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Case Report

Reversible Cerebral Vasoconstriction and Subarachnoid Hemorrhage following Blood Transfusion in a Pediatric Patient with Sickle Cell Disease

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Abstract

Reversible Cerebral Vasoconstriction Syndrome (RCVS) is a clinico-radiologic diagnosis consisting of "thunderclap" headache and segmental cerebral vasoconstriction. We present a case of RCVS complicated by subarachnoid hemorrhage (SAH) in a 5-year-old male with sickle cell disease (SCD) following a packed red blood cell (pRBC) transfusion. RCVS is rarely reported in children, which highlights the need for further research into the underlying mechanism, treatment, and prevention of RCVS in childhood. Additionally, we describe the diagnostic challenges in pediatric patients that may lead to incorrect diagnoses and underreporting.

Keywords: Reversible Cerebral Vasoconstriction, Sickle Cell Disease, Blood Transfusion

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is a clinico-radiologic syndrome characterized by "thunderclap" headache with or without neurologic deficits as well as vasoconstriction on neuroimaging, which typically resolves within three months. Pediatric presentations may range clinically from pure cephalgia to permanent, disabling neurologic deficits and death.1 In adults, RCVS typically presents in middle aged women2–6, but has a male predominance in pediatric patients.7 The pathophysiology of RCVS remains poorly understood, and although calcium channel blocking agents are often used as treatment, they have not been shown to improve outcome in large studies.2,8–10 RCVS is well-documented in adult patients, but fewer than 40 cases have been reported in children.7,11–14 To our knowledge, this is the second case of a male child with sickle cell disease presenting with RCVS and subarachnoid hemorrhage (SAH) following blood transfusion11, which underscores the need for further investigation into risk factors and outcomes in childhood RCVS.

The Case

Case Report

A 5-year-old boy with sickle cell disease (Hb SS) was admitted for acute chest syndrome and pneumonia. Baseline hemoglobin level was 5.3g/dL with 87% HgB S. Hemoglobin improved to 8.2g/dL after a simple packed red blood cell 15mL/kg transfusion. He was given two more simple 10mL/kg transfusions of packed red blood cells over the next 2 days, with his hemoglobin improving to 10.1g/dL with a HgB S of 30.1%. He was discharged from the hospital on antibiotics 10 days after admission, and 8 days after his last packed red blood cell transfusion. The day following discharge, however, he complained of a headache followed by a generalized tonic clonic seizure which resolved with lorazepam and levetiracetam administered intravenously by emergency medical technicians. He was intubated and on initial evaluation in the emergency department had pinpoint, minimally reactive pupils (likely due to sedative effect), but was moving all extremities spontaneously against gravity. His systolic blood pressure was 106 mmHg. Magnetic resonance brain imaging (MRI) showed an abnormal T2/FLAIR hyperintense signal in the sulci of the right occipital region [Figure 1A]. Susceptibility weighted imaging (SWI) did not demonstrate intracranial hemorrhage, and there was no diffusion restriction on diffusion weighted imaging. Magnetic resonance angiography (MRA) of the head and neck demonstrated only mild narrowing of the cavernous segment of the internal carotid artery on the right [Figure 1B]. Magnetic resonance venogram (MRV) was normal. Lumbar puncture was performed and cerebrospinal fluid (CSF) was reported as blood stained. CSF analysis revealed glucose of 66mg/dl [nl 45-80mg/dl], protein of 44mg/dl [nl 15-40mg/dl], 1980 red blood cells/mm3, 9 white blood cells/mm3 [nl 0-5 cells/mm3] (92% neutrophils [nl 0-6%], 7% lymphocytes [nl 40-80%], 1% monocyte [nl 15-45%]), a negative gram stain and culture, and negative herpes simplex virus, Epstein-Barr virus, and cytomegalovirus by polymerase chain reaction. A 20-minute electroencephalogram (EEG) showed moderate diffuse encephalopathy and no seizures. As the diagnosis was uncertain based on initial imaging, a repeat MRI of the brain was obtained the next day, demonstrating new bilateral, patchy, cortically-based diffusion restriction and gyral swelling with edema [Figure 1C, 1D].

