Submitted: 03 December, 2024 Accepted: 31 March, 2025 Published: 08 August, 2025 DOI:10.22514/sv.2025.119

Open Access
Signa Vitae

CASE REPORT

Epstein–Barr virus-associated focal cerebral arteriopathy in a child with stroke: a case report

Zih-Yang Lin[1], Cheng-Chieh Huang[1,2], Wen-Liang Chen[2], Cheng Hsu Chen[1,2], Chu-Chung Chou[1,3], Yan-Ren Lin[1,3,4,*]

[1]Department of Emergency and Critical Care Medicine, Changhua Christian Hospital, 500 Changhua, Taiwan
[2]Department of Biological Science and Technology, National Yang Ming Chiao Tung University, 300 Hsinchu, Taiwan
[3]School of Medicine, Chung Shan Medical University, 402 Taichung, Taiwan
[4]Department of Post Baccalaureate Medicine, College of Medicine, National Chung Hsing University, 402 Taichung, Taiwan

***Correspondence**
117214@cch.org.tw
(Yan-Ren Lin)

Abstract

Background: Pediatric stroke is a rare but potentially life-threatening condition that often presents with nonspecific symptoms such as headache and vomiting, as well as focal neurological deficits or seizures in a minority of patients, making early diagnosis challenging. **Case**: A previously healthy child who presented with acute neurological deficits and was diagnosed with focal cerebral arteriopathy (FCA) on the basis of neuroimaging and serological findings. After treatment, she fully recovered without any neurological deficits. **Conclusion**: This case underscores the need for increased awareness of virus-associated arteriopathies in pediatric stroke patients, and emphasizes the importance of early recognition, neuroimaging, viral workup and treatment.

Keywords

Pediatric stroke; Emergency department; Focal cerebral arteriopathy (FCA); Epstein–Barr virus (EBV)

1. Introduction

Although infrequent, pediatric stroke is associated with significant morbidity and mortality, with mortality rates ranging from 10% to 25% and a high recurrence rate of 25% [1, 2]. Notably, approximately 70% of strokes result in persistent neurological deficits, seizure disorders or developmental challenges. Diagnosis is often challenging, as 61–64% of pediatric stroke patients present with non-localizing symptoms such as headache, vomiting and altered mental status, whereas 15–31% exhibit focal or generalized seizures [3]. Among the various causes of arterial ischemic stroke (AIS) in children, focal cerebral arteriopathy (FCA) is one of the most common etiology [4]. FCA is characterized by inflammatory changes in the cerebral arterial wall, leading to transient vasculitis triggered by antecedent viral infections, followed by progressive vasculopathy [5]. While varicella zoster virus (VZV) has been identified as a causative agent of FCA [6], few reports have specifically linked FCA with other herpes viruses, including Epstein–Barr virus (EBV).

2. Case report

A previously healthy 10-year-old girl presented to our emergency department (ED) with acute left-sided weakness and headache. Upon arrival, she was fully conscious, and her vital signs were stable without fever. Neurological examination revealed left hemiplegia, dysesthesia, absence of the left nasolabial fold and a positive Babinski sign on the left side. The family medical history was unremarkable, and there were no known preexisting medical conditions.

A brain computerized tomography scan revealed nonspecific findings. Brain magnetic resonance imaging revealed an area of restricted diffusion over the right globus pallidus caused by ischemic infarction in the vascular territory of the right middle cerebral artery (Fig. 1). Magnetic resonance angiography (MRA) revealed narrowing of the supraclinoid portion of the right internal carotid artery (Fig. 2), suggesting arteriopathy. Complete blood count, differential count, and biochemical laboratory test results revealed nonspecific findings. In addition, viral tests using nasopharyngeal swabs (including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus, influenza virus, parainfluenza virus and respiratory syncytial virus) and serum samples (Epstein-Barr virus (EBV) and herpes simplex virus (HSV)) were performed; the results of these tests were negative except for positive serum EBV Immunoglobulin G (IgG). The patient received a loading dose of 300 mg of aspirin in the emergency department and was subsequently admitted to the intensive care unit for supportive treatment, including the maintenance of normotension and normoglycemia, as well as dehydration prevention with the administration of maintenance isotonic intravenous fluids. Routine investigations, including tests for coagulopathies (D-dimer, factor V Leiden mutation, factor VII assay, homocysteine, protein S and C, antithrombin III levels, antiphospholipid antibodies, and lactic acid), metabolic disorders (lipid profile, plasma amino acids, ketone body, zinc and copper blood levels, folic acid and thyroid function), congenital heart disease (echocardiogram and 24-h Holter electrocardiogram), immune system abnormalities (anti-dsDNA, IgG, Immunoglobulin A (IgA), Immunoglobulin

