38%) 8 (33%)/1 (4%)	0	0.002*	9 (19%) 8 (17%)/1 (2%)
Cortical SAH	4 (17%) 4 (17%)/0	0	0.109*	4 (8%) 4 (8%)/0
PRES	2 (8%) 2 (8%)/0	0	0.489*	2 (4%) 2 (4%)/0
Infarction	2 (8%) 1 (8%)/1 (8%)	0	0.489*	2 (4%) 1 (2%)/1 (2%)
ICH	1 (4%) 1 (4%)/0	0	1.000	1 (2%) 1 (2%)/0
No findings of vasoconstriction on initial MRA at the time of onset	1 (4%)	0	1.000	1 (2%)
Bilateral vasoconstriction on MRA	21 (88%)	21 (88%)	1.000	42 (88%)
Location of vasoconstriction on MRA (Initial MRA/MRA at the time of TCH remission)				
M2/3	22 (92%)/15 (63%)	19 (79%)/12 (50%)	1.000/0.561	41 (85%)/27 (56%)
P2/3	21 (88%)/18 (75%)	20 (83%)/15 (63%)	1.000/0.534	41 (85%)/33 (69%)
A2/3	4 (17%)/3 (13%)	3 (13%)/2 (8%)	1.000/1.000	7 (15%)/5 (10%)
M1	0/18 (75%)	0/0	–/<0.001	0/18 (38%)
P1	0/17 (71%)	0/0	–/<0.001	0/17 (35%)
A1	0/12 (50%)	0/0	–/<0.001	0/12 (25%)
IC	0/3 (13%)	0/0	–/ 0.234	0/3 (6%)
Ba terminal portion	1 (4%)/0	0/0	1.000/–	1 (2%)/0
Ba trunk	0/6 (25%)	0/0	–/0.022	0/6 (13%)
VA	0/3 (13%)	0/0	–/0.234	0/3 (6%)
Vasoconstriction of distal artery at the time of TCH remission				
Persistent	18 (75%)	16 (67%)	0.752	34 (71%)
Deterioration	6 (25%)	2 (8%)	–	8 (17%)

RCVS: reversible cerebral vasoconstriction syndrome; TCH: thunderclap headache; CPV: centripetal propagation of vasoconstriction; MRI: magnetic resonance imaging; SAH: subarachnoid hemorrhage; PRES: posterior reversible encephalopathy syndrome; ICH: intracerebral hemorrhage; MRA: magnetic resonance angiography; M: middle cerebral artery; P: posterior cerebral artery; A: anterior cerebral artery; IC: internal cerebral artery; Ba: basilar artery; VA: vertebral artery.

Values represent n (%) unless otherwise stated. *Significance of associated stroke lesions on MRI was calculated from data that were combined findings of initial MRI and MRI at the time of TCH remission.

Percentages in the "Number of patients" row show the percentages of the total number of patients, whereas percentages in the "with CPV" and "without CPV" columns indicate the percentages of patients with and without CPV, respectively.

portions) that were depicted on MRA persisted after remission of TCH, and the overall frequency of persistence of vasoconstricted distal arteries was 71% (34 of 48 cases) (Table 3).

Clinical features of the chronic stage

As seen on MRA, multifocal vasoconstriction, which disappeared within 12 weeks, was confirmed in all 48 RCVS

patients. No patients with progression of periventricular WMH were seen in either RCVS patient group. In RCVS patients with CPV at the time of TCH remission, the frequency of the progression of DSWMH (42%: 10 of 24 cases) was higher than in RCVS patients without CPV at the time of TCH remission (33%: 8 of 24 cases), but the difference was not statistically significant. DSWMH of 3 mm or more appeared only in five out of 48 patients (10%), four of whom were RCVS patients with CPV, but no significant difference was present. Three months later, the modified Rankin scale score was 0 in all 48 of these RCVS patients, and they were all able to resume their prior daily activities.