He was treated supportively in the pediatric intensive care unit with maintenance normal saline and antibiotics for his known pneumonia. He did not receive steroid therapy. Four days later, he developed a severe, persistent headache and seizure. Repeat MRI of the brain showed progression of the diffusion restriction into the right temporal and parietal lobes and the pulvinar region of the thalamus [Figure 1E]. He was given a simple transfusion of 10mL/kg of packed red blood cells as initiation of therapy for presumed cerebrovascular disease in sickle cell disease, with his serum hemoglobin rising from 8.7 g/dl to 11.2g/dL. Blood pressures were in the 100s-130s mmHg systolic during this time period. He had another seizure two days later and EEG revealed focal epileptiform activity arising from the right occipital lobe and his dose of levetiracetam was increased. He then developed elevated blood pressure to 180 mmHg systolic and new onset anisocoria prompting brain computed tomography (CT) which showed subarachnoid hemorrhage [Figure 1F]. Repeat MRA and MRV showed narrowing of the left A2 and A3

segments of the anterior cerebral artery (ACA) and right greater than left bilateral M2 and M3 segments of the middle cerebral arteries (MCA), as well as bilateral narrowing of the P2 and P3 segments of the posterior cerebral arteries (PCA) [Figure 1G]. No aneurysm was visualized. Nimodipine at 10mg/kg/dose by mouth scheduled every 4 hours was initiated at this point for management of both hypertension and vasospasm. Further MRI and MRA of the brain performed 3 days later demonstrated resolving restricted diffusion and improved caliber of the ACA and MCA consistent with reversible cerebral vasoconstriction syndrome[1H]. The nimodipine was weaned off over the next 5 days and he had no worsening of seizures, headaches, or encephalopathy.

The patient was discharged on day twenty-two of admission without antihypertensive medication, though he was on oral levetiracetam 60mg/kg/day for seizure prophylaxis, and clindamycin for his resolving lung infection. On evaluation in clinic one month later, he had no further headaches or seizure-like activity, and his neurologic examination was normal. A repeat MRI brain obtained 6 months after his initial presentation was normal, with no encephalomalacia, and all previously seen areas of intracranial vessel irregularity now resolved. He had a small area of cortical hemosiderin staining on susceptibility weighted imaging secondary to his prior subarachnoid hemorrhage.

Discussion

We describe a pediatric patient with sickle cell disease who presented with reversible cerebral vasoconstriction syndrome about 1 week following red blood cell transfusion. He was also treated with red blood cell transfusions after presentation, the standard of care for cerebrovascular events in sickle cell disease. The patient continued to do well at follow-up 1 month after discharge.

RCVS is characterized by severe, sudden-onset headache and segmental cerebral vasoconstriction, often with cortical subarachnoid hemorrhage as well. The diagnostic criteria proposed in 2007 by Calebrese are included in Table 1.8 Our patient met these criteria as documented in our case presentation. Although RCVS has been extensively reported, the pathophysiology remains unknown. It classically presents in women in the 5th decade of life with male-to-female ratio of 1:2-4.10,15 The most common predisposing factor is the postpartum period.1 Pharmacologic triggers may include sympathetic and adrenergic agonists, serotonin agonists (including ergots and triptans), and illicit drugs (marijuana, cocaine). In addition, sexual activity, exercise, Valsalva maneuver, metabolic derangements