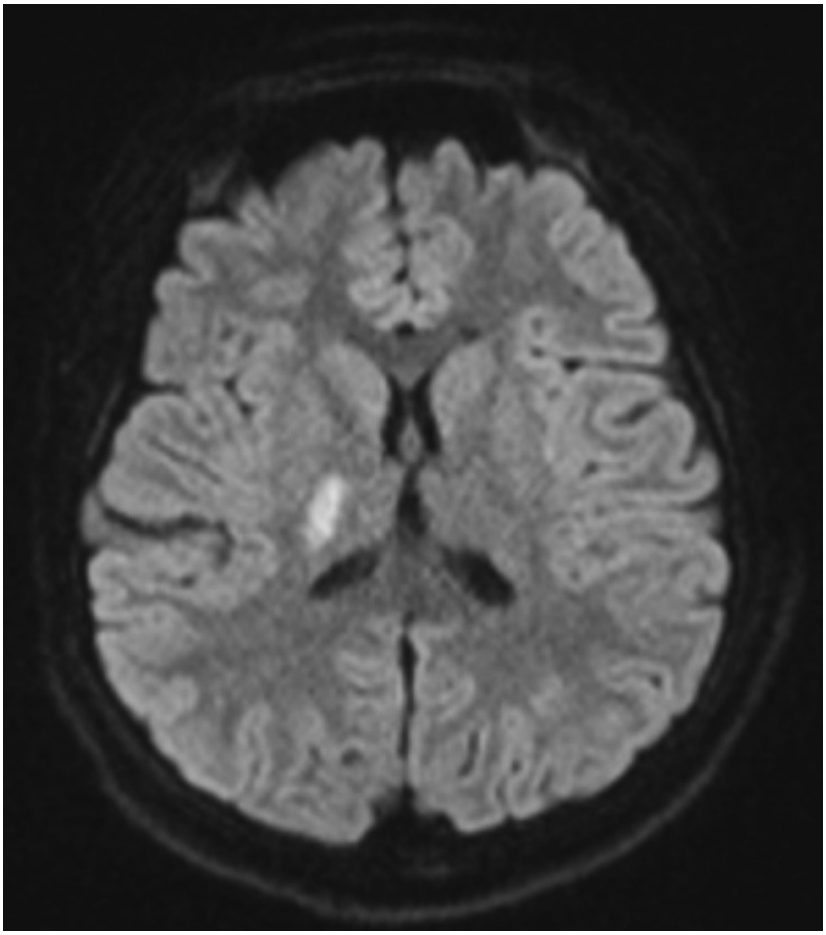

FIGURE 1. Brain magnetic resonance imaging revealed an area of restricted diffusion over the right globus pallidus.

