Article

Reversible Cerebral Vasoconstriction Syndrome: A Comprehensive Systematic Review

Tae-Jin Song1, † , Keum Hwa Lee2,† , Han Li3†, Jung Yoon Kim2, Kathleen Chang4, Seong Heon Kim5, Kyoung Hee Han6, Bo Yi Kim7, Andreas Kronbichler8, Anne Ducros9, Ai Koyanagi10,11, Louis Jacob10,12, Min Seo Kim13,14, Dong Keon Yon15, Seung Won Lee16, Jee Myung Yang17, Sung Hwi Hong18,19, Ramy Abou Ghayda18,20, Joon Won Kang21,\*, Jae Il Shin2,\* and Lee Smith22

1Department of Neurology, Ewha Womans University Mokdong Hospital, Seoul, South Korea

2Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Republic of Korea

3University of Florida College of Medicine, Gainesville, FL 32610, USA

4Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia

5Department of Pediatrics, Pusan National University Children's Hospital, Yangsan, South Korea

6Department of Pediatrics, Jeju National University School of Medicine, Jeju, South Korea

7College of Medicine, Ewha Womans University, Seoul, South Korea

8Department of Internal Medicine IV, Medical University Innsbruck, Innsbruck, Austria

9Department of Neurology, Montpellier University Hospital, Montpellier, France

10Parc Sanitari Sant Joan de Déu/CIBERSAM, Universitat de Barcelona, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona 08830, Spain

11ICREA, Pg, Lluis Companys 23, Barcelona 08010, Spain

12Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux 78180, France

13Korea University, College of Medicine, Seoul, Republic of Korea

14Cheongsan Public Health Center, Ministry of Health and Welfare, Wando, Republic of Korea

15Department of Pediatrics, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea

16Department of Data Science, Sejong University College of Software Convergence, Seoul, Republic of Korea

17Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

18Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA; sunghwihong@gmail.com (S.H.H.); ramy.aboughayda@gmail.com (R.A.G.)

19Yonsei University College of Medicine, Seoul 03722, Republic of Korea

20Division of Urology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA 21Department of Pediatrics, Chungnam National University College of Medicine, Daejeon, South Korea

22The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge CB1 1PT, UK

Tae-Jin Song, Keum Hwa Lee, and Han Li contributed equally to this work.

**\*** Co-correspondence:

Prof. Jae Il Shin; Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Korea; Tel: +82-2-2228-2050; [shinji@yuhs.ac](mailto:shinji@yuhs.ac); Address: Yonsei-ro 50, Seodaemun-gu, C. P. O. Box 8044

Prof. Joon Won Kang; Department of Pediatrics, Chungnam National University College of Medicine, 282 Munwha-ro, Jung-gu, Daejeon 35015, South Korea; Tel: +82-42-280-8244 Fax: +82-42-255-3158; childlove@cnu.ac.kr

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**Abstract: — OBJECTIVE:** We aimed to analyze clinical characteristics, treatment patterns, and prognosis of patients with reversible cerebral vasoconstriction syndrome (RCVS).

**MATERIALS AND METHODS**: Two investigators independently searched PubMed and EMBASE, and 191 cases were included in this study. Information regarding demographics, triggering factors, brain imaging findings, treatment modalities, recurrence, and clinical outcome were collected.

**RESULTS:** The mean age of the patients was 39.9 years, and 155 (81.2%) were female. The most common triggering factor for RCVS was an exposure to vasoactive substances (41.4%), followed by pregnancy/postpartum (20.9%), and sexual intercourse (10.5%). Multifocal stenosis (84.0%) and beading shape (82.4%) were the leading abnormal findings on angiography, while cerebral ischemic lesions (47.6%) and cerebral hemorrhage (mainly subarachnoid hemorrhage) (35.1%) were main findings on brain computed tomography (CT)/magnetic resonance imaging (MRI). Calcium channel blockers (nimodipine/verapamil) were the most commonly used medications (44.5%) in the treatment of RCVS. Multivariate analysis identified that RCVS was precipitated by trauma/surgery/procedure (hazard ratio (HR): 3.29, 95% confidence interval (CI) (1.21–8.88), p=0.019), and presence of aphasia/neglect/apraxia during the acute phase of the disease (HR: 3.83, 95% CI (1.33–11.05), p=0.013) were found to be the two independent risk factors for residual neurological deficit after RCVS.

**CONCLUSIONS:** In our systematic review, vasoactive substances were most frequent triggers for RCVS, which was most commonly accompanied by angiographic findings of multifocal stenotic lesions. Patients with RCVS precipitated by trauma or surgical procedures and those with focal cortical deficits had a higher risk of residual neurological deficits, and these patients should closely be monitored.

**Keywords:**

Reversible cerebral vasoconstriction syndrome; Call-Fleming syndrome; Benign angiopathy of the central nervous system; Thunderclap headache; Reversible vasospasm; Migrainous vasospasm; Drug-induced cerebral arteritis; Postpartum cerebral angiopathy; Central nervous system pseudovasculitis

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches, often thunderclap headaches, with or without focal deficits and seizures, and a multifocal constriction of cerebral arteries, which generally resolves spontaneously within 3 months 1. The thunderclap headaches are described by the International Classification of Headaches as sudden high-intensity headaches, described "thunderclap" because they reach maximum intensity within seconds 2. In the context of RCVS, they are triggered frequently following vasoconstrictor exposure, postpartum, or neurosurgical procedures, though it is possible that there may be additional triggers not described by the available case reports in the literature 2. On imaging, RCVS is accompanied by a "string of beads" appearance of cerebral vessels due to the alternating, simultaneous dilatation and constriction, both of which (dilatation and constriction) resolve completely within 3 months 2. Although RCVS predisposes toward transient ischemic attack, stroke, and other constrictive diseases of cerebral vessels, the syndrome possesses distinct factors on history and clinical findings. Namely, transient ischemic attacks and stroke involve acute neurologic defects resultant of underlying ischemia, while RCVS can present as vasoconstriction of cerebral arteries with or without presence of ischemia or neurologic symptoms. Furthermore, RCVS cannot be diagnosed if subarachnoid hemorrhage 2. RCVS tends to occur over a period of one week to a month, and more acute symptoms that resolve more rapidly than this time period should raise suspicion for other phenomena, including transient ischemic attacks or cold-stimulus headaches. Recently, it has been argued that RCVS should be considered as multiple disorders accompanied by reversible vasoconstriction of cerebral vessels rather than a single disease 2-4.