(hypercalcemia, porphyria), and tumors (carcinoid, pheochromocytoma) may also trigger RCVS in susceptible individuals8. The typical clinical presentation has good prognosis in approximately 78-90% of cases and outcomes may range from pure cephalgia to permanent neurologic deficits. In rapid and severe cases, in-hospital death has been reported, with estimated mortality between 1 - 5%.16 Subarachnoid hemorrhage (SAH) is a known complication of RCVS, occurring frequently adult patients.10 RCVS is also a rare complication following blood transfusion.17 It has previously been reported in a teenage girl with HbSS disease, occurring about 1 week after simple packed red blood cell transfusion, similar to the case reported here.18 Although pathophysiology remains unknown, increased blood viscosity, reperfusion injury, and a lack of stored nitrous oxide in transfused red blood cells have been among the proposed mechanisms for cerebral vasospasm after blood transfusion.17,19

Owing in part to its rarity in the pediatric population, RCVS is likely underdiagnosed in children and our case highlights some of the challenges in recognizing RCVS in children.3,20 RCVS has similar radiologic features compared to cerebral angiitis but should be managed very differently, as steroid administration in RCVS has been associated with worse outcomes.4 One of the most useful diagnostic tools in distinguishing RCVS from cerebral angiitis is the history, specifically the description of the headaches.21,22 The typical headache for RCVS is sudden, reaching peak intensity within minutes and then resolving over hours, whereas headaches associated with cerebral angiitis tend to have a more gradual onset.8,9 Due to our patient's age, he was unable to provide this important descriptive detail. In addition, he presented with altered mental status and a seizure, which is less common than headache in adult RCVS.15 A case series of 13 children with RCVS demonstrated male predominance (11 male patients, 2 female), which differs from adult presentations of RCVS. Although the exact reason for this sex discrepancy is not fully understood, androgens have a poorly understood role in cerebral vascular tone, with both vasoconstrictive and vasodilatory functions noted in animal models.7 Thus, it would be reasonable to speculate that an increase in androgens in prepubescent males may increase their risk for RCVS, but further studies are needed to validate this assumption. The atypical presentation and inability to provide detailed history demonstrates the importance of approaching the pediatric patient with a broad differential, consulting appropriate services for expert guidance, and maintaining a low threshold for advanced and repeat neuroimaging studies to correctly diagnose pediatric patients.

This patient also had patchy T2 FLAIR changes in the occipital-parietal regions, which is frequently seen in Posterior Reversible Encephalopathy Syndrome (PRES). There have been several reported cases of PRES in pediatric patients, including pediatric patients with sickle cell anemia after blood transfusion.23–25 A 2017 article by Kamide, et al., presented a case of RCVS with radiographic features similar to PRES as well.26 A recent review article found 5 out of 13 cases of pediatric RCVS had MRI imaging consistent with PRES.14 PRES and RCVS can have overlapping clinical features including headache and altered mental status evolving over minutes to hours.27 Though the pathophysiology of

both PRES and RCVS remain incompletely understood, precipitating factors such as impaired cerebral autoregulation and endothelial dysfunction are possible common pathophysiologic factors in both conditions. The authors of a pediatric patient with sickle cell disease presenting with PRES days after blood transfusion noted that a possible explanation for the association of PRES and transfusion in sickle cell disease is a rapid increase in blood viscosity (from a serum hemoglobin increase of at least 5g/dL or more) leading to acute endothelial dysfunction several days later. These mechanisms, however, remain unproven and are only speculative at the time of this publication. Given the overlap of PRES, RCVS, and known association of PRES and sickle cell disease, we feel it is reasonable for treating physicians to obtain vessel imaging in patients presenting with clinical and/or radiographic features concerning for PRES, in particular for patients with hematologic disease.

A recent review article by Maldonado-Soto and Fryer on pediatric RCVS found that 7 out of 26 documented cases of pediatric RCVS had rheumatologic or hematologic risk factors, suggesting that physicians should maintain a low threshold for imaging in pediatric patients presenting with thunderclap headache with comorbid hematologic or rheumatologic disease.14 As mentioned above, blood transfusion has been associated with PRES in sickle cell patients. Our patient had a good outcome, perhaps in part to recognition of the diagnosis of RCVS and a low threshold for reimaging. The similarity between our patient and previously reported cases indicates that this condition may be more common than previously believed, further indicating the need for future investigations.