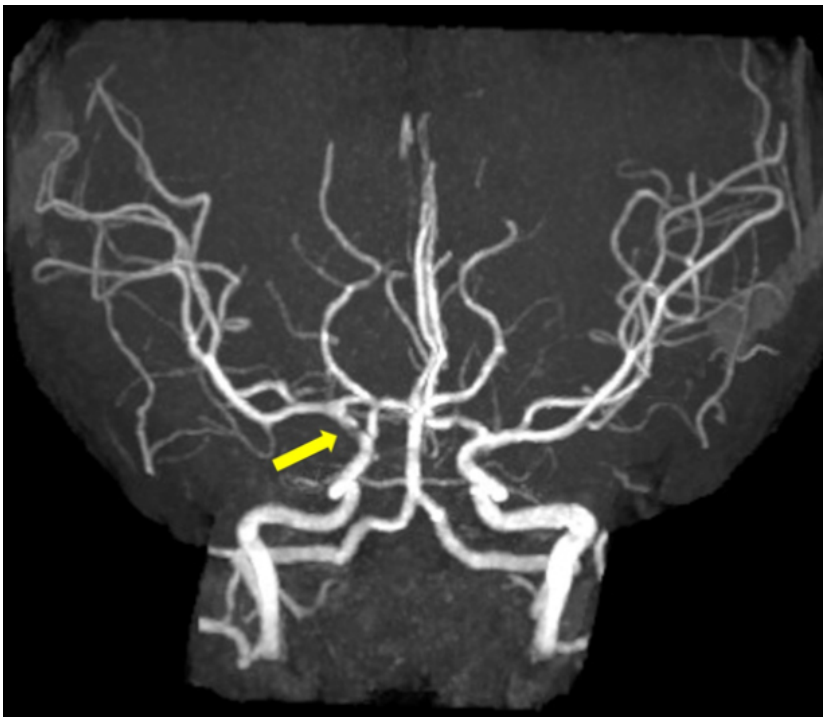

FIGURE 2. Magnetic resonance angiography revealed narrowing of the supraclinoid portion of the right internal carotid artery (yellow arrow).

M (IgM), Anti-Sjögren's Syndrome A/Anti-Sjögren's Syndrome B antibody (SSA/SSB Ab) and C3/C4) and electroencephalography, were conducted to explore potential underlying causes of childhood ischemic stroke; all the results were negative. The patient began a rehabilitation program on the fifth day of hospitalization and was discharged without neurological deficits on the 24th day. Brain MRA performed 4 months after discharge revealed patent intracranial vessels (Fig. 3).

3. Discussion

Pediatric stroke is often diagnosed after a significant delay and is increasingly acknowledged as a risk factor for childhood disability, with an annual incidence ranging from 1.2 to 13 per 100,000 children [7]. The most relevant risk factors for the occurrence of stroke in children are vasculopathies, infections, cardiac causes, and coagulopathies [1]. FCA in childhood with unilateral stenosis of the anterior circulation is reported to account for up to one-quarter of childhood AIS cases. In the early stages, FCA can rapidly progress over days to weeks. Patients with progressive arteriopathies have a greater risk of recurrence [8]. The majority of FCA cases regress or stabilize over time; therefore, FCA is retrospectively defined as transient cerebral arteriopathy [9]. Most cases are presumed to be inflammatory. Among AIS patients, up to 40% had previous medical conditions, such as fever, cough or flu-like symptoms, and had a medical visit one month before stroke [10]. In addition, in a vaccinated population, VZV may play a modest role in childhood stroke pathogenesis [11].

Like VZV, EBV is a herpesvirus in the herpes family and is known to be a trigger for systemic vasculitis, including Kawasaki disease [12], systemic lupus erythematosus [13], and rheumatoid arthritis [14]. In a recent study, Gatto *et al.* [15] observed significant increases in interleukin-6 (IL-6) and interleukin-1β (IL-1β) levels in the cerebrospinal fluid of a 2-year-old female with EBV-induced ischemic stroke. The possible cause for this increase is that EBV infection triggers the activation of host macrophages and lymphocytes, leading to the release of pro-inflammatory cytokines (IL-6 and IL-1β). These cytokines have been implicated in initiating the coagulation cascade and promoting thrombus formation [16], which contributes to the subsequent development of ischemic stroke. This could suggest another pathogenesis of EBV-associated arteriopathy distinct from the inflammatory pathway.

