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Seminars in PEDIATRIC NEUROLOGY

Reversible cerebral vasoconstriction syndrome in children: an update

Angel R. Maldonado-Soto, and Robert H. Fryer

Headaches are one of the most common neurologic complaints leading to emergency room visits in pediatric patients. Of the different type of headache presentations, thunderclap headaches require a particularly urgent work-up. In children, recurrent thunderclap headaches are more often associated with reversible cerebral vasoconstriction syndrome (RCVS) than other etiologies such as subarachnoid hemorrhage. RCVS is a vascular disorder of incompletely understood etiology, characterized by diffuse vasoconstriction of the cerebral arterial vasculature, and commonly associated with recurrent severe headaches. Patients may experience focal neurological deficits, due to hemorrhages, infarcts, and even posterior reversible encephalopathy syndrome . Although RCVS has been best characterized in adults, it does occur in children. This review summarizes the presentation of RCVS in children and highlights some of the differences with the adult population.
Semin Pediatr Neurol 40:100936

Thunderclap Headaches

Headaches are one of the most common complaints encountered by pediatric neurologists in routine practice.[1] Pediatric headaches can account for almost 3% of all pediatric emergency room visits, and in the past years there may have been an increase in pediatric patients presenting with headaches.[2, 3] Although many of these patients will have primary headaches such as migraine, an important proportion of these patients will present with headaches that require urgent work-up. Thunderclap headache (TCH), as defined in the International Classification of Headache Disorders (ICHD-3), is a severe sudden onset headache that reaches its maximum intensity within the first minute and lasts for at least 5 minutes.[4] TCH accounts for close to one percent of pediatric headache presentations.[5] Recognition of TCH is of vital importance as the underlying etiologies include disorders associated with significant morbidity and mortality such as subarachnoid hemorrhage (SAH), cerebral sinus venous thrombosis and RCVS.[6]

Columbia University Irving Medical Center, New York, NY.
Address reprint requests to: Robert H. Fryer, Columbia University Irving Medical Center, 180 Fort Washington Ave, Harkness Pavilion, 5th Floor, New York, NY 10032 E-mail: rf203@cumc.columbia.edu

RCVS

Reports of "benign" or reversible cerebral vasoconstriction were described in the literature beginning in the 1960s and in 1988 Gregory Call and Marie Fleming proposed that the presentations in some of these patients may be due to reversible vasoconstriction,[7] leading to the eponym Call-Fleming syndrome. The term RCVS was first coined in 2007 by Calabrese and colleagues, who described unified criteria to aid in the diagnosis and work-up of patients, centered around the multifocal segmental vasoconstriction and reversibility of this process.[8] Since then, many case reports and series have been published describing this group of patients and their presentations.

RCVS has been best characterized in adult patients. Large cohorts of adult patients have shown an overwhelming predominance of middle-aged females, ranging between 64% and 89% of patients.[9–14] Each of these cohorts included between 77 to 139 patients. By contrast, the largest review of pediatric RCVS patients included 13 patients and most of the available pediatric cases constitute individual case reports or small series.[15–17] Here we compiled the case reports that were not included by Coffino and Fryer and listed them in Table 1. Of the 29 pediatric patients published in the literature, 19 were male (65.5%) with a median age of 13 years-old (range 6-18 years-old, Table 2). While confounded by the low total number of pediatric cases, the predominance of

https://doi.org/10.1016/j.spen.2021.100936

Table 1 Review of Pediatric RCVS Cases not Included in Coffino and Fryer (2017)

