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Reversible Cerebral Vasoconstriction Syndrome in Children and Adolescents: A Case Series and Literature Review

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Reversible cerebral vasoconstriction syndrome (RCVS) is a clinical radiographic phenomenon characterized by thunderclap headaches and transient vasoconstriction of cerebral vessels, which typically resolve within 3 months of symptom onset. Although RCVS has been extensively studied in adults, research on this condition in pediatric populations is limited, likely due to its perceived rarity. This comprehensive review aims to bridge the knowledge gap by examining the clinical presentation, diagnostic methods, treatment strategies, and prognostic outcomes of pediatric RCVS cases, including two case reports contributed by the authors. This study demonstrates an inconclusive sex distribution of RCVS in children, attributed to the scarcity of comprehensive studies of this demographic. Additionally, we identified several predictors of adverse neurological outcomes in children with RCVS, including motor deficits, aphasia, hypertension, and renal disease. This study offers a thorough overview of RCVS in the pediatric population, providing valuable insights to inform future research in this area.

Keywords: Vasospasm, intracranial; Headache disorders, primary; Migraine disorders; Cerebral angiography; Nimodipine

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is a complex neurovascular and clinical radiological syndrome characterized by multiple headaches, particularly thunderclap headaches, which may be accompanied by other neurological symptoms. This syndrome involves reversible diffuse vasoconstriction of the cerebral vessels [1,2]. Typically, these vasoconstrictions begin in the peripheral arterioles and progress centripetally to larger vessels over a span of days [3]. They typically resolve within 3 months of clinical onset [4].

Although descriptions reflecting RCVS can be traced to publications from the 1960s, it was the report by Call and Fleming in 1988 that advanced its recognition as a distinct syndrome [5]. Previously, terms such as "Call-Fleming syndrome," "benign angiopathy of the central nervous system," "postpartum angiopathy," and "migrainous vasospasm" were used, varying based on the medical specialty of the treating physician [6]. It was not until 2007 that Calabrese et al. [7] established a set of diagnostic criteria for the syndrome, which included: (1) acute severe headache, often thunderclap in nature, with or without accompanying neurological signs and symptoms; (2) evidence of multifocal segmental cerebral ar-

tery vasoconstriction on direct (catheter) or indirect angiography; (3) absence of aneurysmal subarachnoid hemorrhage; (4) normal or near-normal cerebrospinal fluid analysis; and (5) reversibility of angiographic abnormalities within 12 weeks of the onset of the disease [7].

Adult RCVS exhibits a female preponderance among individuals in their late 40s, corresponding to the perimenopausal period. In contrast, their male counterparts are most commonly affected when approximately 10 years younger [8]. The scarcity of comprehensive RCVS studies in the pediatric population precludes a definitive conclusion regarding sex distribution; however, case reports suggest a male preponderance [5-7,9,10].

Although RCVS has been extensively studied in adults, its presentation, diagnosis, and management in children and adolescents remain poorly understood. With this comprehensive review and case series, we sought to offer a detailed analysis of RCVS in the pediatric population by examining the currently available literature, as well as two of our own experiences with RCVS.

Materials and Methods

1. Selection of case reports and literature review

We conducted a systematic search of the English-language literature to gather case reports on RCVS in children under 18 years old. Our methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for data extraction, analysis, and reporting. From August 1, 2023, to August 31, 2023, two investigators (LM and KS) independently performed searches on PubMed and extracted relevant data. The search term used was "Reversible cerebral vasoconstriction syndrome" or "RCVS." Only pediatric case reports were included, and of the 1,042 articles identified, 49 met our inclusion criteria. The articles were screened by reviewing titles, abstracts, and full texts sequentially. Any disagreements were discussed and resolved through consensus among the three investigators: LM, KS, and JWK.

2. Data extraction

For each eligible case report, we systematically collected data on patient demographics, including age, sex, and ethnicity. We also identified potential triggers, such as medications, recreational drug use, postpartum conditions, sexual activity, smoking habits, physical exercise, travel, blood transfusion, energy drink consumption, upper respiratory tract infection, surgery, tumor, emotional stress, peritoneal dialysis, showering, and performance of the Valsalva maneuver. Additionally, we documented neurological symptoms, medical and surgical histories, and other clinical presentations. Imaging techniques and findings from computed tomography (CT) and magnetic resonance imaging (MRI) were noted, along with treatment strategies, radiological and clinical outcomes, and instances of RCVS recurrence.

3. Case reports

We conducted a retrospective review of the medical records of pediatric patients (aged 18 years or younger) who presented with severe headaches and focal neurological deficits at the pediatric department of Chungnam National University Hospital between March 2013 and August 2023 and were diagnosed with RCVS. Two eligible patients were identified and included in a case report article. The requirement for informed consent was waived by the Institutional Review Board of Chungnam National University Hospital due to the study's retrospective nature (IRB number 2023-08-083).