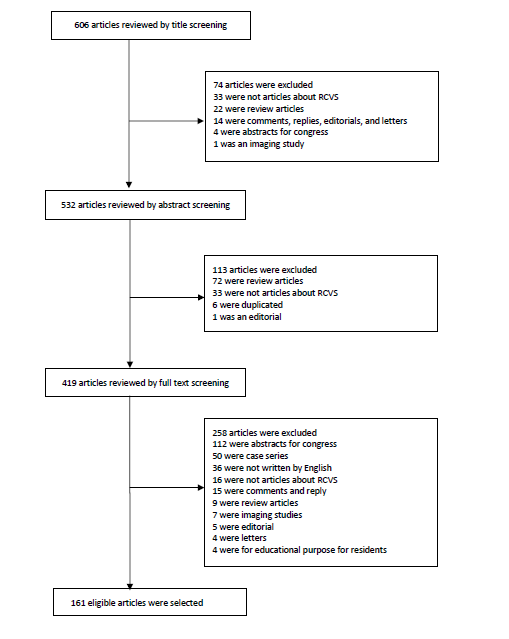
Before the name RCVS was proposed and the diagnostic criteria published in 2007, the symptoms of RCVS were described under various other names 5. After the diagnostic criteria for RCVS were published, the diagnosis of RCVS increased due to improved imaging and diagnostic approaches, and the number of articles related to this disease have continuously increased 2, 5, 6. Although RCVS has been thought to be mostly "reversible" with a good prognosis 7, 8, several studies, including large series, showed that cerebral infarction and/or cerebral hemorrhage were the main complications of this syndrome. Furthermore, this syndrome may also be accompanied by reversible brain edema consistent with a posterior reversible encephalopathy syndrome (PRES) in the postpartum state 9, 10, suggesting that this syndrome may not always have a favorable or reversible prognosis. Furthermore, recurrence of RCVS has also been reported 9, 11-13.

Whereas the clinical features and the various causes of RCVS have been described in sporadic case reports, there have been few reports on the patterns of imaging, treatment options, and the outcomes related to prognosis. Therefore, the aim of this study was firstly to analyze clinical characteristics, treatment patterns, and prognosis of the patients with RCVS by a systematic review approach and to find the risk factors for the residual neurological deficits after RCVS events.

Materials and Methods

**Search strategy for the literatures and study selection**

We performed an English literature search to systematically collect the case reports of RCVS. The PRISMA guidelines were followed during data extraction, analysis, and reporting 14. Two investigators (JW Kang and TJ Song) independently searched PubMed and EMBASE and extracted the data. Most of the articles retrieved from PubMed were duplicated in EMBASE. The search term was: “Reversible cerebral vasoconstriction syndrome” or “RCVS”. Reports of pediatric cases (below the age of 18) were not excluded. We labeled all the articles by examining titles, abstracts, and full texts in order, and any discrepancies were discussed and resolved by consensus among the 3 investigators (JW Kang, TJ Song, and JI Shin). The detailed process of screening and selection of articles is presented in Fig 1 (supplemental references). Among these, 188 cases showed a confirmed RCVS with multifocal vasoconstriction on computed tomography (CT)/magnetic resonance imaging (MRI) or transfemoral angiography and normalized angiography within 3 months, and 3 cases had a confirmed RCVS by using the transcranial doppler method. A detailed flow-chart of screening and choosing eligible articles is presented in Figure 1.



**Figure 1.** Flow chart of literature search.

**Data extraction**

For each eligible case report, we extracted and recorded information about age, sex, ethnicity, potential triggers (medications and drugs, postpartum, sexual intercourse, smoking, exercise, travel, blood transfusion, energy drink intake, upper respiratory tract infection, surgery, tumor, emotional stress, peritoneal dialysis, shower, and Valsalva), usage of specific possible provocative medications and drugs for RCVS (such as antidepressants, addictive drugs, sympathomimetics, hormone substitution, etc.), past medical history (such as headache, psychologic diseases, hypertension, smoking, etc.), accompanying neurologic symptoms (such as headache, motor weakness, visual abnormality, seizure, mental change, etc.), other accompanying clinical manifestations (nausea, vomiting, pain, respiratory symptoms, etc.), frequency and type of performed imaging modality, brain parenchymal (ischemic or hemorrhagic lesions) and/or angiographic (multifocal, hemispheric, beading, and focal stenotic pattern) findings from CT and/or MRI, treatment modalities (medications and/or other interventions), radiologic outcome (improved (recovered) or not-improved (or progressed)), clinical outcome (fully recovery or residual deficit), and recurrence of RCVS.

**Statistical analysis**

Statistical analyses were performed using SPSS for Windows version 21.0 (IBM, USA) and MedCalc version 15.8 (MedCalc Software, Belgium). The independent t-test was used for continuous variables and the Chi-square or Fisher’s exact test for categorical variables. To find the factors associated with the residual neurologic deficit, univariate and multivariate Cox regression analyses were performed. For multivariate analysis, age, sex and the factors with a *p-value* < 0.1 in univariate analysis used as independent variables. All differences were considered statistically significant at a *p-*value < 0.05.

Results

Our literature search yielded 191 cases with a mean age of 39.9 ± 15.2 years (median 40, interquartile range 30 – 51 years), including 155 females (81.2%). There were 18 cases under the age of 18. Ethnicity was unknown in 82.7%. Out of those with known ethnicity, 5.8% were Asian, 8.4% were Caucasian, and 3.1% were African. All studies were published after the seminal 2007 publication establishing set diagnostic criteria. Diagnostic criteria was established by individual case reports but consisted of 1) multifocal segmental cerebral artery vasoconstriction on angiography, 2) absence of aneurismal subarachnoid hemorrhage, 3) normal or near-normal cerebrospinal fluid, 4) severe, acute headaches, and 5) reversibility of cerebral vasoconstriction within 12 weeks, or, if death occurs before 12 weeks, an autopsy rule out of other conditions that present with headache or stroke 2.

In most patients (88.5%), RCVS was secondary to various triggers, while only 22 (11.5%) had no identifiable causes (idiopathic RCVS). The most common potential triggers for RCVS were exposures to vasoactive medications and drugs (41.4%) and pregnancy/postpartum (20.9%). Twenty cases had a history of coitus (10.5%) as a trigger. Other potential triggers are listed in Table I. The most commonly reported provocative substances were antidepressants (n=20, 13.9%), addictive drugs (n=14, 9.7%), and sympathomimetic medications (n=12, 8.3%). Other possible provocative medications and drugs are listed in Supplementary Table I. Regarding past medical history, underlying or preexisting headache (particularly migraine) was the most common (21.9%) to associate with RCVS, and psychological diseases (10.9%), hypertension (8.3%), smoking (7.3%), and vascular disease (7.3%) were the major comorbid conditions (Table II).