Study	Age/Sex	Possible Risk Factors	Triggers	Symptoms and Exam	Brain Imaging	Vessel Imaging	Other Work-up	Treatment	Outcome
Agarwal et al., 2014	13 y female	No past medical history reported	HUS, HTN, azotemia, dialysis	Global aphasia, right sided facial droop and hemiparesis. Did not develop headache (was encephalopathic)	CT: hypodensity in left frontal region. MRI: Multifocal T2/FLAIR lesions, predominantly in left frontal, bilateral frontal and parietal regions consistentwith PRES; no diffusion restriction	MRA: Vasoconstriction right MCA and PCA	Serological work-up normal, CSF normal	Nicardipine drip, followed by oral antihypertensives (unspecified). Received IVIG and methylprednisolone initially when there was concern for vasculitis.	Deficits resolved after 8 d
Akazawa et al., 2015	9 y male	Loeys-Dietz Syndrome, total aortic replacement following massive aortic dissection 2 mo prior	Left subclavian artery dissection	TCH, nausea, vomiting. Developed visual disturbances and seizure on 6th d of admission	MRI: right parietal cortical SAH; on day of seizure MRI showed FLAIR lesions in left occipital and right temporal lobes, bilateral cerebellar hemisphere res consistentwith PRES	MRA: Narrowing of bilateral distal ICA, left subclavian artery dissection; on 5th day of admission MRA showed worsening of ICA narrowing	Increased D-dimer, otherwise unremarkable	Nicardipine	Resolution of symptoms by 13th d and imaging findings by 2 mo
Trollietetal., 2016	13 y male	No past medical history reported	Body building	TCH, altered mental status, nausea, vomiting (signs of increased ICP)	MRI: No cerebral lesions identified	MRA: Bilateral MCA multifocal vasoconstriction	Normal CSF profile but elevated intracranial pressure (55 mm Hg); elevated velocities in trasncranial doppler	Corticosteroids for presumed angiitis, subsequently stopped when RCVS was suspected	Symptoms resolved within 2 mo, and imaging findings resolved within 3 mo
Ueki etal., 2016	16 y female	Refractory cytopenia of childhood (diagnosed 41 months priorto presentation)	Cyclosporine, methylprednisolone	Throbbing headache gradually worsening over 4 d to 7 out of 10 scale	MRI: No cerebral lesions identified	MRA: Bilateral ICA and ACA beading	None reported	Lomerizine	Headache resolved 5 d after lomerizine was started.; repeat imaging showed resolution of ICA vasocons-triction
Oikawa et al., 2017	10 y male	No past medical history reported	Cerebellitis diagnosed 18 d priorto headache; treatmentwith IVIG and methylprednisolone 6 days prior to headache	TCH, vomiting, seizure on day 18 of cerebellitis admission; headache and worsening ataxia on day 22 of admission	MRI: T2 hyperintensities in bilateral frontal and parietal lobes	MRA: Diffuse cerebral vasodilation on day 18 of hospitalization; multifocal segmental vasoconstrictions on day 22	CSF white blood cell count 121 and +GluD2 antibody in serum and CSF(18 d priorto headache onset)	Plasmapheresis, IVIG and methylprednisolone; no further treatment after vasoconstriction noted	Symptoms resolved, no recurrence, able to walk without ataxia
Kamide et al., 2017	10 y male	No past medical history reported	Exercise	TCH, no neurological deficits	MRI: Restricted diffusion and FLAIR lesions consistentwith PRES, left cerebellar infarct	Bilateral MCA and right PCA narrowing	Normal serological and CSF labs	None	Resolution of symptoms by admission, no deficits
Zuccoli et al, 2018	18 y female	SCD; VOC and ACS 1 wk priorto headache	Blood transfusions, synthetic cannabinoid use, alcohol use	TCH, left leg weakness, visual changes, involuntary shaking; on day 2 of admission developed worsening severe headache and altered mental status	CT: SAH in left frontal lobe MRI: on admission showed leftfrontal SAH and cortical edema in leftfrontal and occipital lobes consistentwith PRES; on day 2 of admission developed new bilateral frontal and parietal infarcts	MRA: on admission did not show abnormalities; on day 2 of admission showed segmental vasoconstrictions of bilateral ACA and VA	Hemoglobin 13.1; slowing on electroencephalography	Did not receive calcium channel blocker	Discharged 2 mo later with significant neurological deficits

Table 1 (*Continued*)