4. Statistical analysis

Data collection and cleaning were conducted using Microsoft Excel (Microsoft, Redmond, WA, USA), and the cleaned data were imported into SPSS version 27 (IBM Corp., Armonk, NY, USA) for all statistical analyses. Normally distributed data are presented as the mean±standard deviation. Frequency comparisons were performed using the chi-square exact test. Analysis of variance was utilized to assess differences in clinical parameters and neurological outcomes between the two groups. A statistical P value of less than 0.05 was considered to indicate statistical significance.

Case Series

1. Case 1

A 15-year-old boy presented with a sudden onset of headache. The patient had a history of migraines and frequent mild headaches. He was alert but reported persistent headaches in the left temporal region. Additionally, the patient exhibited motor aphasia. MRI showed no lesions in the brain parenchyma; however, magnetic resonance angiography (MRA) revealed multiple vasoconstrictions in the M3 and M4 segments of the left middle cerebral artery (Fig. 1A). Treatment included mannitol, dexamethasone, and nimodipine. By the second day, the patient's dysarthria had improved, and by the fourth day, the headache had completely subsided. Follow-up MRA conducted 4 days after the initial presentation showed that the vasoconstrictions in the M3 and M4 segments of the left middle cerebral artery had also resolved (Fig. 1B).

2. Case 2

An 8-year-old boy presented with a sudden onset of headache,

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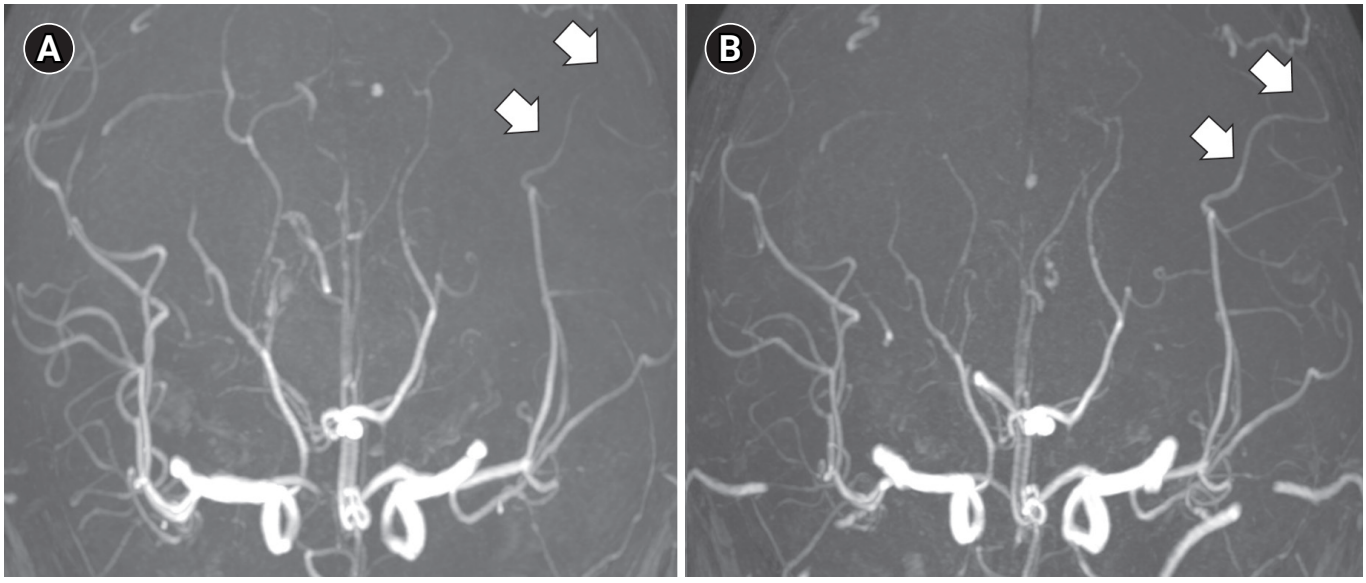

Fig. 1. A 15-year-old boy presented with a headache and expressive aphasia. (A) Coronal three-dimensional reformatted time-of-flight magnetic resonance angiography (MRA) shows a faint M3 segment and an invisible M4 segment of the left middle cerebral artery (arrows). (B) Follow-up MRA performed 4 days later shows resolution of vascular findings.

right-sided weakness, and dysarthria. Laboratory tests were performed under the suspicion of coagulopathy, arteriopathy, infectious disease, or autoimmune disorder. The results, including complete blood counts, chemistries, inflammatory markers, autoimmune profiles, complement and immunoglobulin levels, and procoagulant screening tests, all fell within normal limits. MRI revealed no evidence of brain parenchymal lesions. However, MRA indicated narrowing of the M4 segment of the left middle cerebral artery. The patient's symptoms improved spontaneously after several hours. One week later, the boy returned to the emergency room due to numbness in his right arm, although no neurological deficits were noted. MRI again revealed no brain parenchymal lesions, but MRA displayed multiple areas of vasoconstriction in the anterior cerebral artery, the middle cerebral artery, and the distal branch of the posterior cerebral artery (Fig. 2A). The symptoms resolved without the administration of any medication. Repeat brain MRA, performed 4 months later, showed no vasoconstriction (Fig. 2B).