Our case of RCVS in a pediatric patient with sickle cell disease and following blood transfusion underscores the crucial need for further research into the pathophysiology of RCVS, especially in children. Furthermore, the role that blood transfusion may play in vasospasm needs to be understood so that these complications are not overlooked. The atypical presentation also demonstrates the importance of maintaining an appropriate clinical differential diagnosis. A more comprehensive understanding of this disease could prevent serious complications, potentially permanent neurologic damage, or death in future patients.

Table 1 Diagnostic Criteria of RCVS

1. Transfemoral angiography or indirect CTA or MRA documenting multifocal segmental cerebral artery vasoconstriction
2. Uniphasic disease course with no new symptoms after 1 month
3. No evidence of aneurysmal SAH
4. Normal or near-normal CSF labs

5. Severe acute headaches with or without other neurologic signs or symptoms
6. Reversibility of angiographic abnormalities within 12 weeks of onset

Works Cited

1. Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol. 2012;11(10):906-917. doi:10.1016/S1474-4422(12)70135-7

2. Ducros A. L37. Reversible cerebral vasoconstriction syndrome: Distinction from CNS vasculitis. Presse Med. 2013;42(4):602-604. doi:10.1016/j.lpm.2013.01.037

3. Ducros A, Bousser MG. Reversible cerebral vasoconstriction syndrome. Pract Neurol. 2009;9(5):256-267. doi:10.1136/jnnp.2009.187856

4. Gupta S, Zivadinov R, Ramasamy D, Ambrus JL. Reversible cerebral vasoconstriction syndrome (RCVS) in antiphospholipid antibody syndrome (APLA): the role of centrally acting vasodilators. Case series and review of literature. Clin Rheumatol. 2014;33(12):1829-1833. doi:10.1007/s10067-013-2434-9

5. Marder CP, Donohue MM, Weinstein JR, Fink KR. Multimodal Imaging of Reversible Cerebral Vasoconstriction Syndrome: A Series of 6 Cases. American Journal of Neuroradiology. 2012;33(7):1403-1411. doi:10.3174/ajnr.A2964

6. Hammad TA, Hajj-Ali RA. Primary Angiitis of the Central Nervous System and Reversible Cerebral Vasoconstriction Syndrome. Curr Atheroscler Rep. 2013;15(8):346. doi:10.1007/s11883-013-0346-4

7. Coffino SW, Fryer RH. Reversible Cerebral Vasoconstriction Syndrome in Pediatrics: A Case Series and Review. J Child Neurol. 2017;32(7):614-623. doi:10.1177/0883073817696817

8. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative Review: Reversible Cerebral Vasoconstriction Syndromes. Ann Intern Med. 2007;146(1):34. doi:10.7326/0003-4819-146-1-200701020-00007

9. Younger DS, Calabrese LH, Hays AP. Granulomatous angiitis of the nervous system. Neurol Clin. 1997;15(4):821-834. doi:10.1016/s0733-8619(05)70349-2

10. Singhal AB. Reversible Cerebral Vasoconstriction Syndromes. Arch Neurol. 2011;68(8):1005. doi:10.1001/archneurol.2011.68

11. Regling K, Pomerantz D, Narayanan S, et al. Reversible Cerebral Vasoconstriction Syndrome and Sickle Cell Disease: A Case Report. J Pediatr Hematol Oncol. 2021;43(1):e95-e98. doi:10.1097/MPH.0000000000001683

12. Kazato Y, Fujii K, Oba H, et al. Reversible cerebral vasoconstriction syndrome associated with brain parenchymal hemorrhage. Brain Dev. 2012;34(8):696-699. doi:10.1016/j.braindev.2011.11.001