Currently, there are no standard treatment guidelines for AIS because of its various etiologies. Generally, treatment begins with supportive care, focusing on the maintenance of normotension, euglycemia, and euvolemia, followed by emergent MRI to determine the subsequent treatment strategy [7]. The most comprehensive multicenter trial on intravenous tissue plasminogen activator (tPA) use in pediatric stroke patients is the Thrombolysis in Pediatric Stroke (TIPS) study, which was published in 2015 [17]. Unfortunately, the study was terminated because of poor recruitment. Therefore, no specific inclusion criteria for the use of intravenous thrombolytics in children have been created to date. The use of heparin [18], low-molecular weight heparin (LMWH) [19] or warfarin [2] as anticoagulants is determined by the physician on the basis of the patient's clinical condition, which is particularly necessary in children with congenital heart disease [20]. For patients with human herpesvirus infection-related FCA, aspirin (3–5 mg/kg/day) [21], corticosteroids (methylprednisolone, 10–20 mg/kg per dose, up to 1 g per day for 3–5 days) [22] and acyclovir (10–15 mg/kg daily for 10–14 days) are acceptable treatments [22] (Table 1 (Ref. [21, 22])). Aspirin may reduce recurrence in children [23], and a previous retrospective

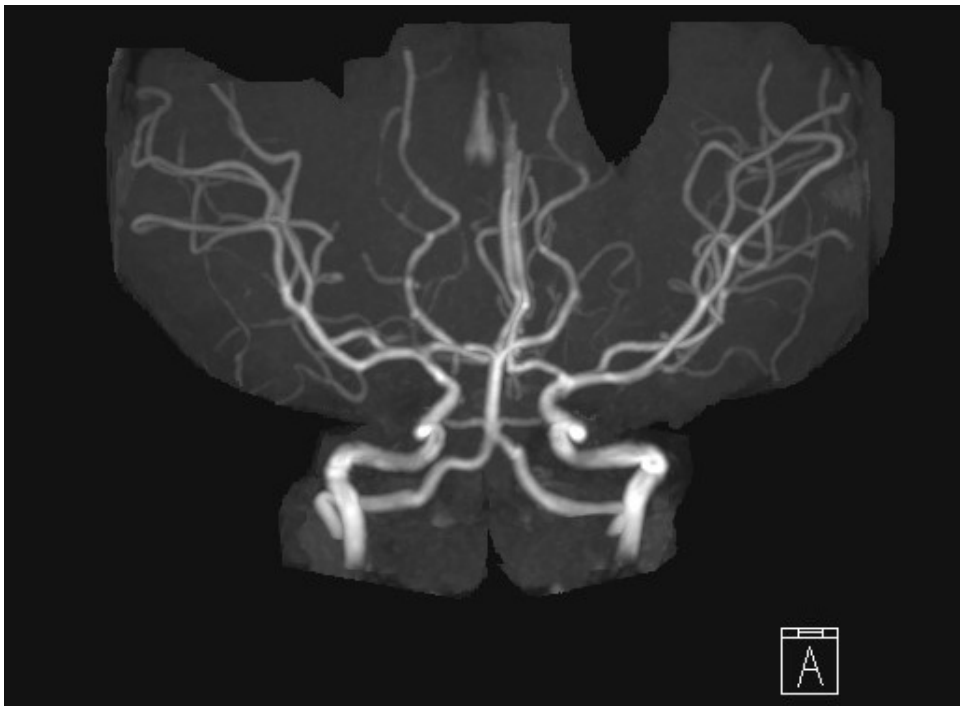

FIGURE 3. Brain MRA 4 months after discharge from the hospital revealed that cerebral arteriopathy had resolved.

TABLE 1. Treatment options for focal cerebral arteriopathy.

Medication	Dose
Aspirin	3–5 mg/kg/day, maximum 150 mg/day [21]
Corticosteroid	Methylprednisolone, 10–20 mg/kg per dose, up to 1 g per day for 3–5 days, followed by tapering and a shift to oral prednisolone for 10 weeks [21]
Acyclovir	10–15 mg/kg day for 10–14 days, followed by oral antivirals for several months for recurrent disease or immunocompromised patients [22]

study suggested that administering corticosteroids may improve functional outcomes due to the underlying acute inflammation process [21]. Recently, a randomized controlled trial was conducted with the aim of providing stronger evidence in support of corticosteroid treatment [24].

