



A survey of clinical symptoms with RCVS in a Japanese regional headache center

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Introduction

- Reversible cerebral vasoconstriction syndrome (RCVS) manifests various clinical and radiologic features, which mainly involve sudden onset of thunderclap headache (TCH) and segmental vasoconstriction of cerebral arteries that resolves in 1 to months [1, 2].
- RCVS can either occur spontaneously or relate to an exposure trigger, but the precise pathophysiology of RCVS remains unknown [3]. Postulated mechanisms include small vessel and endothelial dysfunction, microthrombotic dysfunction with oxidant stress, hormonal and biochemical factors, and genetic predisposition [3].
- Most RCVS patients have a favorable prognosis; however, for some patients, the condition may result in permanent disability or even death in a small minority of patients, secondary to complications such as ischemic stroke or intracerebral hemorrhage [2, 3].
- Several studies have reported meaningful findings for RCVS; however, characteristics of RCVS in Japan remain inconclusive. Thus, we have characterized the clinical profile of RCVS in Japan by surveying RCVS patients.

Subjects and Method

- The Headache Center: Tomioka hospital located in Osaka, Japan
- Survey period: February 2011- January 2019; 8 years
- Diagnostic:
 - RCVS-2/ICHD-3-structured questionnaires
 - Full neurological examination
 - RCVS was diagnosed based on the diagnostic criteria of Calhoun et al.
 - Cerebrospinal fluid (CSF) analysis was performed only if subarachnoid hemorrhage could not be ruled out.
- In cases with suspected RCVS and no vasospasm in the first magnetic resonance angiography (MRA)/computed tomography angiography (CTA), multiple imaging tests were performed.
- Diagnosis of "Headache attributed to RCVS" was based on ICHD-3.
- Number of patients with RCVS: 32 (M:F=5:27)
- Mean age: 44.9 ± 15.5 (SD) yrs (range 17-61 yrs)
- The clinical characteristics of cases with RCVS were examined retrospectively by medical chart.

Diagnostic criteria for RCVS

- Thunderclap headache or transient CTA or MRA documenting multifocal segmental cerebral artery vasoconstriction
- No evidence for aneurysmal subarachnoid hemorrhage
- Normal or absent meningeal cerebrospinal fluid analysis (protein level < 80 mg/dL, leukocyte < 10/mm³, normal glucose level)
- Severe, acute headache, with or without additional neurologic signs or symptoms
- Reversibility of angiographic abnormalities within 12 weeks after onset.
- If death occurs before the follow-up studies are completed, autopsy rules out such conditions as aneurysmal, intracerebral, subarachnoid, and meningeal subarachnoid hemorrhage, which can also manifest with headache and stroke

Result

Demographic data of the study population

	N
Age, yrs ± (SD) (range)	44.9±15.5 (17-61)
Sex, females	27 (84.3%)
History of migraine	17 (53.1%)
Hypertension	5 (15.6%)

Personal history of migraine was assessed in all patients by headache specialist certified by Japan Headache Society according to the diagnostic criteria of ICHD-3/ICHD-3. Hypertension was defined as systolic blood pressure ≥160/90 Hg and diastolic pressure ≥100 Hg in two separate measurements after the acute phase or use of antihypertensive drugs before recruitment.

Cause of RCVS

Identities	27 (84.4%)
<ul style="list-style-type: none"> Drug induced: 4 Selective serotonin reuptake inhibitors: 2 Antidepressants: 2 Mefenamic acid: 1 	
<ul style="list-style-type: none"> Idiopathic: 1 Coding system: 1 Prophylactic complication: 0 Postoperative: 0 	

Precipitating conditions associated with RCVS

Trigger	N
No trigger	12 (37.5%)
Urination / Defecation	5 (15.6%)
Walking	4 (12.5%)
Cough	4 (12.5%)
Intense exercise	3 (9.4%)
Sexual activity	3 (9.4%)

Twenty cases (62.4%) had some trigger of RCVS.

Days from TCH onset to consultation

Days	N
0-5	12 (37.5%)
6-9	9 (28.1%)
10-11	11 (34.4%)
Mean	10.4 ± 1.1

Days from TCH onset to vasospasm

Days	N
0-7	30 (93.8%)
8-14	14 (43.8%)
15-18	8 (25.0%)
Mean	13.2 ± 13.0

Number of MRA and CTA until vasospasm was revealed.

Number of MRA and CTA	N
1 time	12 (37.5%)
2 times	17 (53.1%)
3 times	3 (9.4%)
Mean	1.7 ± 0.6

First MRA or CTA was normal in 20 cases (62.5%) with RCVS.