Study	Age/Sex	Possible Risk Factors	Triggers	Symptoms and Exam	Brain Imaging	Vessel Imaging	Other Work-up	Treatment	Outcome
Durrleman et al., 2019	11 y female	SLE, on mycophenolate mofetil for > 1 week	Rituximab, methylprednisolone, blood transfusion started within one week of TCH	TCH on presentation, developed seizures within first week	MRI: Initial did not show brain lesions; repeated in first wk after seizure showed FLAIR lesions in right cerebellar and left occipital cortex consistentwith PRES	MRA: bilateral ICA, ACA, MCA, PCA and SCA stenoses	Normal CSF studies	Did not receive calcium channel blocker	Complete recovery by 5 mo
	14 yo female	SLE, on cyclophosphamide and methylprednisolone for > 1 wk	No medication started within 1 wk from TCH	Mild headaches, hallucinations, CN palsies, blurred vision	MRI: no cerebral lesions identified	MRA: bilateral ICA, ACA, MCA, PCA and PICA stenoses	Normal CSF studies	Did not receive calcium channel blocker	Complete recovery by 1 mo
	13 y female	SLE, on no medications for > 1 wk	Mycophenolate mofetil, methylprednisolone started within one week from TCH	TCH, nausea, vomitinge; in second wk developed unilateral paresthesia	MRI: intiial did not show brain lesions; repeated in second week showed centrum semiovale infarct	MRA: bilateral ICA, ACA, MCA, PCA and SCA stenoses	CSF normal WBC, elevated protein and RBC	Nimodipine	Complete recover by 3 mo
Kayfan et al., 2019	13 y female	History of headaches (unspecified)	None reported	Throbbing headache 8 of 10 intensity, altered mental status and slurred speech, followed by blurry vision	No cerebral lesions identified on CT or MRI	MRA: narrowing of right ACA and left PCA	Normal serological studies; decreased perfusion of right cerebral hemisphere on ASL	Verapamil for 3 mo	Only had 2 recurrent but mild headaches. Repeat angiography 10 mo after had improved
	6 y male	History of headaches (unspecified) with transient right-sided weakness	None reported	Headache (unspecified), slurred speech and left-sided weakness	MRI: FLAIR signal throughout right cerebral hemisphere with associated diffusion restriction	MRA: narrowing of right ACA and MCA	Decreased perfusion of right hemisphere on ASL	Verapamil for 1 mo	Not reported
Regling et al., 2021	8 y male	SCD, VOC, ACS	Blood transfusions	TCH, left leg weakness, seizure on d 6 of admissior for VOC	MRI: SAH in right l frontal lobe	MRA: MCA and bilateral PCA	Normal serologic electrolytes, hemoglobin S level 38%	Nicardipine (blood pressure)	Discharged home without deficits 2 wk later

ACS, acute chest syndrome; ACA, anterior cerebral artery; ASL, arterial spin labeling; CSF, cerebrospinal fluid; FLAIR, fluid attenuated inversion recovery; HUS, hemolytic uremic syndrome; ICA, internal carotid artery; IVIG, intravenous immunoglobulin; MCA, middle cerebral artery; PCA, posterior cerebral artery; PRES, posterior reversible encephalopathy syndrome; SCD, sickle cell disease; SAH, subarachnoid hemorrhage; SLE, systemic lupus erythematosus; TCH, thunderclap headache; VOC, vaso-occlusive crisis; VA, vertebral artery.

Table 2 Pediatric RCVS Patient Characteristics in Published Literature

Study	Current Study	Coffino and Fryer, 2017	Total
Pediatric patients (total number)	13	13	26
Male sex			19 (65.5)
Median age, in y (range)	13 (6-18)	13 (7-16)	13 (6-18)
Secondary RCVS	9 (69.2)	6 (46.2)	15 (57.7)
TCH / Severe headache present	10 (76.9)	13 (100)	23 (88.5)
Steroid use prior to symptom onset	5 (38.5)	0	5 (19.2)
Calcium channel blocker treatment	7 (53.8)	8 (61.5)	15 (57.7)
Specific agents used (total number)	Nimodipine (1) Verapamil (2) Lomerizine (1) Nicardipine (3)	Nimodipine (3) Verapamil (3) Nifedipine (2)	
No residual deficits	11 of 12 (91.7)	13 (100)	24 of 25 (96)
Patients with brain imaging available for review (total number)	13	11	24
Any lesion on imaging	9 (69.2)	8 (72.7)	17 (70.8)
Infarct on imaging	3 (23.1)	4 (36.4)	7 (29.2)
Hemorrhage on imaging	3 (23.1)	3 (27.3)	6 (25)
PRES on imaging	5 (38.5)	1 (9.1)	6 (25)

Values presented are total number (percentage), unless otherwise noted. Abbreviations: PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome; TCH, thunderclap headache.

males in pediatric RCVS is in sharp contrast to the female predominance in adult RCVS cases. Three of the pediatric patients did not have any additional data available and will not be included in subsequent analyses.