One limitation of our report is the inability to confirm Epstein–Barr virus (EBV) reactivation. At our institution, EBV serology is assessed using enzyme-linked immunosorbent assay (ELISA), which yields only qualitative results based on predefined thresholds: values >11 Net Tulare Units (NTU) are considered positive, <9 NTU negative and 9–11 NTU equivocal. However, the exact NTU values are not available for clinical interpretation. Therefore, we do not perform repeated testing of EBV IgM and IgG to confirm reactivation. In this case, the patient was negative for EBV IgM and positive for EBV IgG. This pattern may reflect a very early stage of acute infection, where the EBV IgM level had not yet reached the 9 NTU threshold, along with prior exposure to EBV, which could explain the presence of EBV IgG antibodies.

Only one previous case report reported chronic EBV infection leading to diffuse central nervous system (CNS) vasculopathy in an 18-year-old male with X-linked lymphoproliferative disease [25]. In our case report, we present the case of a previously healthy 10-year-old girl who developed FCA due to EBV infection. The establishment of a relationship between FCA and EBV infection is supported by the detection of seroconversion against EBV, with all other stroke-related examinations yielding normal results. Although corticosteroids and acyclovir were not used in this patient's treatment, we achieved a satisfactory outcome through the use of aspirin, adequate intravenous hydration to maintain euvolemia, and the implementation of early aggressive rehabilitation. More education on pediatric strokes is needed because of their subtle signs and rarity. This case reminds ED doctors to consider EBV infection as a potential differential diagnosis for pediatric stroke patients; EBV infection should be treated as soon as possible to potentially improve patient prognosis.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

ZYL—Investigation, Writing–Original Draft. CCH—Investigation, Writing–Review & Editing. WLC—Validation. CHC—Writing–Review & Editing. CCC—Methodology, Project Administration. YRL—Conceptualization, Supervision; ZYL and CCH—mainly written manuscript. CCC and YRL—helped with the revision of the manuscript. WLC and CHC—contributed invaluable assistance to the revision process. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board (IRB) of Changhua Christian Hospital (IRB No. 240707). Written informed consent was obtained from the patient and the patient's legal representative prior to publication.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Hollist M, Au K, Morgan L, Shetty PA, Rane R, Hollist A, *et al*. Pediatric stroke: overview and recent updates. Aging and Disease. 2021; 12: 1043–1055.

[2] Oesch G, Perez FA, Wainwright MS, Shaw DWW, Amlie-Lefond C. Focal cerebral arteriopathy of childhood: clinical and imaging correlates. Stroke. 2021; 52: 2258–2265.

[3] Mastrangelo M, Giordo L, Ricciardi G, De Michele M, Toni D, Leuzzi V. Acute ischemic stroke in childhood: a comprehensive review. European Journal of Pediatrics. 2022; 181: 45–58.

[4] Davila-Williams D, Barry M, Vargas C, Vossough A, Bernard TJ, Rafay MF. Cerebral arteriopathies of childhood—current approaches. Seminars in Pediatric Neurology. 2022; 43: 101004.

[5] Fullerton HJ, Stence N, Hills NK, Jiang B, Amlie-Lefond C, Bernard TJ, *et al*.; VIPS Investigators. Focal cerebral arteriopathy of childhood: novel severity score and natural history. Stroke. 2018; 49: 2590–2596.

[6] Ganesan V, Prengler M, McShane MA, Wade AM, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. Annals of Neurology. 2003; 53: 167–173.

[7] Rawanduzy CA, Earl E, Mayer G, Lucke-Wold B. Pediatric stroke: a review of common etiologies and management strategies. Biomedicines. 2022; 11: 2.

[8] Amlie-Lefond, C, Kristin M, Dwight B. Recurrence risk counseling following childhood stroke (P9-5.009). Neurology. 2024; 102: 9.

[9] Slavova N, Muenger R, Sanchez-Albisua I, Regényi M, Oesch G, Fluss J, *et al*. Inflammatory type focal cerebral arteriopathy of the posterior

circulation in children: a comparative cohort study. Stroke. 2024; 55: 1006–1014.

[10] Cornet MC, Grose C, Vexler Z, Wu YW, Fullerton HJ. The role of infection and inflammation in the pathogenesis of pediatric arterial ischemic stroke. Seminars in Pediatric Neurology. 2022; 44: 100995.