**Table I.** Potential triggers of reversible cerebral vasoconstriction syndrome.

|  |  |  |
| --- | --- | --- |
| **Potential triggers** | **Total**  **(n = 191)** | **Detailed components of provocative factors** |
| Medications and drugs | 79 (41.4) |  |
| Pregnancy/postpartum | 40 (20.9) |  |
| Sexual intercourse | 20 (10.5) |  |
| Smoking | 7 (3.7) |  |
| Exercise | 5 (2.6) | Skiing, dive, road race, lifting weights, swimming |
| Travel | 4 (2.1) | 3 Airplanes, 1 high altitude |
| Blood transfusion | 3 (1.6) |  |
| Energy drink intake | 2 (1.0) |  |
| Upper respiratory tract infection | 2 (1.0) | Uterine artery embolization, nasal sinus surgery |
| Surgery | 2 (1.0) |  |
| Tumor | 1 (0.5) | Bronchial carcinoid tumor |
| Emotional stress | 1 (0.5) | Death of friends |
| Peritoneal dialysis | 1 (0.5) |  |
| Shower | 1 (0.5) |  |
| Valsalva | 1 (0.5) |  |
| Unidentifiable causes | 22 (11.5) |  |

Values are presented as number (percent).

**Table II.** Past medical histories of reversible cerebral vasoconstriction syndrome.

|  |  |
| --- | --- |
| **Past medical histories** | **Total**  **(n = 191)** |
| Headache (31 migraine, 7 unspecified, 3 sexual, 1 tension-type) | 42 (21.9) |
| Psychologic disease (18 depression, 1 obsessive compulsive disorder, 1 bipolar, 1 anxiety) | 21 (10.9) |
| Hypertension | 16 (8.3) |
| Smoking | 14 (7.3) |
| Vascular disease (2 fibromuscular dysplasia, 3 ICA stenosis or occlusion, 1 arterio-venous malformation, 1 cerebellar artery aneurysm, 1 renal artery stenosis, 1 atherosclerosis, 1 venous sinus stenosis, 1 aortic dissection, 1 moyamoya disease, 1 cerebral infarction, 1 hepatic artery constriction) | 14 (7.3) |
| Respiratory disease (4 asthma, 3 upper respiratory infection, 1 tonsillitis, 1 otitis media, 1 chronic obstructive pulmonary diseases) | 10 (5.2) |
| Hematologic disease (4 anemia, 3 leukemia, 1 myelodysplastic syndrome) | 8 (4.2) |
| Cardiac disease (2 valve disease, 1 tetralogy of Fallot, 1 hypertrophic cardiomyopathy, 1 dilated cardiomyopathy, 2 atrial fibrillation, 1 myocardial infarction) | 8 (4.2) |
| Dyslipidemia | 8 (4.2) |
| Tumor (prostate, breast, retinoblastoma, ovary, melanoma, bilateral carotid paraganglioma, benign neurinoma, each 1 case) | 7 (3.7) |
| Obstetric condition (2 miscarriages, menorrhagia, endometriosis, menstrual cycle disturbances, menopause, uterine myoma) | 7 (3.7) |
| Autoimmune disease (3 systemic lupus erythematous, 3 multiple sclerosis, Takayasu arteritis) | 7 (3.7) |
| Trauma (traffic accidents, spinal compression fractures, fall, tibia fracture) | 6 (3.1) |
| Nephrologic and urologic disease (Nephrotic syndrome, bladder diverticula, neurogenic bladder, nephrolithiasis, end-stage renal disease) | 5 (2.6) |
| Genetic abnormality (2 ATP1A2 gene mutation, 1 Loeys-Dietz Syndrome, 1 mitochondrial encephalomyopathy) | 4 (2.1) |
| Diabetes mellitus (including gestational diabetes mellitus) | 4 (2.1) |
| Preeclampsia (nonspecific, seizure before delivery, preeclampsia related hypertension) | 3 (1.6) |
| Hypothyroidism | 3 (1.6) |
| Obesity | 3 (1.6) |
| Drug allergy | 2 (1.0) |
| Blindness | 2 (1.0) |
| Neuropathy | 2 (1.0) |
| Musculo-skeletal symptom (neck pain, cervical spondylosis) | 2 (1.0) |
| Slow transit bowel syndrome | 1 (0.5) |
| Sleep apnea | 1 (0.5) |

Values are presented as number (percent).

**Table III.** Accompanying neurologic symptoms of reversible cerebral vasoconstriction syndrome.

|  |  |
| --- | --- |
| **Accompanying neurologic symptom** | **Total**  **(n = 191)** |
| Any types of headache | 178 (93.2) |
| Motor weakness (39 hemiparesis, 19 limbs, 8 face, 2 quadriplegia, 1 ptosis, 1 swallowing difficulty) | 70 (36.6) |
| Visual abnormality (13 anopsia, 12 blurred, 12 blindness, 8 visual disturbance, 7 visual field defects, 3 diplopia, 2 nystagmus, 1 scotoma) | 58 (30.4) |
| Mental change (18 confusion, 7 unconsciousness, 5 comas, 3 drowsy, 3 mental change, 2 stupor, 1 somnolent) | 39 (20.4) |
| Seizure (15 unspecified, 12 generalized tonic-clonic, 2 status epilepticus, 2 focal, 1 generalized tonic) | 32 (16.8) |
| Speech disturbance | 30 (15.7) |
| Sensory deficit | 26 (13.6) |
| Photophobia | 21 (11.0) |
| Reflex abnormality (10 hyperreflexia, 5 Babinski sign, 4 meningeal irritation signs, 1 pyramidal symptom, 1 areflexia) | 21 (11.0) |
| Phonophobia | 11 (5.8) |
| Dizziness | 10 (5.2) |
| Behavior abnormality (8 agitation, 2 visual hallucination) | 10 (5.2) |
| Functional deficit (3 apraxia, 3 dysmetria, 1 amnesia, 1 spatial neglect, 1 dysequilibrium) | 9 (4.7) |
| Gait abnormality (4 ataxia, 2 imbalance) | 6 (3.1) |
| Meningeal irritation sign | 4 (2.1) |
| Gaze abnormality | 3 (1.6) |
| Abnormal motor symptom (1 bradykinesia, 1 myoclonus) | 2 (1.0) |
| Cognitive impairment | 1 (0.5) |
| Osmophobia | 1 (0.5) |
| Ear fullness | 1 (0.5) |
| Urinary retention | 1 (0.5) |

Values are presented as number (percent).

The most common neurologic symptom of RCVS was headache (93.2%). Others were motor weakness (36.6%), visual abnormality (30.4%), mental change (20.4%), and seizure (17.3%). Other accompanying neurologic symptoms are listed in Table III. Nausea (26.7%) and vomiting (16.8%) were the most common accompanying non-neurological symptoms (see Supplementary Table II for detailed description).

Angiographic findings were reported for 188 of the 191 cases (98.4%) (Supplementary Table III) and mostly showed multifocal stenosis (84.0%) and beading shape (82.4%) (Table IV). CT/MRI revealed cerebral ischemic lesions (47.6%) and cerebral hemorrhage (35.1%) as leading parenchymal abnormalities. Among subjects with cerebral hemorrhage, subarachnoid hemorrhage (67.2%) was most commonly observed (Table IV).