Multivariate analysis was not performed due to the small number of RCVS patients with CPV at the time of TCH remission ($n = 24$).

Discussion

Localization of vascular lesions that cause TCH in RCVS

The mechanisms of TCH are still speculative. One possible mechanism of TCH is that abrupt stretching of vessel walls due to sudden vasoconstriction and vasodilation in small distal vessels may stimulate perivascular pain-sensitive fibers of the trigemino-vascular system, causing TCH (5–7,15). In the RCVS patients in our study with or without CPV, more than 70% of the vasoconstricted distal arteries such as M2/3 or P2/3 that were depicted on MRA persisted at the time of remission of TCH. Similarly, vasoconstriction of major cerebral arteries became apparent as CPV on MRA at the time of TCH remission. Therefore, the fact that visible vasoconstriction persists and even continues to worsen after cessation of TCH shows that TCH is not due to the visible vasoconstriction of large and medium-sized cerebral arteries. In this study, we analyzed sequential MRI findings including MRI at the time of TCH remission, and our observations supported the hypothesis that TCH is not caused by vasoconstriction of large and medium-sized arteries (2,3). Thus, we infer that based on current knowledge of headache mechanisms, a process continues in more distal vessels that are invisible on MRA and could play a role in TCH. In the future, it will be necessary to study the concrete pathophysiology of these distal vessels including vasoconstriction, dilatation, or instability due to cerebral vascular tone dysregulation that causes TCH. Then, an effective treatment including pain relief of TCH could be developed.

The beginning and the conclusion of CPV in RCVS

Many researchers have described CPV in RCVS (2,5,6,16). Recently, Topcuoglu et al. inferred that the anatomic basis of CPV may be due to differences in the density and distribution of receptors that control arterial tone and the innervation of cerebral arteries from adrenergic and serotonergic pathways emanating from the hypothalamus, locus coeruleus, raphe nuclei, first division of the trigeminal nerve, and dorsal root of C2 (16). However, the precise mechanisms underlying CPV in RCVS remain unclear.

In our study, in the RCVS patients with CPV at the time of TCH remission, sequential MRI between onset and TCH remission showed findings of CPV before TCH remission, and the findings of CPV progressed and became clear on MRI at the time of TCH remission. Additional progress of CPV was not depicted on sequential MRI after TCH remission. On the other hand, in the RCVS patients without CPV at the time of TCH remission, CPV was not depicted on sequential MRI after TCH remission. From these results, we hypothesize that CPV gradually progresses after the onset of RCVS and peaks at the time of TCH remission. Thus, CPV does not progress after TCH remission.

Previous MRA studies by Chen et al. (3) have shown that maximal vasoconstriction scores are reached at a mean of 16 days after clinical onset, close to the average timing of headache resolution (mean 16 days). However, in terms of the timing of MRA, their study included a wide range of RCVS patients who had their initial MRA done within 30 days after headache onset (3). Because the initial MRA in this study was performed at a mean of 10.4 ± 7.0 days (median, 9 days; range, 1–30 days) after TCH onset (3), the number of patients who underwent initial MRA within 72 h of onset is low. In addition, MRI at the time of remission was not carried out routinely in their study. Thus, Chen reported that CPV at the time of remission was not frequent (3,5).

On the other hand, in Chen's study (3) and our study, the MRAs were not repeated (every 5–7 days) in all patients until the maximum vasoconstriction score was reached. However, from Chen's study (3) and our study, the fact that both the maximum vasoconstriction score and peak of CPV occurred at the time of TCH remission is extremely important. In other words, we believe that TCH remission may be a signal that the progression of both vasoconstriction and CPV has terminated.