[11] Fullerton HJ, Hills NK, Wintermark M, Dlamini N, Amlie-Lefond C, Dowling MM, *et al.*; VIPS II Investigators. Evidence of varicella zoster virus reactivation in children with arterial ischemic stroke: results of the VIPS II study. Journal of the American Heart Association. 2025; 14: e039184.

[12] Tao L, Zhang T, Zhou Y, Liu X, Ding C, Yu J, *et al*. Epstein-Barr virus downregulates the α7 nicotinic acetylcholine receptor of CD8+ T lymphocytes might associate with coronary artery lesions in Kawasaki disease patients. Microbes and Infection. 2023; 25: 105168.

[13] Chen CJ. Epstein-Barr virus reactivation and disease flare of systemic lupus erythematosus. Taiwanese Journal of Obstetrics & Gynecology. 2024; 63: 161–164.

[14] Banko A, Cirkovic A, Jeremic I, Basaric M, Grk M, Miskovic R, *et al*. Uncovering the role of Epstein-Barr virus infection markers for remission in rheumatoid arthritis. Biomedicines. 2023; 11: 2375.

[15] Gatto A, Angelici S, Soligo M, Di Giuda D, Manni L, Curatola A, *et al*. Pediatric cerebral stroke induced by Epstein-Barr virus infection: role of Interelukin overexpression. Acta Biomedica. 2021; 92: e2021135.

[16] Fassbender K, Rossol S, Kammer T, Daffertshofer M, Wirth S, Dollman M, *et al*. Proinflammatory cytokines in serum of patients with acute cerebral ischemia: kinetics of secretion and relation to the extent of brain damage and outcome of disease. Journal of the Neurological Sciences. 1994; 122: 135–139.

[17] Rivkin MJ, deVeber G, Ichord RN, Kirton A, Chan AK, Hovinga CA, *et al*. Thrombolysis in pediatric stroke study. Stroke. 2015; 46: 880–885.

[18] Tipu Sultan. Pediatric stroke: a review. Pakistan Journal of Neurological Sciences. 2022; 17: 68–77.

[19] Klučka J, Klabusayová E, Musilová T, Kramplová T, Skřišovská T, Kratochvíl M, *et al*. Pediatric patient with ischemic stroke: initial approach and early management. Children. 2021; 8: 649.

[20] Sporns PB, Fullerton HJ, Lee S, Kirton A, Wildgruber M. Current treatment for childhood arterial ischaemic stroke. The Lancet. Child & Adolescent Health. 2021; 5: 825–836.

[21] Steinlin M, Bigi S, Stojanovski B, Gajera J, Regényi M, El-Koussy M, *et al*.; Swiss NeuroPediatric Stroke Registry. Focal cerebral arteriopathy: do steroids improve outcome? Stroke. 2017; 48: 2375–2382.

[22] Nagel MA, Bubak AN. Varicella zoster virus vasculopathy. The Journal of Infectious Diseases. 2018; 218: S107–S112.

[23] Ganesan V, Prengler M, Wade A, Kirkham FJ. Clinical and radiological recurrence after childhood arterial ischemic stroke. Circulation. 2006; 114: 2170–2177.

[24] Brechbühl D, Steiner L, Münger R, Oesch G, Piechowiak E, Massatsch P, *et al*. High dose steroids in children with stroke and unilateral focal arteriopathy: a multicenter randomized controlled trial. Pediatric Stroke. 2023; 6: 21–42.

[25] Weeks JK, Helton KJ, Conley ME, Onciu M, Khan RB. Diffuse CNS vasculopathy with chronic Epstein-Barr virus infection in X-linked lymphoproliferative disease. AJNR. American Journal of Neuroradiology. 2006; 27: 884–886.

How to cite this article: Zih-Yang Lin, Cheng-Chieh Huang, Wen-Liang Chen, Cheng Hsu Chen, Chu-Chung Chou, Yan-Ren Lin. Epstein–Barr virus-associated focal cerebral arteriopathy in a child with stroke: a case report. Signa Vitae. 2025; 21(8): 98-102. doi: 10.22514/sv.2025.119.