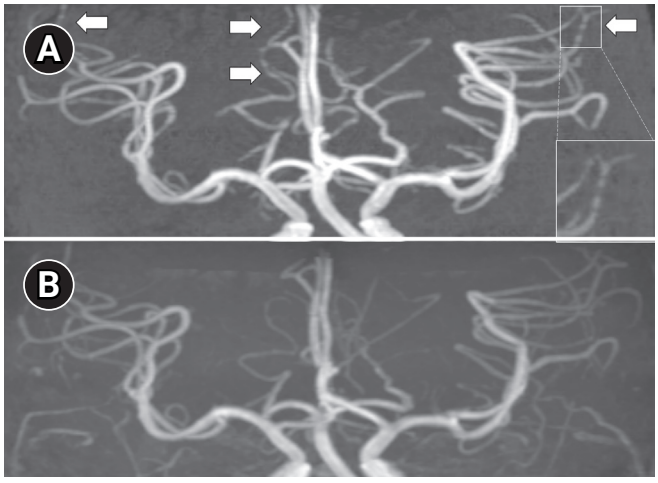

Fig. 2. An 8-year-old boy presented with right-sided weakness and dysarthria. (A) Coronal three-dimensional reformatted time-of-flight magnetic resonance angiography (MRA) shows diffuse multifocal narrowing of the bilateral anterior, middle, and posterior cerebral arteries (arrows). (B) A repeated MRA at 4 months later demonstrates resolution of the vascular findings.

Results

1. Basic demographics

This study included a total of 51 cases, with a mean age of 11.74±4.11 years. Among the patients, 31 (60.8%) were male, and 20 (39.2%) were female. Furthermore, 41 patients (80.4%) experienced complete recovery without residual neurological deficits, while 10 patients (19.6%) were left with residual deficits. All but one patient demonstrated recovery on angiography findings, with a mean recovery time of 71.9±54.6 days.

2. Clinical manifestations and triggers

As indicated in Tables 1 and 2, the predominant clinical manifestation was headache, reported by 44 patients (86.3%). Most cases involved thunderclap headaches (80.4%), while the remaining pa-

Table 1. Accompanying neurological symptoms of reversible cerebral vasoconstriction syndrome (51 cases)

Neurological symptom	No. (%)
Headache	44 (86.3)
Thunderclap	41 (80.4)
Non-thunderclap	3 (5.9)
Motor weakness/Paralysis	16 (31.4)
Hemiparesis	9 (17.6)
Hemiplegia	4 (7.8)
Face	3 (5.9)
Upper limb	5 (9.8)
Lower limb	3 (5.9)
Seizure	14 (27.5)
Generalized	8 (15.7)
Focal	2 (3.9)
Unknown	4 (7.8)
Mental changes	12 (23.5)
Drowsy	1 (2.0)
Stupor	1 (2.0)
Coma	2 (3.9)
Loss of consciousness, not otherwise specified	2 (3.9)
Altered/impaired awareness, not otherwise specified	6 (11.8)
Functional deficit	8 (15.7)
Aphasia	4 (7.8)
Slurred speech	4 (7.8)
Photophobia	8 (15.7)
Visual abnormalities	7 (13.7)
Blurred vision	6 (11.8)
Visual disturbance (described as such)	1 (2.0)
Gait abnormality	6 (11.8)
Sensory deficit	6 (11.8)
Behavior change	3 (5.9)
Agitation	2 (3.9)
Hallucination	1 (2.0)
Irritability	1 (2.0)
Phonophobia	3 (5.9)
Abnormal reflexes	2 (3.9)
Babinski reflex	1 (2.0)
Brisk reflexes	1 (2.0)
Cranial nerve palsy	1 (2.0)
Osmophobia	1 (2.0)
Vertigo	1 (2.0)

tients (5.9%) described non-thunderclap headaches ranging from mild to severe intensity. Motor weakness was observed in 16 patients (31.4%), with hemiparesis noted in nine cases (17.6%). Seizures occurred in 14 patients (27.5%), and alterations in mental status—including confusion, coma, and loss of consciousness—were observed in 12 cases (23.5%). Speech deficits, such as aphasia and dysarthria, were identified in eight patients (15.7%), and one patient exhibited cranial nerve palsy.

Overall, 44 (86%) of the cases had identifiable triggers, while the triggers for seven cases could not be discerned. Medications—particularly antimigraine medications, chemotherapy agents, and nasal decongestants—represented the most common triggers, accounting for 35.3% of patients. Other notable triggers were exercise (19.6%) and surgery or other intervention (15.7%), the latter of which included dialysis-related procedures (three cases), neurovascular surgery (two cases), and cardiac transplantation (two cases). Recreational drug use was a less common trigger, with only three cases attributed to post-cannabis use, one of which also involved alcohol consumption. In one case, the triggering event was associated with the postpartum period, specifically delivery via cesarean section due to fetal distress. Overall, 58.8% of cases were reported to have a single trigger, while 15.7% had two triggers and 11.8% had at least three potential triggering factors.