RCVS can be divided into primary (no identifiable precipitant) and secondary (associated with a precipitant event or drug). Factors associated with secondary RCVS include use of vasoactive medications, post-partum state and iatrogenic immunosuppression.[18] In pediatric studies, most of the published cases can be categorized as secondary RCVS (15 of 26 patients with available data, see Table 2). Comorbid conditions present in children with RCVS ranged from cerebellitis and systemic lupus erythematosus (SLE), to sickle cell disease (SCD)[17,19–25] (Table 3). Out of 26 pediatric cases of RCVS, 7 children were noted to have hematologic or rheumatologic disease, suggesting that these disorders may place children at higher risk of developing RCVS.

This includes patients with SCD, cytopenias, and anemias of childhood, as well as those with SLE.[25]

Table 3 Comorbid Medical Conditions in Pediatric RCVS Patients

Study	Condition	Number of Patients
Both	None	7
Coffino and Fryer, 2017	Cardiomyopathy (hypertrophic)	1
	Aplastic anemia	1
	Migraines (on treatment)	1
	Migraines (not on treatment)	2
	Obesity	3
Current study	Headaches (unspecified)	2
	Hemolytic uremic syndrome	1
	Subclavian artery dissection	1
	Refractory cytopenia of childhood	1
	Cerebellitis	1
	Sickle cell disease	2
	Systemic lupus erythematosus	3
	Total	26

Presentation

Most patients with RCVS present with severe thunderclap headache early in the disease course. The ICHD-3 criteria for headache attributed to RCVS include at least one of the following: (1) sudden onset severe headache (ie, thunderclap headache), (2) triggered by exertion (including sexual activity and emotions) or bathing and/or showering, and (3) recurring headaches occurring over $\leq$ 1 month.[4] The headaches in RCVS often precede onset of typical angiographic findings of vasoconstriction, which can lead to delays in diagnosis. Patients with recurrent TCH without signs of vasoconstriction on initial imaging are diagnosed with probable RCVS, which is pathognomonic with RCVS and these patients should be treated as if vasoconstriction was present.[26] Repeat imaging later in the course (days to weeks) is needed to confirm the diagnosis. Patients occasionally present with focal neurological deficits that vary depending on the affected area of the brain.

The main complications experienced by patients with RCVS are SAH and infarcts. In adults who developed hemorrhagic and/or ischemic complications, SAH seems to be more common, seen in 79% of these patients, compared to intracerebral hemorrhage (29%) and ischemic stroke (25%).[27] Interestingly, hemorrhages tend to occur within the first 7 days after onset, whereas ischemic injury occurred after one week.[27] By contrast, in pediatric RCVS infarcts and hemorrhage had more similar incidences (29% and 25%, respectively; Table 2).

Most children with RCVS present with severe headache (23 of 26 patients, Tables 1 and 2). Of the three pediatric patients that did not present with TCH, 2 had milder headaches that did not satisfy criteria for TCH. The third patient developed acute encephalopathy and aphasia and was unable to confirm the presence of TCH. PRES has been described in up to 38% of adult RCVS patients[9,12] and in 25% of pediatric RCVS patients (Table 2). This correlation has led to the hypothesis that these 2 disease processes may share similar underlying pathophysiology. Pediatric patients who developed signs of PRES included one child of each with SLE, Loey-Dietz, hemolytic uremic syndrome, SCD and 2 without prior medical history.[17,20–22,24]

Evaluation

Given that most RCVS patients present with TCH, appropriate work-up must first include imaging to rule out intracranial hemorrhage. Noncontrast computer tomographic (CT) imaging of the brain is an appropriate first-line imaging modality to assess for SAH. Magnetic resonance (MR) imaging can be useful to rule out ischemic or hemorrhagic injuries, especially in those patients presenting with focal neurological deficits. A lumbar puncture should be considered in these patients to definitively rule out SAH, as well other possible causes of headache such as infection or inflammation. Cerebrospinal fluid studies in RCVS patients are usually unremarkable, and any abnormal result should prompt consideration of alternate diagnoses.