**Table IV.** Radiologic findings of reversible cerebral vasoconstriction syndrome.

|  |  |
| --- | --- |
|  | **Cases, n (%)** |
| **Angiographic findings (n = 188)\*** |  |
| Multifocal stenosis | 158 (84.0) |
| Hemispheric stenosis | 16 (8.5) |
| Focal stenosis | 12 (6.4) |
| Normal | 2 (1.1) |
| Presence of beading shape | 155 (82.4) |
| **Brain image findings (n = 191)†** |  |
| Ischemic lesion | 91 (47.6) |
| Hemorrhage | 67 (35.1) |
| Subarachnoid hemorrhage | 45 (67.2) |
| Intracranial hemorrhage | 14 (20.9) |
| Subarachnoid + intracranial hemorrhage | 7 (10.4) |
| Subdural hemorrhage | 1 (1.5) |

Values are presented as number (percent).

\*: Brain angiographies were performed in 188 (98.4%) patients among total included 191 subjects.

†: Brain images were performed in total 191 patients.

Regarding treatment modalities, calcium channel blockers (79.1%, mainly nimodipine/verapamil) were most commonly used in the management of RCVS. After calcium channel blockers, analgesics (21.5%, mainly aspirin) and steroids (16.8%, mainly methylprednisolone) were most commonly used. Further treatment approaches are described in Supplementary Table IV. It was not uncommon for multiple medications to be used in combination in RCVS: 22.5% were treated with two kinds of therapy, 10.5% were treated with three kinds, 5.8% with four kinds, and 2.6% with 5 kinds. The most common treatment combinations were calcium channel blockers with magnesium (4.2%), calcium channel blockers with anticoagulants (3.7%), and calcium channel blockers with steroids (3.7%). Out of the 191 cases, 39.3% were treated with only one therapy. The remainder of treatment modality combinations are reported in Supplementary Table V.

Detailed data regarding clinical and imaging follow-up, as well as recurrence rates, are described in Supplementary Table VI. Of the 191 cases, improved abnormal finding (stenosis or beading) in brain imaging were noted in 155 (81.1%) cases. Among the 155 cases, improvement of abnormal finding was recorded in 149 cases after a mean time period of 73.8 ± 89.2 days (median 60 days). In most cases, brain image findings were improved within 1 to 3 months (51.6%). Regarding neurologic symptoms and prognosis, 124 of the 191 cases had a clear description of neurologic deficit at the time of last follow-up (mean 42.7 ± 55.3 days, median 25 days). Among them, there were 26 (20.9%) cases with prolonged neurologic deficit. Including cases with unclear follow up periods, neurologic deficits remained in 36 of the 191 cases (18.8%). Recurrent RCVS was reported in 4.7% of the cases, and 66.7% of them had a second recurrence during follow-up.

Comparison of demographic and associated factors between patients with and without residual neurologic deficit showed that older age (*p*=0.011), trauma/surgery/procedure related precipitating factors (*p*=0.029), motor weakness (*p*=0.014), and aphasia/neglect/apraxia (*p*=0.010) were more frequently noted in cases with residual neurologic deficit (Table V). In multivariate analysis, after adjusting for age, sex, and additional variables associated with RCVS with a p-value < 0.1 in univariate analysis, trauma/surgery/procedure (hazard ratio: 3.29, 95% confidence interval (1.21–8.88), *p*=0.019) and aphasia/neglect/apraxia (hazard ratio: 3.83, 95% confidence interval (1.33–11.05), *p*=0.013) remained significantly independent predictors for residual neurologic deficit (Table VI).

**Table V.** Comparison of demographic and associated factors according to clinical outcome.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Fully recovered**  **(n = 98)** | **Residual deficit**  **(n = 26)** | **Total**  **(n = 124)** | ***p-*value** |
| **Demographic data** |  |  |  |  |
| Sex, female | 80 (81.6) | 22 (84.6) | 102 (82.3) | 0.723 |
| **Age** | **38.2 ± 14.9** | **46.7 ± 14.2** | **40.0 ± 15.1** | **0.011** |
| Race |  |  |  | 0.458 |
| Not documented | 75 (76.5) | 22 (84.6) | 97 (78.2) |  |
| Asian | 9 (9.2) | 0 (0.0) | 9 (7.3) |  |
| Caucasian | 10 (10.2) | 3 (11.5) | 13 (10.5) |  |
| African | 4 (4.1) | 1 (3.9) | 5 (4.0) |  |
| **Precipitating factors** |  |  |  |  |
| Offending drugs | 44 (44.9) | 10 (38.5) | 54 (43.5) | 0.556 |
| Pregnancy/endometriosis | 24 (24.5) | 2 (7.7) | 26 (21.0) | 0.101 |
| Sexual activity | 14 (14.3) | 2 (7.7) | 16 (12.9) | 0.519 |
| Recent trip | 4 (4.1) | 0 (0.0) | 4 (3.2) | 0.578 |
| **Trauma/surgery/procedure** | **7 (7.1)** | **6 (23.1)** | **13 (10.5)** | **0.029** |
| Anemia | 2 (2.0) | 0 (0.0) | 2 (1.6) | 1.000 |
| Valsalva | 4 (4.1) | 1 (3.8) | 5 (4.0) | 1.000 |
| **Past medical history** |  |  |  |  |
| Migraine | 24 (24.5) | 6 (23.1) | 30 (24.2) | 1.000 |
| Previous thunderclap or sexual headache | 4 (4.1) | 2 (7.7) | 6 (4.8) | 0.446 |
| Hypertension | 10 (10.2) | 4 (15.4) | 14 (11.3) | 0.489 |
| Other vascular risk factors\* | 17 (17.3) | 5 (19.2) | 22 (17.7) | 0.779 |
| Malignancy | 4 (4.1) | 1 (3.8) | 5 (4.0) | 1.000 |
| Smoking | 3 (3.1) | 3 (11.5) | 6 (4.8) | 0.106 |
| Anxiety/Depression | 9 (9.2) | 3 (11.5) | 12 (9.7) | 0.714 |
| Genetic disease | 6 (6.1) | 0 (0.0) | 6 (4.8) | 0.342 |
| Autoimmune | 6 (6.1) | 0 (0.0) | 6 (4.8) | 0.342 |
| Asthma/UTI | 2 (2.0) | 2 (7.7) | 4 (3.2) | 0.193 |
| Epilepsy | 1 (1.0) | 1 (3.8) | 2 (1.6) | 0.377 |
| **Accompanying neurologic symptoms** |  |  |  |  |
| Any type of headache | 92 (93.9) | 24 (92.3) | 116 (93.5) | 0.772 |
| **Motor weakness** | **31 (31.6)** | **15 (57.7)** | **46 (37.1)** | **0.014** |
| Seizure/mental change | 29 (29.6) | 13 (50.0) | 42 (33.9) | 0.051 |
| Vision related | 37 (37.8) | 12 (46.2) | 49 (39.5) | 0.436 |
| Sensory | 10 (10.2) | 4 (15.4) | 14 (11.3) | 0.489 |
| **Aphasia/neglect/apraxia** | **3 (3.1)** | **5 (19.2)** | **8 (6.5)** | **0.010** |
| Ataxia | 2 (2.0) | 2 (7.7) | 4 (3.2) | 0.193 |
| **Brain image findings** |  |  |  |  |
| PRES or ischemic lesion | 47 (48.0) | 15 (57.7) | 62 (50.0) | 0.378 |
| Cerebral hemorrhage | 32 (32.7) | 8 (30.8) | 40 (32.3) | 1.000 |
| **Angiographic findings** |  |  |  |  |
| Location |  |  |  | 0.164 |
| Focal | 5 (5.1) | 3 (11.5) | 8 (6.5) |  |
| Hemispheric | 5 (5.1) | 4 (15.4) | 9 (7.3) |  |
| Diffuse | 85 (86.7) | 18 (69.2) | 103 (83.1) |  |
| Bead pattern | 81 (82.7) | 19 (73.1) | 100 (80.6) | 0.272 |
| **Treatment modality/medication** |  |  |  |  |
| Verapamil | 20 (20.4) | 6 (23.1) | 26 (21.0) | 0.789 |
| Nimodipine | 42 (42.9) | 8 (30.8) | 50 (40.3) | 0.369 |
| Labetalol | 3 (3.1) | 1 (3.8) | 4 (3.2) | 1.000 |
| Other antihypertensive agents | 23 (23.5) | 9 (34.6) | 32 (25.8) | 0.313 |
| Steroid | 15 (15.3) | 8 (30.8) | 23 (18.5) | 0.090 |
| Antithrombotics | 16 (16.3) | 1 (3.8) | 17 (13.7) | 0.120 |
| Antiepileptic drugs | 10 (10.2) | 3 (11.5) | 13 (10.5) | 1.000 |
| Pain killer | 11 (11.2) | 1 (3.8) | 12 (9.7) | 0.457 |
| Antianxiety/psychotics | 3 (3.1) | 1 (3.8) | 4 (3.2) | 1.000 |
| Mannitol | 2 (2.0) | 0 (0.0) | 2 (1.6) | 1.000 |
| Cyclophosphamide | 3 (3.1) | 2 (7.7) | 5 (4.0) | 0.281 |
| Magnesium | 8 (8.2) | 0 (0.0) | 8 (6.5) | 0.202 |
| Surgery | 3 (3.1) | 2 (7.7) | 5 (4.0) | 0.281 |
| **Recurrent RCVS** |  |  |  |  |
| Recurrence | 4 (4.1) | 2 (7.7) | 6 (4.8) | 0.605 |
| Times |  |  |  | 0.459 |
| 1 | 1 (1.0) | 0 (0.0) | 1 (0.8) |  |
| 2 | 2 (2.0) | 2 (7.7) | 4 (3.2) |  |
| 3 | 1 (1.0) | 0 (0.0) | 1 (0.8) |  |