Table 2. Potential triggers of reversible cerebral vasoconstriction syndrome (51 cases)

Provoking factor	No. (%)	Breakdown of provoking factors
Medications/drugs	18 (35.3)	Various medications[a]
Exercise	10 (19.6)	Swimming/diving (4), weightlifting (2), football (2), curling (1), karate (1)
Surgical/Intervention	8 (15.7)	Dialysis (3), head/neurosurgery (2), cardiac surgery (2), cesarean section (1)
Unidentifiable risk factor	7 (13.7)	
Genetic diseases	6 (11.8)	SCD (2), SIOD (2), LDS (1), NF-1 (1)
Migraine	6 (11.8)	
Blood transfusion	3 (5.9)	
COVID-19	3 (5.9)	
Recreational drugs/Alcohol	3 (5.9)	Cannabis (3), with one case involving concurrent alcohol intake
Cerebellitis	1 (2.0)	
Energy drink intake	1 (2.0)	
Hypertension	1 (2.0)	
Shower (hot)	1 (2.0)	
Spices (Carolina reaper peppers)	1 (2.0)	

SCD, sickle cell disease; SIOD, Schimke immuno-osseous dysplasia; LDS, Loeys-Dietz syndrome; NF-1, neurofibromatosis type 1; COVID-19, coronavirus disease 2019.
[a]Types of medications/drugs included chemotherapy (e.g., cyclosporine, vincristine, methotrexate), antimigraine medications (e.g., eletriptan), steroids (e.g., prednisolone), and nasal decongestants (e.g., oxymetazoline), etc.

3. Medical histories

In the examination of medical history (Table 3), the most common finding was recurrent headaches, affecting 10 patients (19.6%). Migraine headaches accounted for six (11.8%) of these cases. Nephrological diseases were the second most prevalent finding, observed in seven patients (13.7%). Within this group, three individuals had end-stage renal disease (ESRD), three had lupus nephritis, and one had acute renal failure in association with hemolytic uremic syndrome. Malignancies and vascular diseases were found in

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Table 3. Medical histories (51 cases)

Condition	No. (%)
Headache	10 (19.6)
Migraine	6 (11.8)
Non-specified headache	3 (5.9)
Tension-type headache	1 (2.0)
Nephrological disease	7 (13.7)
ESRD	3 (5.9)
Lupus nephritis	3 (5.9)
ARF	1 (2.0)
Genetic abnormality	6 (11.8)
SCD	2 (3.9)
SIOD	2 (3.9)
LDS	1 (2.0)
NF-1	1 (2.0)
Respiratory disease	6 (11.8)
Allergic rhinitis	3 (5.9)
Asthma	2 (3.9)
Reactive airway disease	1 (2.0)
Vascular disease	6 (11.8)
Hypertension	3 (5.9)
Aortic dissection Stanford B	1 (2.0)
Cerebrovascular atherosclerosis	1 (2.0)
Takayasu arteritis	1 (2.0)
Tumor/malignancy	6 (11.8)
ALL	2 (3.9)
MDS	1 (2.0)
Pheochromocytoma	1 (2.0)
Retinoblastoma	1 (2.0)
T-cell lymphoma	1 (2.0)
Cardiovascular disease	4 (7.8)
DCM	2 (3.9)
HCM	1 (2.0)
TOF	1 (2.0)
Autoimmune disease (SLE)	3 (5.9)
COVID-19	3 (5.9)
Hematological disease	3 (5.9)
Sickle cell anemia	2 (3.9)
Aplastic anemia	1 (2.0)
Pregnancy-related disease (post-cesarean section)	1 (2.0)
Psychological disease (anxiety/ADHD)	1 (2.0)
Trauma (mild blunt force head trauma)	1 (2.0)

ESRD, end-stage renal disease; ARF, acute renal failure; SCD, sickle cell disease; SIOD, Schimke immuno-osseous dysplasia; LDS, Loeys-Dietz syndrome; NF-1, neurofibromatosis type 1; ALL, acute lymphocytic leukemia; MDS, myelodysplastic syndrome; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; TOF, tetralogy of Fallot; SLE, systemic lupus erythematosus; COVID-19, coronavirus disease 2019; ADHD, attention deficit hyperactivity disorder.

six patients (11.8%). Notable hematological conditions included sickle cell disease in two patients (3.9%) and aplastic anemia in one patient (2.0%). Additionally, the medical histories included several rare genetic diseases: two cases (3.9%) of Schimke immuno-osseous dysplasia, one case (2.0%) of Loeys-Dietz syndrome (LDS), and one case (2.0%) of neurofibromatosis type 1.