Clinical significance of CPV in RCVS

In our study, the interval from first to last TCH in RCVS patients with CPV was significantly longer than that of RCVS patients without CPV. Furthermore, the incidence of brain lesions as a complication of RCVS was significantly higher in the RCVS patients with CPV. However, regarding the relevance of

a relationship between the presence of CPV and clinical/radiological worsening, only one patient developed infarction after CPV. Otherwise, eight (including one infarction) of nine brain lesions were identified on initial MRI at the time of onset. From these results, we believe that brain lesions, CPV, and a long interval from the first to last TCH occur in patients with severe dysfunctional regulation of cerebral vascular tone as a central element of the pathogenesis of RCVS at the time of onset that is caused by sympathetic overactivity, endothelial dysfunction, and oxidative stress. The severe dysfunctional regulation of cerebral vascular tone results in failure of autoregulation and breakdown of the blood-brain barrier, and will merge cortical SAH, PRES, ICH, and infarction, in the acute stage of RCVS. In the acute phase of RCVS, infarction could occur either due to abnormalities of distal vessels that cause TCH, or transformation of vasogenic edema into cytotoxic edema in patients with PRES (2). In addition, later in the course of RCVS, due to gradual progression of CPV from onset to TCH remission when the vasoconstriction of major vessels is added to the vasoconstriction at the M2/3 or P2/3 level, watershed infarction is more likely to develop. In the future, we need to accumulate more cases of RCVS for analysis of the relevance of the relationship between CPV and the timing of occurrence of other brain lesions.

As mentioned above, the cause of TCH is likely abnormalities of distal vessels that are not depicted on MRA. Therefore, in cases with a long interval from first to last TCH, abnormalities of peripheral vessels persist for a long time. Ducros (2) described that vasoconstriction of large cerebral arteries may represent a reaction to distal blood flow abnormalities as a pathophysiology of CPV. In our study, CPV gradually progressed after the onset of RCVS and peaked at the time of TCH remission. CPV did not continue to worsen upon TCH remission. Evidence of vasoconstriction increases with time, and thus we speculate that cases with long periods of distal vessel abnormalities due to severe dysfunctional regulation of cerebral vascular tone are likely to have CPV.

Diagnosis of RCVS without CPV

According to the International Classification of Headache Disorders version III-β, a diagnosis of primary TCH requires the strict exclusion of a secondary cause (17). CPV at the time of TCH remission is an informative neuroradiological finding that may allow diagnosis of RCVS with greater confidence if the clinician remains unsure of the diagnosis during the early stages of RCVS (10). Conversely, in RCVS patients without CPV, diagnosis of RCVS remains difficult because typical findings of segmental vasoconstriction of major vessels cannot be obtained. In general, MRA of healthy young individuals usually shows relatively good depiction of large and medium-sized arteries (18). Most patients with RCVS are 50 years of age or younger. Therefore, in young patients reporting TCH, if the depiction of distal vessels on MRA in the acute phase is relatively poor, evaluation of vasoconstriction of distal vessels should be conducted carefully, while considering a diagnosis of RCVS (10).

In this study, we experienced only one RCVS patient with normal findings on initial MRA at the time of onset. Despite having a typical recurrent TCH, many probable RCVS (RCVS without visible vasoconstriction) cases were not diagnosed and may have been overlooked, because sequential MRA was not performed due to normal initial MRA at the time of onset. We emphasize that adequate repeat MRA should be performed until the chronic phase (5,10,19) in patients with typical TCH to strictly rule out RCVS, even if the initial MRA at the time of onset is normal and CPV is not present at the time of TCH remission.

Limitations

To evaluate CPV in this study, we required that the first baseline MRI was performed in the acute phase within 72 h of RCVS onset. To judge the remission of lightning headache, we needed to confirm that no headache was present for at least 12 h, and thus, MRI at the time of TCH remission was defined as ''48 h within TCH remission''. However, as this is a retrospective study, and the criteria for selecting the patients were defined after all patients had undergone imaging studies, a selection bias may be present, and the possibility that this bias influenced the results cannot be excluded.