Values are presented as number (percent). UTI: urinary tract infection, PRES: posterior reversible encephalopathy syndrome, RCVS: reversible cerebral vasoconstriction syndrome.Other vascular risk factors: diabetes mellitus, smoking, hyperlipidemia.

**Table VI.** Independent risk factors for residual neurologic deficit in reversible cerebral vasoconstriction syndrome.

|  |  |  |
| --- | --- | --- |
|  | **HR (95% CI)** | **p-value** |
| Sex (female) | 0.44 (0.11 – 1.73) | 0.245 |
| **Age** | **1.03 (0.99 – 1.07)** | **0.057** |
| **Trauma/surgery/procedure** | **3.29 (1.21 – 8.88)** | **0.019** |
| Motor weakness | 1.84 (0.64 – 5.21) | 0.251 |
| Seizure/mental change | 2.47 (0.89 – 6.82) | 0.081 |
| **Aphasia/neglect/apraxia** | **3.83 (1.33 – 11.05)** | **0.013** |

HR: hazard ratio, CI: confidence interval.

Discussion

RCVS is a syndrome characterized by thunderclap headaches and multifocal constriction of cerebral arteries that has been associated with benign prognoses in most cases 7, 8. However, as more cases are reported, there have been recent associations of RCVS with cerebral hemorrhage, infarction, and edema 9, 10. There have been only a handful of previous systematic and narrative reviews aggregating the evidence on RCVS. Sattar et al. used 4 case series to identify clinical characteristics of the condition, with a focus on diagnostic characteristics on imaging and CSF analysis, but did not focus on predisposing factors toward unfavorable neurologic outcome in RCVS patients 15. The most recent systematic review to our knowledge on RCVS was performed by Valencia-Mendoza et al., which focused on prognostic factors in fatal cases in RCVS but not residual deficits from the disease 16. As it stands, there remains a drastic need to both further aggregate clinical characteristics of RCVS and identify precipitating symptoms and factors for poor clinical outcomes. Our study is a systematic review analyzing all the published case reports of subjects with RCVS in the literature. We found that patients with trauma/surgery/procedure as precipitating factors for RCVS and aphasia/neglect/apraxia as acute neurologic symptoms of the disorder had a poor clinical outcome with persistent neurologic deficits.

**Clinical manifestations/Triggers**

In our analysis, RCVS occurred at various ages ranging from 4 months to 80 years with a female preponderance, which were consistent with the previous reports 1, 8, 15, 16. It has been reported that up to 60% of RCVS patients have a triggering or precipitating factor 1, 13, 17-20. In our study, various kinds of triggering factors were noted in the vast majority of cases (90.1%). Concomitant medications and drugs and postpartum were the major precipitating factors. A higher frequency of secondary RCVS was observed in our systematic review, possibly because we included reports of RCVS in which the authors might preferentially publish new potential triggers. In general, the main drugs suspected for triggering RCVS are thought to be sympathomimetic medications used as nasal decongestants 10, 21. In our report, however, the most commonly reported precipitants were antidepressants (13.9%), followed by addictive drugs (9.7%) and sympathomimetic medications (8.3%). These proportions are higher than in the two large published Taiwanese and Korean series (antidepressants <2%; illicit drugs 0%; sympathomimetics 1%) 17, 18, and lower than in the two large series from France and the USA (antidepressants 21-34%, illicit drugs 20-32%, sympathomimetics 13%) 8, 19. These different proportions may reflect a variable susceptibility to RCVS in subjects from Asia and from Western countries, possibly due to different genetic backgrounds. Moreover, in our data set, one-fifth of the total cases occurred at postpartum, which is much higher than in other reports from Asia (1-5%) 17, 18 and Western countries (12-13%) 8, 19. It is thought that increased pro- and antiangiogenic factors in the post-partum period could be associated with the development of RCVS 4.