CT and MR angiography are both widely used and described in the RCVS literature. Direct comparisons are lacking between the 2 modalities' sensitivity to detect RCVS. As mentioned above, thunderclap headache usually precedes signs of vasoconstriction in some RCVS patients. On average, signs of vasoconstriction are noticed within 7-14 days of headache onset.[10,27,28] Thus, when patients present with recurrent TCH and negative imaging findings, repeat imaging, including vessel imaging, should be performed within 2 weeks of the initial encounter.[28] Notably, distal (ie, smaller vessel) vasoconstriction is seen within the first week of disease, whereas more proximal (ie, larger vessel) vasoconstriction is observed 1 or more weeks after symptom onset.[27] This "centripetal spread" of vasoconstriction has been described in several case series, but its mechanism remains unclear. Although all cerebral vasculature can be involved, vasoconstriction of the middle and posterior cerebral arteries (MCA and PCA, respectively) has been associated with a higher degree of developing PRES and infarcts.[10] Patients may have no brain imaging findings initially, and the findings in each patient may vary throughout the disease course.[29] Imaging in pediatric RCVS cases showed lesions such as stroke, hemorrhage, and PRES in 70% of cases (Table 2).

Pathophysiology

The precise underlying mechanism of RCVS remains unclear. The main proposed hypothesis is that RCVS may be caused by alterations in the autonomic regulation of cerebral arterial tone, which leads to vasoconstriction seen on imaging and clinical symptoms experienced by patients. This theory is supported by the diverse vasoactive and sympathomimetic medications that have been associated with RCVS. Serotonergic agents, such as antidepressants and triptans, are associated with developing or worsening of symptoms, which implicates a role of serotonin signaling in the pathophysiology of the disorder.[30] Studies looking at endothelial cells function have shown decreased reactivity of endothelial cells in RCVS patients in both the anterior and posterior circulation, compared with healthy controls.[31]

Disruption in arterial tone may also lead to increased leakage of the blood-brain barrier, similarly to what has been postulated for PRES. *In vivo* data is sparse, but Wu and colleagues showed contrast-enhanced MRI that suggested increased arterial permeability in RCVS patients.[32] Flow instability may have a role in the development of RCVS as several cases have followed blood transfusions.[20,23,33] Importantly, these patients also had signs of PRES on their imaging, perhaps indicating a dysregulation in cerebral capillary function. Hyperviscosity, which can be present in blood dyscrasias, has been proposed as a possible trigger for the vasoconstriction seen with RCVS. It appears that smaller blood vessels are affected earlier in the disease course, leading to breakdown of the BBB and complications such as SAH and PRES, whereas later in the course larger vessels are affected, which can then lead to ischemic injury.[27] How this shift from small to large vessels occur remains unknown.

High stress and emotional situations, which are usually accompanied by a physiologic increase in endogenous catecholamine release (sympathomimetic signaling), are associated with RCVS occurrence.[26,34,35] These can include such events as sexual activity, Valsalva maneuvers, bathing, submersion in water, grief, post-traumatic stress disorder, among others.[26,34] Interestingly, submersion in water or bathing in cold water is one of the most common identified triggers for RCVS and may in part be regulated through the trigeminal-cardiac reflex, which helps regulate cerebral arterial tone when the face is exposed to water.[36]

Treatment

Calcium channel blockers (CCB) are the most used treatment in the available literature. The most widely used CCB among adult patients with RCVS is nimodipine, with multiple studies spanning over the past 2 decades.[18,37] Nimodipine can be given both intravenously (IV) or orally, and clinical practices vary widely between studies. As a rule, IV nimodipine is reserved for patients with more severe symptoms, worse vasoconstriction or more complications.[18] More than half of pediatric patients were treated with CCB (Table 2), including nimodipine, nicardipine, nifedipine, verapamil, and lomerazine.

Despite their common use, CCB lack conclusive evidence to support their use in RCVS patients. Large retrospective studies have shown no particular benefit of nimodipine in long-term functional outcomes of adult RCVS patients.

Patients treated with nimodipine did not have statistically significant differences in modified Ranking Scale scores and more than a third of patients developed recurrent TCH.[9,12] However, other studies have shown symptomatic benefit in patients treated with calcium channel blockers, with patients who are treated earlier in the disease course experiencing less frequent and less severe headaches.[11,38] Thus, it seems like nimodipine treatment does help alleviate symptoms, but the long-term benefits may require more work to better elucidate. Use of intra-arterial vasodilators such as milrinone has been reported in more severe cases, and appear to improve vasoconstriction acutely, although not sustainably so their utility is still under investigation.[30,39]

Glucocorticoids worsen clinical and radiologic findings and are associated with worse outcomes in RCVS patients.[30] Moreover, glucocorticoids and other immunosuppressive treatments, such as calcineurin inhibitors, have been associated with onset of RCVS.[19,24,25] In children, 5 out of 26 pediatric RCVS patients were exposed to glucocorticoids, 4 of which had started treatment within the week prior to symptom onset (Tables 1 and 2). Thus, these medications should be avoided in this patient population.

