Case Report

Childhood posterior circulation arterial ischemic stroke – An unusual case with a possible COVID-19-related arteriopathy

Athulya Gopal[1], I Riaz[2], Sheeja Sugunan[3], Sankar Vaikkom Hariharan[4]

From [1]Junior Resident, [2,3]Associate Professor, [4]Additional Professor, Department of Paediatrics, SAT Hospital, Government Medical College, Trivandrum, Kerala, India

ABSTRACT

Viral infections are known to increase predilection to stroke and coronavirus disease 2019 (COVID-19) has proven these concerns true. We are presenting the case of a 6-year-old previously normal male child diagnosed with posterior circulation stroke who had all etiological workups negative except for the COVID antibody. Imaging showed thrombi over the V3 segment of the vertebral artery at C1–C2 level causing near complete occlusion, with embolic infarct in the bilateral posterior inferior cerebellar artery, bilateral posterior cerebral artery, bilateral anterior inferior cerebellar artery, and the left superior cerebellar artery. The child was managed with methylprednisolone, anticoagulation, and supportive care and was able to restore near-normal neurological status within months. This case is unique in terms of the involvement of posterior circulation which is rare in the pediatric population. A possibility of inflammation-related arteriopathy secondary to infection should be considered in the etiological workup of stroke. Anti-inflammatory measures to control cytokine storm along with supportive care will ensure a good outcome.

Key words: Arteriopathy, COVID-19, Stroke

Posterior circulation stroke in children is a rare entity, reported in around 10–43% of cases of childhood arterial ischemic stroke in various studies [1]. Children usually present with benign symptoms such as headache, vertigo, nausea, vomiting to seizures, weakness, and unsteadiness which are often attributed to other common neurological disorders causing a delay in diagnosis and treatment [1]. According to a study done by Lee *et al.*, the risk factors of childhood ischemic stroke included vasculopathy followed by cardiac disease, metabolic disorder, and infection [2].

Here, we are presenting the case of a 6-year-old boy diagnosed with posterior circulation stroke where an etiological workup was suggestive of coronavirus disease (COVID-19)-related arteriopathy.

CASE REPORT

A 6-year-old male child with no significant medical or surgical illness in the past presented with on-and-off headaches for 3 weeks, vomiting for 4 days, and unsteady gait for 1 day. His parents and sibling were COVID-19-positive 1 month back, though he was asymptomatic and tested negative back then. Examination revealed normal vitals and neurological examination showed intact cranial nerves, normal reflexes with negative Babinski sign, and no extrapyramidal signs. Cerebellar signs were present predominantly over the left side and meningeal signs were absent. Fundus examination was normal.

Contrast magnetic resonance imaging brain at 12 h of admission revealed a posterior circulation stroke (Fig. 1). CT angiogram of the brain showed a thrombus within the V3 segment of the left vertebral artery at C1–C2 level causing near complete occlusion, with embolic infarct in the bilateral posterior inferior cerebellar artery, bilateral posterior cerebral artery, bilateral anterior inferior cerebellar artery, and the left superior cerebellar artery (Fig. 2). Inflammatory markers and second-line markers for multisystem inflammatory syndrome in children (MIS-C) were negative. Stroke workup, coagulation parameters, and autoimmune workup were within normal limits (Table 1). A cerebrospinal fluid (CSF) study has ruled out the infectious etiology. Echo showed a sound heart and ultrasonography of the neck with Doppler ruled out emboli. COVID antibody testing was reactive; however, COVID antigen by reverse transcriptase-polymerase chain reaction (RT-PCR) was negative.

The child was treated with methylprednisolone pulse dose (30 mg/kg for 5 days) followed by 2 mg/kg oral steroids tapered over 1 weeks. As the window for thrombolysis is over, the child was managed with low molecular weight heparin. Anti-cerebral

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Correspondence to: Sankar Vaikkom Hariharan, Department of Paediatrics, SAT Hospital, Government Medical College, Trivandrum - 695011, Kerala, India, E-mail: sankarvh@gmail.com