4. Radiological findings

Angiographically, 46 patients (90.2%) presented with multifocal stenoses; among these, six who were initially diagnosed with focal stenosis later experienced progression to multifocal stenoses. Additionally, five patients (9.8%) exhibited focal stenosis, while two (3.9%) displayed hemispheric stenosis. Neuroimaging, utilizing either MRI or CT, revealed posterior reversible encephalopathy syndrome (PRES) in 10 patients (19.6%). Furthermore, three patients (5.9%) experienced ischemia, and seven (13.7%) displayed cerebral hemorrhage, with six cases of subarachnoid hemorrhage and one case of intraparenchymal hemorrhage (Table 4).

5. Comparison of factors based on neurological outcomes

A comparison of various factors with respect to neurological outcomes (Table 5) revealed that a medication trigger for RCVS was significantly more common among the patients who fully recovered than among those with residual neurological deficits (P=0.021). Hypertension, whether at the time of presentation or during hospitalization, was significantly more frequent in the group with residual deficits compared to those who fully recovered (P=0.006). Additionally, the prevalence of genetic and nephrological diseases was significantly higher among patients with residual deficits (P<0.01). Clinical manifestations that were predictive of poor neurological outcomes included motor weakness (P=0.03) and aphasia (P=0.004). However, other factors, such as radiological findings, treatment approaches, and the number of headache recurrences, did not exhibit significant differences between the two groups.

Discussion

1. Demographics

The data presented in this article augment the pediatric RCVS case pool by adding 25 new cases to the 26 previously reported in a case series review by Maldonado-Soto and Fryer [10]. The growing body of published pediatric RCVS cases indicates that the condition may be more common in this patient population than once believed. The present study included 51 cases, with a mean patient age of 11.74±4.11 years. Of the 51 patients reviewed, 31 (60.8%) were male, supporting the previously observed trend of a male predominance in pediatric RCVS. This contrasts with the higher prevalence of female patients in adult RCVS cases [10,11]. While additional research is necessary, fluctuations in sex hormones could be implicated in the pathophysiology of RCVS. Estrogen is known to participate in the regulation of vascular tone and the permeability

Table 4. Radiologic findings of reversible cerebral vasoconstriction syndrome (51 cases)

Findings	No. (%)
Angiographic findings	
Multifocal stenosis	46 (90.2)
Hemispheric stenosis	5 (9.8)
Focal stenosis	2 (3.9)
Brain imaging findings	
Ischemia/PRES	13 (25.5)
PRES	10 (19.6)
Subarachnoid hemorrhage	6 (11.8)
Ischemia	3 (5.9)
SAH+ICH	2 (3.9)
Intracranial hemorrhage	1 (2.0)

PRES, posterior reversible encephalopathy syndrome; SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage.

of the blood-brain barrier. This hormone diminishes sympathetic tone by activating the endothelial nitric oxide synthase gene, which leads to the production of prostacyclin, a potent vasodilator. Consequently, periods of rapid hormonal fluctuation, such as the female postpartum and perimenopausal stages and the male peripubertal/pubertal phases, may act as potential triggers or modifiers of the disease, supporting the hypothesis of hormonal involvement [1]. Additionally, the literature includes frequent links between glucocorticoids and unfavorable outcomes in RCVS. Glucocorticoids amplify the effects of vasoconstrictors such as epinephrine, angiotensin II, and endothelin, while also exerting direct effects on vascular smooth muscle cells [12].

Therefore, the association between steroid molecules and disease processes in RCVS may be plausible, given the increased synthesis of steroid hormones during male puberty [10].

2. Clinical manifestations and triggers

The clinical manifestations observed in our study closely resembled those seen in adults, with headaches being a prominent symptom. These headaches were often described as thunderclap or severe, accounting for 44 of the 51 reported cases. Neurological features, including motor deficits, seizures, and changes in mental status, were seen more frequently than anticipated in pediatric cases of RCVS [13]. However, cranial nerve palsies were rare, with only one instance documented in this study. In general, children seldom report symptoms such as headaches. It remains unclear whether the delayed reporting of symptoms and subsequent diagnosis in pediatric patients may explain the relatively high rates of these neurological symptoms. Consequently, comparing the time from symptom onset to diagnosis between adult and pediatric RCVS cases could provide valuable insights.

RCVS can present as either idiopathic (arising without a known trigger) or secondary (occurring in response to an identified trigger). While not an exhaustive list, common triggers among adults include pregnancy, postpartum changes, exercise, hypertension, sympathomimetic drugs, illicit drug use, serotonergic agonists, dialysis, and surgery, especially neurovascular procedures [4,8,14].

Consistent with the available literature, triggers were identified in 44 of 51 (86.3%) cases, with only seven cases having unidentifiable triggers. The most common triggers were drugs of various classes, including nasal decongestants, antimigraine medications, and chemotherapy agents. Exercise and emergence following surgery were also frequently noted. Most of these procedures were neurovascular and cardiac operations. Although postpartum physiology is recognized as a common trigger for adult RCVS, it appears to be relatively rare in the pediatric-adolescent population. Our study reported only one case involving postpartum development of RCVS, arising on the first day following a cesarean section. This rarity can be attributed to the focus of our study on pediatric cases, which inherently reduced the likelihood of encountering pregnant patients.