Regarding clinical manifestations of RCVS, headache was the most common symptom in our study. Most of the headaches related to RCVS are severe headache or thunderclap headache, associated with nausea, vomiting, and increased blood pressure 22. Visual abnormality and consciousness impairment are uncommon 1, which is consistent with our findings. In addition to thunderclap headache in conjunction with RCVS, stroke, focal neurologic deficit, seizure, posterior reversible encephalopathy syndrome (PRES), and cerebral edema may occur 23.

In our analysis, ischemic lesions were noted in about half of the included cases, and cerebral hemorrhages (mainly subarachnoid) were found in 35% of the cases, which comprised the two main causes for stroke in RCVS 7, 10, 15, 16, 24-26. Risk factors for subarachnoid hemorrhages are reported to be a history of migraine, female sex, and older age 7, 10, 15, 16, 24-28. In addition, it should be noted that cerebral hemorrhage is usually observed within 1 week of RCVS-related symptom onset including headache, while ischemic stroke may be confirmed 1 to 2 weeks after the occurrence of RCVS-related symptoms or even after complete resolution of headache 1.

**Treatments/Recurrence**

Regarding treatment of RCVS, calcium channel blockers (nimodipine or verapamil in particular) were used in about 80% of the patients in our analysis. Although there has been no randomized clinical trial, there have been some reports showing that calcium channel blockers could relieve the symptoms of RCVS in prospective or retrospective studies 22, 29-32. However, the beneficial effect of calcium channel blockers on cerebral vasoconstriction or stroke severity remains unclear 1. Other treatments, such as the use of steroids and other medications or balloon angioplasty, have not been proven to be effective yet 33-35. In our analysis, we could not find any medications or treatment modalities related with clinical prognosis. Further studies, including randomized controlled trials, are needed to determine the relationship of treatment modality and outcome of RCVS.

The recurrence of RCVS has rarely been reported 13, 14, 36. Although the exact rate of recurrence is unknown, it was found in about 4.7% of the cases in our systematic review, and multiple recurrences were not uncommon in this subset. In previous studies, recurrence of an episode of RCVS after resolution of the initial symptomatic period was infrequent, about 5% in one report, and usually manifests as an isolated thunderclap headache without vascular complications, such as hemorrhagic stroke 17, 36, 37. Nevertheless, the exact recurrence rates could not be drawn from our analysis, since the follow-up period of most cases was short. Therefore, prospective studies of large cohorts are required to determine the recurrence rate.

**Prognosis**

The prognosis of RCVS is known to be favorable in most cases, since clinical and angiographic abnormalities generally resolve within several days to weeks. In particular, the prognosis of RCVS is dependent on the occurrence of stroke with potential neurologic deficits 8, 22, 38, eventually leading to residual deficits or even fatality 9, 10, 22, 39. Altogether, 47.6% of the patients in our systematic review had a stroke during RCVS and 6.8% were left with a residual deficit. We also found that trauma/surgery/procedure and accompanying neurologic symptoms of aphasia/neglect/apraxia as precipitating factors were associated with residual deficits in RCVS.

**Limitations**

Our study has several limitations. First, our study was a systematic review of case reports published in the literature and is therefore to subject to multiple biases. Namely, the absence of prospective cohorts increases the likelihood of selection, publication, and reporting bias. As case reports vary in focus and investigator, there was heterogeneity in described clinical features and follow-up amongst reports, as well as the likelihood of differences in the certainty of RCVS diagnoses. The aforementioned biases in case reports made treatment effects, as well as the causality of triggering events and risk factors, difficult to assess. Second, when extracting the data from the case reports, it was difficult to organize the data set according to the pre-specified criteria, and therefore, the outcome analysis could not be done in all cases. Third, because it was difficult to obtain a data set for laboratory or serial brain imaging findings from each case report, we could not perform the analysis regarding the relationship between these factors and clinical outcome.

Conclusions

In conclusion, our study analyzed the various potential triggers, past medical histories, accompanying neurologic symptoms, brain imaging patterns, and clinical outcomes in RCVS by a systematic review approach. Furthermore, our study suggests that precipitating factors of trauma/surgery/procedure and accompanying neurologic symptoms of aphasia/neglect/apraxia may be associated with residual neurological deficits in RCVS, which are importantly associated with the prognosis of the disease.

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**Supplementary Table I.** Possible provocative medications and drugs of reversible cerebral vasoconstriction syndrome

|  |  |  |
| --- | --- | --- |
|  | **Name** | **Total**  **(n = 191)** |
| Antidepressants | Citalopram, escitalopram, fluoxetine, paroxetine, sertraline, trazodone, venlafaxine, amitriptyline | 20 (13.9) |
| Addictive drugs | Marijuana, cocaine, LSD | 14 (9.7) |
| Sympathomimetics | Pseudoephedrine, amezinium, oxymetazoline, Phenylephrine | 12 (8.3) |
| Hormone | Levonorgestrel, estrogen, oral contraceptive drug, hydrocortisone, methylprednisolone, prednisolone, levothyroxine | 11 (7.6) |
| Triptan | Sumatriptan, zolmitriptan, naratriptan, eletriptan | 9 (6.3) |
| Opiate | Dextromethorphan hydrobromide, morphine, hydrocodone, fentanyl | 9 (6.3) |
| Chemotherapy | Vincristine, carboplatin, daunorubicin, pirarubicin, L-asparaginase | 6 (4.2) |
| NSAIDs | Aspirin, etodolak, naproxen | 5 (3.5) |
| Immune | Thymoglobulin, beta interferon, natalizumab, bevacizumab | 4 (2.8) |
| Benzodiazepine | Clonazepam, clobazam, diazepam | 4 (2.8) |
| Herbal | Red clover, khat, phytooestrogens | 4 (2.8) |
| Immunomodulator | Fingolimod, dimethyl fumarate, glatiramer acetate | 4 (2.8) |
| Immunosuppressant | Cyclosporin, tacrolimus | 4 (2.8) |
| MAO inhibitor | Phenelzine, tranylcypromine | 4 (2.8) |
| CNS stimulant | Amphetamine, methamphetamine, methylphenidate | 3 (2.1) |
| Ergoline derivative | Bromocriptine, cabergoline, methylergometrine | 3 (2.1) |
| Fever-reducing drug | Paracetamol, phenacetin | 3 (2.1) |
| Antimalarial | Quinine, hydroxychloroquine | 2 (1.4) |
| Antipsychotic | Fluspirilene, thioridazine | 2 (1.4) |
| NMDA R antagonist | Ketamine | 1 (0.7) |
| Antiarrhythmic | Flecainide | 1 (0.7) |
| Antibiotics | Doxycycline | 1 (0.7) |
| Antihistamine | Hydroxyzine pamoate | 1 (0.7) |
| Beta agonist | Albuterol | 1 (0.7) |
| Beta blocker | Metoprolol | 1 (0.7) |
| Calcium antagonist | Flunarizine | 1 (0.7) |
| GABA analogue | Pregabalin | 1 (0.7) |
| Selective COX-2 inhibitor | Etoricoxib | 1 (0.7) |
| Serotonergic anorectic drug | Dexfenfluramine | 1 (0.7) |
| Others | Cinnamaverin, alcohol, caffein, electronic tabacco, guaifenesin, ferrous sulfate, methenamine, omeprazole, slimming oral product, naphthalene | 11 (7.6) |

NSAIDs: Non-steroidal anti-inflammatory drugs, MAO: Monoamine oxidase, CNS: Central nervous system, NMDA R: N-methyl-D-aspartate receptor, GABA: gamma-aminobutyric acid, COX-2: Cyclooxygenase-2.