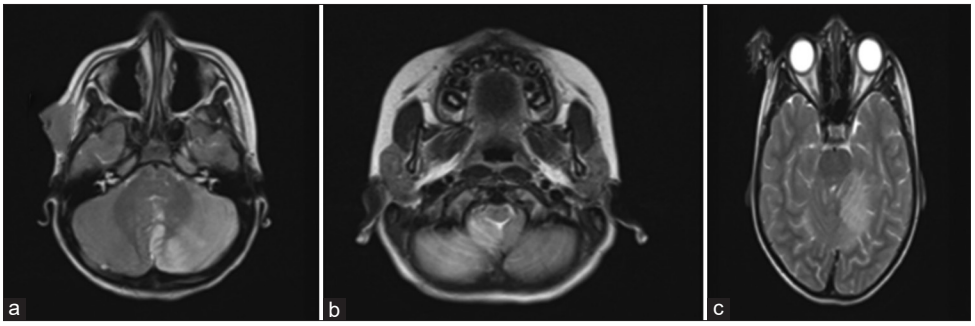

Figure 1: Magnetic resonance imaging brain contrast showing (a) T2 hyper intensities involving the territories of bilateral anterior inferior cerebellar artery; (b) Bilateral posterior cerebral artery; (c) Left superior cerebellar artery

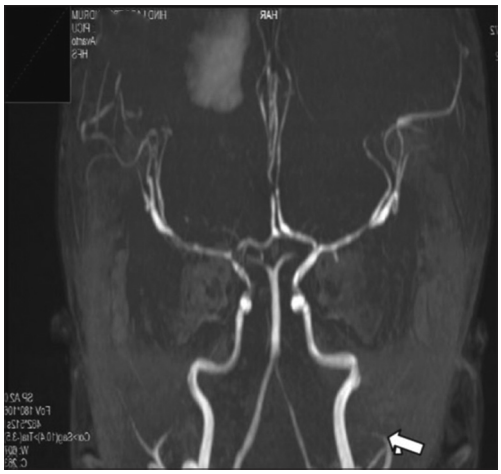

Figure 2: Computed tomography angiogram showing thrombus within v3 segment of the left vertebral artery at C1-C2 level

edema measures started with some improvements. Later, the child needed posterior fossa decompression with midline sub-occipital craniectomy, and the left cerebellar infarct ectomy was done.

Magnetic resonance angiogram and fat-suppressed sequence on the 10th day of admission showed thrombi resolution and ruled out vertebral artery dissection. The child got discharged on the day 22nd of admission on low molecular weight heparin for 3 months along with rehabilitation exercises. At discharge, the child was able to walk without support and was having 4/5 power on the left side. Follow-ups at 6 and 9 months showed the normal neurological status of the child with no limitation for daily activities.

DISCUSSION

Pediatric arterial ischemic stroke is a very rare entity. Clinical presentation is usually non-specific, with headache, nausea and vomiting to limb paresis, speech disturbance, and ataxia. A delay in diagnosis can lead to cerebral edema and brainstem herniation [1]. As compared to anterior circulation stroke, posterior circulation stroke is rare, affecting older children, with less stroke symptom severity at presentation, increased stroke recurrence risk, and better outcomes [1].

It is proven that infections cause inflammation at the tissue level, resulting in a procoagulant effect in the body. This could be through the expression of thromboplastin by monocytes and macrophages, increased serum level of tumor necrosis factor, and inhibition of protein C and protein S [2]. Focal cerebral arteriopathy, the most common cause of pediatric stroke is known to be associated with infectious agents such as varicella, herpes viruses, human immunodeficiency virus, parvovirus B19, influenza A, enteroviruses, and mycoplasma pneumonia confirming that a vascular etiology secondary to an infectious cause could be possible [3]. In our case, we could eliminate all possible infectious etiologies except for the past history of COVID-19.

Similar to our case, Shen *et al*. reported the case of a 17-month-old child with a left pontine ischemic stroke [4] and Appavu *et al*. about an 8-year-old child with a bilateral middle cerebral artery infarct [5]. Both children belonged to COVID-19 endemic regions and had negative COVID RT-PCR but positive for COVID antibodies. All prothrombotic, autoimmune, infectious, and cardiovascular etiology predisposing to stroke were unrevealing [4,5] similar to our case.