In contrast to studies from France and the United States, which identified illicit drug use as a common trigger for RCVS in adults (applying to 20% to 32% of cases), our findings suggest that illicit drug use is rare in pediatric RCVS. The age at which individuals are typically exposed to illicit drugs can vary widely depending on cultural and national contexts; however, pediatric patients are generally less likely to engage in illicit drug use than adults. This difference may explain why illicit drug use is an uncommon trigger in pediatric RCVS. Additionally, RCVS cases have been observed following blood transfusion, particularly in severe cases requiring massive transfusion, such as those involving sickle cell anemia.

3. Comorbidities

The pathophysiology of RCVS remains unexplained; however, overwhelming evidence from several studies suggests that dysregulation of cerebral vascular tone is central to its pathophysiology. This dysregulation can result from sympathetic overactivity, excessive oxidative stress, endothelial dysfunction, or disruption of the blood-brain barrier (BBB). Recent evidence indicates that certain patients may have a pre-existing genetic predisposition to develop RCVS upon exposure to specific triggers, unlike individuals without this genetic predisposition [1,14-16].

A review of medical histories indicated that the most common prior condition was recurrent headaches, with six individuals (60%) reporting a history of migraines. This observation is consistent with research associating certain migraine medications, such as ergot derivatives and triptans, with the onset of RCVS [17]. These medications exert vasoactive effects by targeting 5-hydroxy-

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Table 5. Comparison of demographic and associated factors by clinical outcome (51 cases)

Variable	Fully recovered (n=41)	Residual deficit (n=10)	Total no. (%)	*P* value
Demographic data				
Sex (male/female)	26/15	5/5	51 (100.0)	0.486
Age (yr)	12.2±3.9	9.9±4.8		0.121
Precipitating factors				
Medications/drugs[a]	17	0	17 (33.3)	0.021
Exercise	9	1	10 (19.6)	0.396
Other triggers	7	2	9 (17.6)	0.828
Trauma/surgery	8	1	9 (17.6)	0.479
Anemia	3	1	4 (7.8)	0.777
Pregnancy	1	0	1 (2.0)	0.618
Medical history				
HTN at presentation or during admission	10	7	17 (33.3)	0.006
Migraine	5	2	7 (13.7)	0.520
Nephrological disease	3	4	7 (13.7)	0.007
Vascular abnormalities	4	3	7 (13.7)	0.095
Genetic disorders	2	4	6 (11.8)	0.005
Other headache	5	1	6 (11.8)	0.847
Malignancy	6	0	6 (11.8)	0.198
Cannabis	2	1	3 (5.9)	0.537
Autoimmune disease	3	0	3 (5.9)	0.378
Asthma	2	0	2 (3.9)	0.476
Psychological disorders	1	0	1 (2.0)	0.618
Epilepsy	0	1	1 (2.0)	0.041
Neurological symptoms				
Seizure/mental changes	13	6	19 (37.3)	0.252
Motor weakness	10	6	16 (31.4)	0.03
Vision problems	10	3	13 (25.5)	0.715
Sensory deficits	4	2	6 (11.8)	0.367
Aphasia	1	3	4 (7.8)	0.004
Ataxia	3	0	3 (5.9)	0.378
Neuroimaging findings				
PRES/Ischemia	9	4	13 (25.5)	0.498
Cerebral hemorrhage	7	3	10 (19.6)	0.356
Angiography findings				
Diffuse stenosis	36	8	46 (90.2)	0.676
Focal stenosis	4	1	5 (9.8)	0.981
Hemispheric stenosis	1	1	2 (3.9)	0.269
Treatment given				
Other antihypertensives[b]	13	4	17 (33.3)	0.672
Analgesia	13	1	14 (27.4)	0.302
AED	9	4	13 (25.5)	0.240
Steroids	10	2	12 (23.5)	0.769
Nimodipine	7	3	10 (19.6)	0.356
Anticoagulants	7	3	10 (19.6)	0.165
Verapamil	7	2	9 (17.6)	0.828
Mannitol	2	0	2 (3.9)	0.476
Magnesium	1	0	2 (3.9)	0.618
Surgical procedure	1	1	2 (3.9)	0.269
Labetalol	1	0	1 (2.0)	0.618
Headache recurrence				
Three times or more	6	3	9 (17.6)	0.253
Once	4	1	5 (9.8)	0.981
Twice	3	2	5 (9.8)	0.227

HTN, hypertension; PRES, posterior reversible encephalopathy syndrome; AED, antiepileptic drug.