Prognosis

RCVS usually follows a monophasic pattern, with very few patients experiencing recurrence of symptoms. Long term studies in pediatric RCVS are lacking, but in adults recurrent TCH has been described.[13,40] Even if patients do not experience recurrent TCH, around half of patient still complain of persistent headaches, although these are usually much milder in severity.[41] Independent factors associated with recurrent RCVS included having a prior history of migraines and if the initial headache was associated with exertion,[13] as well as having sexual activity as the trigger for thunderclap headache.[40] None of the patients included in those studies were children, and there is no available data on recurrence rates of RCVS in children. However, it does seem that most children have favorable outcomes, with 24 of 25 patients with available follow-up data lacking any residual deficits (Table 2).

Discussion

Although RCVS has been predominantly described in adult patients, it is increasingly being recognized in younger patients. Even though the number of children described in the literature is still low, some interesting patterns have emerged that warrant further discussion.

RCVS in adults occurs overwhelmingly in middle-aged women. However, in children the opposite is true, and the majority of patients are male. Although the total number of reported pediatric cases is still low, it is possible that this male prevalence is due to underlying physiologic conditions, given that most pediatric patients described in the literature are adolescents. In male patients this may implicate the increase in androgen production seen during adolescence, which has been proposed as one possible explanation for the male predominance in pediatric RCVS cases.[15,17] The observation that glucocorticoids are associated with onset and worse outcomes in RCVS patients may also indicate that steroid molecules in general are associated with this disease, as the production of these also increases during puberty.

Another important finding is that most pediatric patients develop secondary RCVS. One third of the pediatric patients reviewed here had hematologic or rheumatologic disorders, which indicates that these patients are likely at higher risk of developing RCVS. Patients with SCD require frequent blood transfusions, particularly during vaso-occlusive crises, which may lead to altered cerebral blood flow dynamics and the vasoconstriction characteristic of RCVS. Patients with rheumatologic disease are often on immunosuppressants, which have been implicated in RCVS development and progression, in addition to having a higher predisposition to involvement of their vasculature by the underlying disease process. As stem cell transplantation becomes more widely used, a greater proportion of patients with underlying hematologic disease will likely be on immunosuppressant therapy. Thus, a better understanding of their overall risk of developing RCVS is essential to prevent them developing the disease and its complications.

CCB are the main treatment provided to RCVS patients. Although it appears to improve symptoms, the benefits and effects on long-term outcomes have not been conclusively determined. Nimodipine appears to be the most widely used CCB in adult RCVS patients, but in children a greater number of CCB were reported, which makes it difficult to determine the utility of these agents. For those patients that have more severe disease (ie, greater degree of vasoconstriction, infarcts, and hemorrhage) intra-arterial vasodilators have been reported in case reports, but their utility is still under investigation.

Prognosis for most patients with RCVS is favorable. Most adults do well and have no or limited deficits. Of the 26 children reviewed here, one did not have follow-up data[29] and only one other had persistent neurologic deficits. Many pediatric patients who had SAH or small infarcts did well, which has been reported in adults as well. Interestingly, while in adults the most common complication is SAH, in children, infarcts were slightly more prevalent than hemorrhage (29% vs 25%, respectively). Although this may be due to differences in underlying pathophysiology, more cases are needed to validate this observation. As more pediatric RCVS patients are described it will be important to note whether SAH, infarcts, and PRES occur predominantly in patients with specific comorbidities, to better aid these patients.

Conclusion

Although relatively rare, RCVS does occur in children and adolescents. There may be important differences between pediatric and adult patients, such as sex predominance, but larger pediatric studies are required. Children with hematologic and rheumatologic disorders may be at higher risk of

developing RCVS. Most pediatric RCVS patients have favorable outcomes, but more work is needed to further clarify the risks for different populations of patients. In pediatric patients with TCH and co-morbid conditions such as hematologic or rheumatologic disorders, diagnosis of RCVS should be considered early in the presentation, with expedited imaging and evaluation.

Declarations of Interest

None.

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