Arterial ischemic strokes were reported in children having COVID-19 infection [6] and also as a neurological manifestation of MIS-C [7]. Tiwari *et al*. reported the case of a 9-year-old child, satisfying MIS-C criteria having multiple infarcts involving territories of the middle cerebral artery and anterior cerebral artery [7] but our case had all inflammatory markers and second-line markers of COVID-19 were negative and MIS-C criteria were not satisfied.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is reported to have a 7.6 times increase in the risk of stroke in comparison with other coronavirus infections [3]. Possible mechanisms could be immune-mediated events, hypercoagulable state from systemic inflammation, cytokine storm, viral mimicry of the host resulting in autoantibodies, and viral superantigen sequences [5,7,8]. SARS-CoV-2 may enter the central nervous system hematogenously, or by neuronal retrograde dissemination through olfactory and trigeminal nerves, CSF, and lymphatic system [3,6]. Neuroinvasive and neurotropic behavior of SARS-CoV-2, causing progressive endothelial thromboinflammatory syndrome may enhance the multisystemic microvascular thrombotic disease [6]. Another explanation is that of the "Trojan horse mechanism" where the virus infecting leukocytes can cross the blood-brain barrier to enter the central nervous system which can lead to peripheral neuropathies and neuronal injuries [9].

It is possible that the cause of stroke in our patient could be idiopathic but considering the positive COVID serology panel along with extensive negative stroke workup, we would like to consider COVID-19 infection as a trigger for the entire cascade.

Table 1: Investigations result of the patient

Investigations	Results	Normal value
Hemoglobin (g/dL)	13	12–15
Leukocyte count (cells/mm^3)	8200	4000–11000
Platelet×10^3 cells/mm^3	3.05	1.5–4.5
CRP (mg/dL)	NEG	<0.6
ESR (mm/h)	2 mm	0–15
Prothrombin time (seconds)	13.3	11–13.5
INR	1.01	
APTT (seconds)	26.7	21–35
Misc second line markers		
Troponin T	NEG	
Ferritin (mcg/L)	21	24–336
Fibrinogen (mg/dL)	213	200–400
NTproBNP (Pg/mL)	176	<125
D-Dimer	0.24	<0.5
Covid antibody AU/mL	Reactive (2793)	<50-non reactive
Lipid profile		Normal
Nasopharyngeal swab	Negative	
CSF viral panel	Negative	
APLA and ANA profile	Negative	
Protein C activity (%)	114	65–140
Protein S activity (%)	129	77–143
Homocysteine levels (%)	9.53	3–13
IgM mycoplasma	Negative	
CSF cells	3 (polymorphs-0–1 Lymphocyte-0-1)	0–5
CSF sugars (mg/dL)	118	40–70
CSF protein (mg/dL)	10	15–40
CSF culture	Sterile	

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, INR: International normalised ratio, APTT: Activated partial thromboplastin time, NT: proBNP-N-Terminal pro B-type natriuretic peptide, CSF: Cerebrospinal fluid, ANA: Antinuclear antibody, APLA: Antiphospholipid antibody, pg-picogram

Our conclusion can be supported by similar case reports across the world [4,5,7]. Bilateral patchy involvement in multiple major vessel territories of posterior cerebral circulation could be because of an arteriopathy secondary to COVID-19 or due to an unstable infarct in the absence of plaque rupture giving out a shower of emboli distally due to shear stress of blood flowing through the lumen [10].

Our case is unique as it is one among a few stroke reports with exclusive involvement of posterior cerebral circulation. Most of the other studies have involvement of both anterior and posterior circulation. Due to the lack of facilities, we could not carry out a serological study and RT-PCR for COVID-19 in CSF and vessel wall imaging.

In summary, though the incidence of pediatric arterial ischemic stroke is 2.4/1 lakh person, it involves mortality of around 4% and results in neurological and cognitive morbidity in 50% of survivors [11]. Hence, early diagnosis of stroke especially involving posterior circulation is particularly important for recanalization and prevention of complications due to large infarcts. There are limited data on risk factors, stroke subtypes, and recurrence risk for childhood posterior circulation stroke. Infection-mediated arteriopathy should be in their differential diagnosis in children presenting with new onset neurological symptoms. Effective measures to control the cytokine storm along with other supportive care will prevent complications. Further studies are required to understand the pathogenesis of ischemic stroke secondary to infectious causes in the pediatric population and assessment of the neurological and cognitive outcomes in children.

CONCLUSION

With the availability of diagnostic aids, pediatric strokes are now getting diagnosed and reported earlier. As the incidence of pediatric stroke is low, unlike in adults, there is a scarcity of guidelines on the management and efficacy of various treatment modalities which needs to be explored further. As the COVID-19 pandemic is still around us, infections-induced inflammatory arteriopathy needs to be considered as the etiology of pediatric stroke and prompt measures to control the cytokine storm will bring down both morbidity and mortality.

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