In this study, MRI findings were interpreted by senior stroke neurosurgeons, but they were not blinded about the timing of imaging. We also did not measure inter-rater reliability of MRI rating regarding the vasoconstriction and progression of WMH. However, in the case of disagreement between raters, diagnosis was obtained by consensus.

Because nimodipine has not been approved in Japan for use as a calcium channel antagonist for the prevention of vasospasm after SAH due to a ruptured aneurysm, we were unable to administer this drug. Therefore, our results may not apply to hospital facilities in which nimodipine is used. In addition, our results showed no significant differences between the patient groups administered various drugs to treat RCVS. We believe that the natural course of vasoconstriction was not likely to have been altered by treatment in some patients.

Due to flow turbulence at the stenotic portion and/or bent portion, several artifacts, and the small

diameter of peripheral vessels, even with the use of axial source images and MRA images created by 1.5-T MRI, exact measurement and evaluation of the degree of intracranial vessel stenosis are difficult to perform quantitatively (20). Therefore, we were unable to evaluate the severity of vasospasm. Instead, we repeatedly performed MRA in the same patient and tried to obtain accurate qualitative assessment of CPV.

Because sequential MRI that was obtained from 72 h after onset to TCH remission was not performed in all subjects, our hypothesis of gradual progression of CPV from onset to TCH remission was not supported in all cases. In RCVS patients without CPV, because MRI that was obtained within 14 days after TCH remission was not performed again in all subjects, we cannot strictly rule out the possibility that CPV will develop late after remission of TCH. Therefore, we cannot exclude the possibility that the absence of CPV on MRA at the time of TCH remission was a false negative finding as a consequence of an earlier sampling time.

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. Large, multicenter, prospective studies using inclusive diagnostic criteria (as proposed in our algorithm) would be valuable for examining associations, atypical manifestations, and prognosis. Further future investigations with high-resolution MRI vessel wall imaging, cerebral vasomotor reactivity testing using transcranial Doppler ultrasound (21), disease-specific biomarkers, and so on, in large cohorts of RCVS patients, are needed. These will help to increase our understanding of the pathology and will possibly suggest novel therapies.

Conclusions

CPV has clinical significance as an indicator of the severity of RCVS. The presence of CPV is associated with an increased risk of brain lesions and a longer interval from first to last TCH. Moreover, by repeating MRA during the period from onset to TCH remission, assessing CPV can be useful for the diagnosis of RCVS. We hypothesize that CPV gradually progresses after the onset of RCVS, peaks at the time of TCH remission, and does not progress further upon TCH remission. When sufficient repeat MRAs are not carried out, RCVS patients without CPV may be misdiagnosed with primary TCH. Because the frequency of persistent vasoconstriction in distal arteries at the time of TCH remission as depicted on MRA was high, one cause of TCH in RCVS patients may be abnormalities of more distal arteries.

Clinical implications

- Because the frequency of persistent vasoconstriction in distal arteries at the time of thunderclap headache (TCH) remission as depicted on magnetic resonance angiography (MRA) was high, one cause of TCH in patients with reversible cerebral vasoconstriction syndrome (RCVS) may be abnormalities of more distal arteries.
- Centripetal propagation of vasoconstriction (CPV) has clinical significance as an indicator of the severity of RCVS. The presence of CPV is associated with an increased risk of brain lesions and a longer interval from first to last TCH. From results of sequential MRA, CPV gradually progresses after the onset of RCVS, peaks at the time of TCH remission, and does not progress further upon TCH remission.
- CPV gradually progresses, and thus, by repeating MRA during the period from onset to TCH remission, assessing CPV can be useful for the diagnosis of RCVS in the acute stage.
- In young patients reporting TCH, if the depiction of distal vessels on MRA in the acute phase is relatively poor, evaluation of vasoconstriction of distal vessels should be conducted carefully, while considering a diagnosis of RCVS. We emphasize that adequate repeat MRA should be performed until the chronic phase to strictly rule out RCVS, even if the initial MRA at the time of onset is normal and CPV is not present at the time of TCH remission.

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