13. Liu HY, Fuh JL, Lirng JF, Chen SP, Wang SJ. Three paediatric patients with reversible cerebral vasoconstriction syndromes. Cephalalgia. 2010;30(3):354-359. doi:10.1111/j.1468-2982.2009.01955.x

14. Maldonado-Soto AR, Fryer RH. Reversible cerebral vasoconstriction syndrome in children: an update. Semin Pediatr Neurol. 2021;40:100936. doi:10.1016/j.spen.2021.100936

15. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain. 2007;130(12):3091-3101. doi:10.1093/brain/awm256

16. Valencia-Mendoza M, Ramírez-Rodríguez N, Vargas-Avila N, et al. Fatal reversible cerebral vasoconstriction syndrome: A systematic review of case series and case reports. Journal of Clinical Neuroscience. 2019;70:183-188. doi:10.1016/j.jocn.2019.08.014

17. Liang H, Xu Z, Zheng Z, Lou H, Yue W. Reversible cerebral vasoconstriction syndrome following red blood cells transfusion: a case series of 7 patients. Orphanet J Rare Dis. 2015;10(1):47. doi:10.1186/s13023-015-0268-z

18. Zuccoli G, Nardone R, Rajan D, Khan AS, Cummings DD. Nonaneurysmal Subarachnoid Hemorrhage in Sickle Cell Disease: Description of a Case and a Review of the Literature. Neurologist. 2018;23(4):122-127. doi:10.1097/NRL.0000000000000181

19. Yu B, Lei C, Baron DM, Steinbicker AU, Bloch KD, Zapol WM. Diabetes augments and inhaled nitric oxide prevents the adverse hemodynamic effects of transfusing syngeneic stored blood in mice. Transfusion (Paris). 2012;52(7):1410-1422. doi:10.1111/j.1537-2995.2011.03473.x

20. PROBERT R, SAUNDERS DE, GANESAN V. Reversible cerebral vasoconstriction syndrome: rare or underrecognized in children? Dev Med Child Neurol. 2013;55(4):385-389. doi:10.1111/j.1469-8749.2012.04433.x

21. Tan LH, Flower O. Reversible Cerebral Vasoconstriction Syndrome: An Important Cause of Acute Severe Headache. Emerg Med Int. 2012;2012:1-8. doi:10.1155/2012/303152

22. Yang CW, Fuh JL. Thunderclap headache: an update. Expert Rev Neurother. 2018;18(12):915-924. doi:10.1080/14737175.2018.1537782

23. Raj S, Killinger J, Overby P. Blood Transfusion in Sickle Cell Disease Leading to Posterior Reversible Encephalopathy Syndrome (PRES). J Child Neurol. 2013;28(10):1284-1286. doi:10.1177/0883073812453497

24. Kolovou V, Zampakis P, Ginopoulou A, Varvarigou A, Kaleyias J. Reversible Posterior Leukoencephalopathy Syndrome After Blood Transfusion in a Pediatric Patient With Sickle Cell Disease. Pediatr Neurol. 2013;49(3):213-217. doi:10.1016/j.pediatrneurol.2013.04.024

25. Hanafy E, Alshareef D, Osman S, Al Jabri A, Nazim F, Mahmoud G. Posterior reversible encephalopathy syndrome secondary to asymptomatic poststreptococcal glomerulonephritis in a child with sickle cell anemia: a case report. J Med Case Rep. 2018;12(1):24. doi:10.1186/s13256-017-1559-x

26. Kamide T, Tsutsui T, Misaki K, et al. A Pediatric Case of Reversible Cerebral Vasoconstriction Syndrome With Similar Radiographic Findings to Posterior Reversible Encephalopathy Syndrome. Pediatr Neurol. 2017;71:73-76. doi:10.1016/j.pediatrneurol.2017.02.008

27. Hobson E V, Craven I, Blank SC. Posterior reversible encephalopathy syndrome: a truly treatable neurologic illness. Perit Dial Int. 2012;32(6):590-594. doi:10.3747/pdi.2012.00152