[a]Drugs included anticancer drugs (cyclosporine, vincristine, methotrexate, pirarubicin, L-asparaginase, cyclophosphamide), steroid-sparing immunosuppressants (mycophenolate mofetil, tacrolimus, rituximab), steroids (methylprednisolone, prednisolone), antimigraine medications (eletriptan), and a nasal decongestant (oxymetazoline); [b]Other antihypertensives included nicardipine, nifedipine, amlodipine, carvedilol, propranolol, nitroglycerine, and others not specified.

tryptamine receptors on the smooth muscle cells of the cerebral vasculature [18]. Chen et al. [16] investigated circulating microRNAs (miRNAs) in association with RCVS. miRNAs are small non-coding RNAs that play a role in regulating gene expression across various cellular functions. Their study identified elevated levels of the miRNAs let-7q-5p, let-7b-5p, and let-7f-5p during the acute and ictal phases of migraine headaches. These miRNA levels have been proposed to increase in response to pain, although it is also possible that migraine headaches and RCVS could fall on the same clinical spectrum, rather than representing distinct conditions.

Malignancies were present in 12% of the 51 patients and included acute lymphoblastic leukemia, retinoblastoma, and pheochromocytoma. These were primarily associated with the use of chemotherapy and steroids, which acted as triggers for RCVS. The administration of common chemotherapeutic drugs such as methotrexate, vincristine, and daunorubicin poses a risk of direct central nervous system toxicity. Furthermore, in retinoblastoma, the combined impact of effects related to the malignancy (paraneoplastic effects) and those resulting from radiation therapy can lead to a complex interplay that results in autonomic dysregulation. Endothelial dysfunction, which is attributed to the vasoactive effects of metanephrines produced by pheochromocytomas, is also a noteworthy factor [1,19].

All patients with malignancies received chemotherapy and/or steroid therapy. Glucocorticoids have been identified as predictors of unfavorable short- and long-term outcomes [6,18]. Consequently, the actual adverse effects of steroids may have been underestimated in this patient cohort. Evaluation for RCVS is advisable in patients with malignancies who are undergoing treatment, especially in those presenting with symptoms like sudden onset headaches.

This meta-analysis also identified rare genetic diseases, including LDS, neurofibromatosis type 1, two cases of Schimke immuno-osseous dysplasia, and two cases of sickle cell disease. Further investigation is necessary to elucidate any genetic correlations with RCVS. LDS, a rare autosomal dominant connective tissue disorder, is associated with polymorphisms in the genes that encode transforming growth factor beta receptors. Clinical manifestations include aortic aneurysms, arterial tortuosity, and other dysmorphic features [7]. These receptors are implicated in the induction of vascular endothelins and the expression of endothelin-1 receptors, which could potentially mimic an increase in sympathetic activity [1].

The Val allele at codon 66 of the brain-derived neurotrophic factor (BDNF) gene has been reported in patients exhibiting a more severe phenotype of RCVS [20]. BDNF is believed to induce perivascular inflammation and promote the release of neuropeptide Y from nerve endings, which in turn leads to vasoconstriction. Determining whether these gene polymorphisms should be considered in the treatment of patients with RCVS to allow for more targeted therapy warrants further investigation.

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been linked to a variety of cerebrovascular phenomena [21]. Ongoing research is continually uncovering new information about the health impacts of SARS-CoV-2 infection. This review includes three patients affected by both RCVS and SARS-CoV-2 infection. The SARS-CoV-2 virus is known to decrease levels of angiotensin-converting enzyme 2, leading to increased activation of the renin-angiotensin-aldosterone system and subsequent vasoconstriction. Although a direct causal link cannot be conclusively established based on these cases, clinicians should be aware of the possible emergence of RCVS in patients with SARS-CoV-2 infection.

4. Treatment modalities

In the absence of randomized controlled trials for RCVS, management typically depends on the clinician's judgment. In addition to supportive measures, which include analgesia, bed rest, and the avoidance or removal of triggers, certain medications have demonstrated beneficial responses. These include calcium channel blockers, such as nimodipine and verapamil [6,22].

Regarding the treatment of pediatric RCVS, several differences were observed in comparison to the adult population. As previously mentioned, the lack of clinical trials specifically addressing treatment complicates the development of effective regimens. While approximately 80% of adult patients are prescribed calcium channel blockers such as verapamil and nimodipine [13], our study found that only about half of the pediatric patients (54.9%) received these medications. Around 23% were treated with steroids, and 33% were given other antihypertensive agents. The safety profile of nimodipine for pediatric use has not been well-established, which may account for its relatively infrequent use by clinicians. A similar rationale may apply to verapamil, despite its common use as an antiarrhythmic agent in children.

RCVS presents substantial diagnostic challenges due to overlapping features with other severe neurological diseases characterized by thunderclap headaches. The differential diagnosis should include aneurysmal subarachnoid hemorrhage, cerebral vascular accident, venous sinus thrombosis, pituitary apoplexy, and primary angiitis of the central nervous system (PACNS).