Values are presented as number (percent).

**Supplementary Table II.** Other accompanying clinical presentations in reversible cerebral vasoconstriction syndrome

|  |  |
| --- | --- |
| **Other accompanying clinical symptoms** | **Total (n = 191)** |
| Nausea | 51 (26.7) |
| Vomiting | 32 (16.8) |
| Pain (2 neck, 1 low abdomen, 1 knee, 1 eye) | 5 (2.6) |
| Respiratory (3 shortness of breath, 1 dyspnea, 1 desaturation) | 5 (2.6) |
| Cardiac (2 tachycardia, 1 hypertension, 1 hypotension) | 4 (2.1) |
| Fever | 3 (1.6) |
| Other gastrointestinal tract (anorexia, constipation, diarrhea) | 3 (1.6) |
| Chest discomfort | 2 (1.0) |
| Diaphoresis | 2 (1.0) |
| Fatigue | 2 (1.0) |
| Skin (bullae) | 1 (0.5) |

Values are presented as number (percent).

**Supplementary Table III.** Frequency of performed image modality for reversible cerebral vasoconstriction syndrome

|  |  |  |
| --- | --- | --- |
|  | **Number of performed imaging modality, n (%)** | **Positive finding among performed cases, n (%)** |
| CT | 137 (71.7) | 61 (44.5) |
| MRI | 151 (79.1) | 127 (84.1) |
| Angiography | 188 (98.4) | 187 (99.5) |
| CT only | 26 (13.8) | 26 (100.0) |
| MR only | 71 (37.8) | 70 (98.6) |
| Conventional only | 44 (23.4) | 44 (100.0) |
| CT+MR | 8 (4.3) | 8 (100.0) |
| CT+Conventional | 15 (8.0) | 15 (100.0) |
| MR+Conventional | 11 (5.9) | 11 (100.0) |
| All performed | 12 (6.8) | 12 (100.0) |

Values are presented as number (percent).

Positive findings mean presence of cerebral vascular abnormality and/or brain parenchymal abnormalities which may be related with reversible cerebral vasoconstriction syndrome.

**Supplementary Table IV.** Treatment modalities of reversible cerebral vasoconstriction syndrome

|  |  |
| --- | --- |
| **Treatment** | **Total number of patients (n=191)** |
| **Number of patients (%)** |
| **Calcium channel blockers** | **151 (79.1)** |
| Nimodipine | 81 (42.4) |
| Verapamil | 42 (22.0) |
| Nicardipine | 8 (4.2) |
| Nifedipine | 8 (4.2) |
| Amlodipine | 3 (1.6) |
| Lomerizine | 3 (1.6) |
| Lercanidipine | 2 (1.0) |
| Felodipine | 1 (0.5) |
| Diltiazem | 1 (0.5) |
| Unspecified | 2 (1.0) |
| **Analgesics** | **42 (21.5)** |
| Aspirin | 11 (5.8) |
| Opiates | 9 (4.7) |
| Paracetamol | 6 (3.1) |
| Tramadol | 2 (1.0) |
| Ibuprofen | 1 (0.5) |
| Indomethacin | 1 (0.5) |
| Meperidine | 1 (0.5) |
| Naproxen | 1 (0.5) |
| Unspecified | 10 (5.2) |
| **Steroids** | **32 (16.8)** |
| Methylprednisolone | 12 (6.3) |
| Dexamethasone | 5 (2.6) |
| Prednisone | 5 (2.6) |
| Prednisolones | 4 (2.1) |
| Unspecified | 6 (3.1) |
| **Anticoagulants** | **19 (9.9)** |
| Heparins | 10 (5.2) |
| Clopidogrel | 3 (1.6) |
| Coumadin | 1 (0.5) |
| Warfarin | 1 (0.5) |
| Dipyridamole | 1 (0.5) |
| Unspecified | 3 (1.6) |
| **Anticonvulsants** | **18 (9.4)** |
| **Magnesium sulfate** | **15 (7.9)** |
| **Adrenergic antagonists** | **12 (6.3)** |
| Atenolol | 4 (2.1) |
| Labetalol | 4 (2.1) |
| Urapidil | 2 (1.0) |
| Nadolol | 1 (0.5) |
| Propranolol | 1 (0.5) |
| **Antibiotics** | **6 (3.1)** |
| **Hyperosmotics** | **5 (2.6)** |
| Glycerol | 4 (2.1) |
| Mannitol | 1 (0.5) |
| **Immune modulators** | **5 (2.6)** |
| Cyclophosphamide | 3 (1.0) |
| Intravenous immunoglobulins | 2 (1.0) |
| **ACE inhibitors** | **3 (1.6)** |
| Cilazapril | 1 (0.5) |
| Perindopril | 1 (0.5) |
| Ramipril | 1 (0.5) |
| **Prostacyclins** | **3 (1.6)** |
| Epoprostenol | 2 (1.0) |
| Prostacyclin | 1 (0.5) |
| **Antiemetics** | **2 (1.0)** |
| Cyclizine | 1 (0.5) |
| Metoclopramide | 1 (0.5) |
| **Other agents** | **18 (9.4)** |
| Amitriptyline | 1 (0.5) |
| Antihypertensive | 1 (0.5) |
| Antipsychoitcs | 1 (0.5) |
| Cyproheptadine | 1 (0.5) |
| Dihydroergotamine | 1 (0.5) |
| Dopamine | 1 (0.5) |
| Hydrochlorothiazide | 1 (0.5) |
| L-arginine ubidecarenone | 1 (0.5) |
| Noradrenaline | 1 (0.5) |
| Metoclopramide | 1 (0.5) |
| Milrinone | 1 (0.5) |
| Nitroglycerin | 1 (0.5) |
| Olmesartan | 1 (0.5) |
| Phenylephrine | 1 (0.5) |
| Simvastatin | 1 (0.5) |
| Sumatriptan | 1 (0.5) |
| Vitamin | 1 (0.5) |
| Zolmitriptan | 1 (0.5) |
| **Procedure** | **9 (4.7)** |
| Surgery | 7 (3.7) |
| Hypothermia | 1 (0.5) |
| Plasmapheresis | 1 (0.5) |

ACE: angiotensin converting enzyme

Values are presented as number (percent).