Cerebrospinal fluid analysis

- Lumbar puncture was performed in 15 (46.9%) cases.
- All had normal CSF cell counts and CSF protein.
- Slightly elevated CSF protein was shown in one case.

Days from TCH onset to disappearance

Days	N
0-14	12 (37.5%)
15-26	15 (46.9%)
29-30	5 (15.6%)
Mean	19.5 ± 9.2

TCH of 27 cases (84.4%) with RCVS disappeared within 30 days.

Accompanied symptoms

Symptom	N
No neurological deficit	20 (60.6%)
Epilepsy	2 (6.3%)
Transient global amnesia	1 (3.1%)

Abnormality of neuroimaging

Abnormality	N
Cerebral infarction	0
Intracerebral hemorrhage	0
Cerebral subarachnoid hemorrhage	0
Posterior reversible encephalopathy syndrome	1 (3.1%)

Only one case (3.1%) had posterior reversible encephalopathy syndrome.

No case had stroke such as cerebral infarction, intracerebral hemorrhage, and cerebral subarachnoid hemorrhage.

Summary of selected studies including large series of RCVS patients.

	Chen et al., 2010 (n=77) [4]	Kata et al., 2014 (n=76) [5]	Shigfal et al., 2016 (n=130) [6]	Chen et al., 2017 (n=130) [7]	Chen et al., 2018 (n=173) [9]	de Boysson et al., 2018 (n=173) [9]	James et al., 2019 (n=40) [10]	Cetin et al., 2019 (n=102) [11]	Present study
Recruitment	Retrospective, from a headache clinic	Prospective, from two centers with emergency unit	Retrospective, from a single center with emergency unit and stroke unit	Prospective, from a single center with headache clinic, emergency unit, and stroke unit	Prospective, from a single center with headache clinic and department	Prospective, from a single center with emergency unit and stroke unit	Retrospective, from a regional, high-volume comprehensive headache clinic and stroke center	Retrospective, from a network of neurological centers with emergency unit, comprehensive headache clinic, and inpatient consultation	Retrospective, from a single headache center
Demographics	2002-2008 Taiwan	2004-2012 U.S., Argentina	1996-2015 U.S.	2012-2016 Korea	2010-2017 Taiwan	2004-2015 France	2012-2015 U.S.	2010-2018 Italy	2011-2019 Japan
Age, yrs	47.7 ± 11.6	47 (32.54)	43.5 ± 13	50.2 ± 12.1 (median RCVS) 52.0 ± 12.6 (median stroke)	50.1 (26-67)	44.0 (17-85)	48.5 (20-67)	47.2 ± 13.9 (only definite RCVS)	46.0 ± 15.5 (only definite RCVS)
Sex, female	82.6	88.1	77	89.2	89.2	70.5	70.7	83.3	84.8
History of migraine	10.6	27.1	42	16.6	24.6	32.3	29.7	21.8	33.1
History of hypertension	24.7	22.0	37	20.2	10.8	15.0	-	33.3	15.6
Any previous stroke	8	69.5	50	15.4*	9.2	57.2	60.0	20.6	17.2
Prophylaxis	1	29.8	30	4.8*	0	3.1	7.5	7.8	0
Drug induced	3	40.7	69	5.8*	15.3	49.1	62.0	17.0	12.5
TCH	100.0	89	89	89.8	89.2	94.0	65.0	67.6	100.0
Any trigger for headache	80	-	19	37.5*	-	77.0	-	28.4	62.4
Focal neurological deficit	34	33.9	40	4.3	-	23.7	60.0	16.7	0
Ischemic infarction	1.2	3	15	2.1	-	5.2	10.0	16.7	6.3
ICH/SAH	0	25.4	30	5.0	1.5	27.2	77.8	10.7	0
CA/SAH	0	20.1	13	2.3	0	18.5	50.0	7.0	0
Cerebral aneurysm	7.7	3.1	32	4.3	1.4	7.4	25.3	11.2	0
PRES	0.1	6.8	25	3.8	4.0	-	-	36.4	0
CSF analysis	58	76	76	-	-	61.0	-	28.6	15.6
Death	0	8.8	2.5	-	-	-	0	2.5	-
Permanent focal neurological deficit	3	13.6	12	-	-	11.0	80.0	-	0

TCH: thunderclap headache; eSAH: cerebral subarachnoid hemorrhage; ICH: intracerebral hemorrhage; PRES: Posterior reversible encephalopathy syndrome; CSF: cerebrospinal fluid

*Only patients with definite RCVS were included in this analysis