The frequent use of steroids observed in this meta-analysis could be attributed to the rarity of RCVS in the pediatric population. Consequently, a pediatric patient presenting with symptoms con-

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sistent with RCVS may instead be preferentially treated as a case of PACNS, thus receiving steroids. Furthermore, the changes associated with RCVS may not be consistently detectable on neuroimaging, which could necessitate repeated imaging when clinical suspicion remains high. A critical need exists for future clinical trials to clarify the treatment strategies for RCVS in pediatric patients [23].

5. Prognosis and predictors of neurological outcome

Despite generally being considered benign, with full neurological recovery in over 90% of cases, RCVS can lead to complications such as convexity subarachnoid hemorrhage, cerebrovascular accident, PRES, and seizures. These complications can increase the risk of residual deficits in certain patients [18]. PRES, which commonly occurs in individuals with hypertension, has been reported in a few cases of RCVS. Given the overlapping clinical manifestations, PRES and RCVS may coexist on a single clinical spectrum and share similar pathophysiological mechanisms [5].

In our meta-analysis of 51 patients, three (5.9%) experienced ischemia, while 10 (19.6%) exhibited PRES. One patient with intracerebral hemorrhage in the frontal lobe underwent surgical decompression. Chen et al. [15] evaluated BBB permeability using dynamic contrast-enhanced MRI and found a microscopic increase in BBB permeability in all patients with RCVS during the acute phase. This increase may not be evident on standard neuroimaging. Dysfunction of the BBB can lead to hemorrhage/infarction and vasogenic parenchymal edema. This is consistent with observations that most hemorrhages occur in the acute phase of RCVS [1,24]. Crucially, a high index of suspicion is essential for diagnosing RCVS, given the wide variability in clinical presentation and the potential for serious complications.

Angiography revealed reversal of vasospasm in all cases, with a mean duration of 71.86±54.6 days. This finding aligns with the diagnostic criterion established by Calabrese et al. [7], which states that reversal should occur within 3 months (90 days) of onset.

A comparative analysis of various factors between individuals who achieved full recovery and those with residual neurological deficits revealed a significantly higher proportion of medication-triggered cases among those who fully recovered compared to those who did not (P=0.021). This observation may be due to the relative ease of identifying drugs as triggers, which facilitates the prompt removal of the offending agent and positively influences clinical outcomes.

Hypertension at presentation or during hospital admission, as well as genetic disease, showed a significantly higher prevalence in the group with residual neurological deficits (P=0.01). In our study, nephrological diseases were also markedly more common among patients with residual deficits (P=0.007). To our knowledge, this study is the first to report nephrological disease as a risk factor for residual deficits in patients with RCVS. This association may stem from the high rate of hypertension in patients with ESRD, some of whom were undergoing dialysis—a recognized risk factor for endothelial damage—in our study. Another potential link is uremia, which is frequently seen in patients with ESRD and is directly toxic to the central nervous system. Uremia may contribute to endothelial dysfunction and increase the risk of cerebral vasoconstriction. These observations highlight the critical role of endothelial dysfunction in the pathogenesis of RCVS.

Consistent with research conducted by Song et al. [13], which included both pediatric and adult patients, our results indicate that aphasia and motor weakness are associated with relatively poor outcomes (P=0.004 and P=0.03, respectively). However, unlike the findings of the Song et al. [13] study, we observed no significant differences in the history of recent surgery, trauma, or any other procedure between the group that achieved full neurological recovery and the group that did not. One possible explanation for this discrepancy is that the other study incorporated both adult and pediatric patients; some triggers and comorbidities, such as hypertension, are more prevalent among adults and could influence clinical outcomes. Additionally, the study by Song et al. [13] had a larger sample size of 191 cases, compared to our 51 cases, minimizing bias in their comparative analysis.

This systematic review and case series study was susceptible to biases such as publication, selection, and selective outcome reporting. The nature of case reports, which are led by investigators, may result in the omission of certain information that is crucial for analysis, potentially influencing the outcomes. We encountered instances of missing data, including vital signs and key laboratory findings (such as cerebrospinal fluid results) that could have provided insight into alternative clinical presentations. The limited sample size also may have introduced bias. Finally, organizing the data was challenging due to variability in terminology and reporting heterogeneity, which depend on the authors. This variability made it difficult to systematically categorize clinical descriptions and presented obstacles for analysis, including correlation analysis.

Summary

In the present systematic review, we comprehensively examined various factors, including clinical manifestations, triggers, medical histories, and predictors of poor outcomes, in pediatric patients with RCVS. The findings of the study challenge the notion that pediatric RCVS is rare, highlighting the need for a high index of suspicion to ensure accurate diagnosis. This is essential not only for selecting the appropriate treatment approach but also for positively

influencing clinical outcomes. Factors associated with poor neurological outcomes in pediatric RCVS included concurrent nephrological disease, the presence of genetic disorders, and hypertension at presentation or during hospitalization. Motor deficits and aphasia were also identified as predictors of unfavorable neurological outcomes. Continued research and publication regarding RCVS cases is warranted, with a focus on clarifying pathogenesis and establishing effective management strategies.

Conflicts of interest

Joon Won Kang is an editorial board member of the journal, but he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant.

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