**Supplementary Table V.** Combination of treatment for case reported patients with reversible cerebral vasoconstriction syndrome

|  |  |
| --- | --- |
| **Treatment** | **Total number of patients (n=191)** |
| **Number of patients (%)** |
| **Single kind of therapy** | **75 (39.3)** |
| CCB | 60 (31.4) |
| Analgesia | 5 (2.6) |
| Anticoagulant | 5 (2.6) |
| Procedure | 2 (1.0) |
| Anticonvulsant | 1 (0.5) |
| Steroid | 1 (0.5) |
| Other | 1 (0.5) |
| **Two kinds of therapy** | **43 (22.5)** |
| CCB+Mg | 8 (4.2) |
| CCB+Anticoagulant | 7 (3.7) |
| CCB+Steroid | 7 (3.7) |
| CCB+Adrenergic antagonist | 4 (2.1) |
| CCB+Analgesia | 4 (2.1) |
| CCB+Anticonvulsant | 2 (1.0) |
| CCB+Other | 2 (1.0) |
| CCB+Prostaglandin | 1 (0.5) |
| Anticonvulsant+Other | 3 (1.6) |
| Anticonvulsant+Anticoagulant | 1 (0.5) |
| Anticonvulsant+Mg | 1 (0.5) |
| Anticonvulsant+Steroid | 1 (0.5) |
| Anticoagulant+Steroid | 1 (0.5) |
| Anticoagulant+Other | 1 (0.5) |
| **Three kinds of therapy** | **20 (10.5)** |
| CCB+Steroid+Anticoagulant | 1 (0.5) |
| CCB+Steroid+Anticonvulsant | 1 (0.5) |
| CCB+Steroid+Immune modulator | 1 (0.5) |
| CCB+Steroid+Mg | 1 (0.5) |
| CCB+Steroid+Prostacyclin | 1 (0.5) |
| CCB+Steroid+Other | 1 (0.5) |
| CCB+Anticonvulsant+Hyperosmotic | 2 (1.0) |
| CCB+Anticonvulsant+Adrenergic antagonist | 1 (0.5) |
| CCB+Anticonvulsant+Antibiotic | 1 (0.5) |
| CCB+Analgesia+Adrenergic antagonist | 1 (0.5) |
| CCB+Analgesia+Anticoagulant | 1 (0.5) |
| CCB+Analgesia+Procedure | 1 (0.5) |
| CCB+Analgesia+Other | 1 (0.5) |
| CCB+Mg+Anticoagulant | 1 (0.5) |
| CCB+Mg+Prostacyclin | 1 (0.5) |
| CCB+Procedure+Prostacyclin | 1 (0.5) |
| Steroid+Analgesia+Other | 1 (0.5) |
| Steroid+Anticoagulant+Immune modulator | 1 (0.5) |
| Hyperosmotic+Mg+Other | 1 (0.5) |
| **Four kinds of therapy** | **11 (5.8)** |
| CCB+Steroid+Analgesia+Adrenergic anatagonist | 1 (0.5) |
| CCB+Steroid+Analgesia+Steroid | 1 (0.5) |
| CCB+Steroid+Immune modulator+Procedure | 1 (0.5) |
| CCB+Steroid+Immune modulator+Other | 1 (0.5) |
| CCB+Steroid+Anticonvulsant+Procedure | 1 (0.5) |
| CCB+Steroid+Mg+Other | 1 (0.5) |
| CCB+Analgesia+Anticonvulsant+Other | 1 (0.5) |
| CCB+Analgesia+Hyperosmotic+Procedure | 1 (0.5) |
| CCB+ACEi+Adrenergic anatagonist+Antibiotic | 1 (0.5) |
| Anticonvulsant+Antibiotic+Analgesia+Prostacyclin | 1 (0.5) |
| Anticonvulsant+Immune modulator+Steroid+Other | 1 (0.5) |
| **Five kinds of therapy** | **5 (2.6)** |
| CCB+Steroid+Other+Analgesic+Antibiotic | 1 (0.5) |
| CCB+Steroid+Other+Analgesic+Mg | 1 (0.5) |
| CCB+Steroid+Other+Adrenergic antagonist+Anticonagulant | 1 (0.5) |
| CCB+Steroid+ACEi+Adrenergic anatagonist+Anticoagulant | 1 (0.5) |
| CCB+Other+ACEi+Adrenergic anatagonist+Immune modulator | 1 (0.5) |

CCB: Calcium channel blocker; Mg: Magnesium sulfate; ACEi: angiotensin converting enzyme inhibitor.

**Supplementary Table VI.** Image and clinical outcome of reversible cerebral vasoconstriction syndrome

|  |  |
| --- | --- |
| **Image and clinical outcome** | **N(case)/N(total number of evaluated) (%)** |
| Reversed patients | 155/191 (81.2) |
| Imaging relief duration† | 149/155 (96.1) |
| Within 2 weeks | 19/149 (12.8) |
| 2 weeks ~ 1 months | 34/149 (22.8) |
| 1~3 month | 77/149 (51.6) |
| Over 3 months | 19/149 (12.8) |
| Symptom relief duration\* | 124/155 (80.0) |
| Within 2 weeks | 41/124 (33.3) |
| 2 weeks ~ 1 months | 60/124 (48.8) |
| Over 1 month | 23/124 (17.9) |
| Deficit patients | 36/191 (18.8) |
| Weakness | 18/36 (50.0) |
| Visual disturbance | 9/36 (25.0) |
| Aphasia | 7/36 (19.4) |
| Headache | 4/36 (11.1) |
| Cognitive difficulty | 2/36 (5.6) |
| Spasticity | 2/36 (5.6) |
| Seizure | 2/36 (5.6) |
| Ataxia | 1/36 (2.7) |
| Sensory deficit | 1/36 (2.7) |
| Dizziness | 1/36 (2.7) |
| Death | 1/36 (2.7) |
| Recurrence | 9/191 (4.7) |
| Once | 2/9 (22.2) |
| Twice | 6/9 (66.7) |
| Three times | 1/9 (11.1) |

†: Of the 191 cases, cases of clearly described whether brain image and/or angiographic findings were improved or not were noted in 155 (81.1%) cases. Among the 155 cases, 149 cases were noted for the duration until the improvement of the brain angiographic image findings. The image follow-up period was extracted from the patients (n = 149), mean 73.8 ± 89.2 days, median 60 days (IQR: 29.5 - 90.0).

\*: For the prognosis of reversible cerebral vasoconstriction syndrome, the symptom follow-up period was extracted from the patients (n = 124). It means that 124 of the 155 patients who were clearly described about period of improvement. The symptom follow-up period was extracted from the patients (n = 124), mean 42.7 ± 55.3 days, median 25 days (IQR: 11.0 - 45.0).

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