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Pediatric stroke with covid-19 ig-g positive - A case series

[1]Dr Neeraj Panchanadikar, Junior resident, Department of Pediatrics, Bharati Vidyapeeth University Medical College Hospital & Research Centre, Pune- 411043.

[2]Dr Karthik Badarayan V, Junior resident, Department of Pediatrics, Bharati Vidyapeeth University Medical College Hospital & Research Centre, Pune- 411043.

Corresponding Author: Dr Neeraj Panchanadikar, Junior resident, Department of Pediatrics, Bharati Vidyapeeth University Medical College Hospital & Research Centre, Pune- 411043.

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Introduction

COVID-19 infection and post COVID sequalae in children are still under evaluation. COVID19 mostly cause respiratory and gastrointestinal symptoms but large vessel stroke has been reported in adults with active COVID-19 infection and in patients with Post-COVID status.[1] SARS-CoV-2 is reported to have a 7·6 times increase in the risk of resulting in a stroke in comparison with other coronavirus and seasonal infections in adults.[2] We herein describe, 2 children presenting with stroke who were found to be COVID-IgG positive without other etiological correlations.

Cases:

Patient 1: 11 years old male child was brought with complaints of acute onset- continuous, spontaneous, non-rhythmic and repetitive movements of left sided, upper and lower limbs not migrating to other side, which subsided while being asleep and was also associated with difficulty in walking and involuntary facial movements. He had history of a minor upper respiratory tract infection for which he was given some symptomatic treatment by some practitioner. On examination the child was conscious, well oriented and his vitals were stable. CNS examination showed presence of hypotonia in left upper and lower limbs along with reduced power, varied in intensity over different joints on left side of his body. Hemichorea, pronator drift, choreic hand and milk maid grip were well appreciated. On witnessing these choreoid movements, suspecting chorea secondary to stroke, CT brain with MRI diffusion was done which showed acute lacunar infarct in subcortical white matter of right occipital lobe along with narrowing of cavernous segments of bilateral internal carotid arteries. Basic blood investigations sent to rule out infections, bleeding disorders, dyslipidemias were normal. ASO titer, 2D echo sent to rule out rheumatic fever was normal. ANA, ESR, Lupus anticoagulants sent to rule out connective

tissue disorders were normal. Normal Anti cardiolipin antibody levels, anti beta2 antibody levels ruled out Antiphospholipid syndrome. Ceruloplasmin level as well as slit-lamp examination of eye for Kayser–Fleischer rings to rule out Wilson's disease were normal. Sickle cell disease was ruled out by doing sickling test. USG abdomen and pelvis and renal Doppler done to see for changes of vasculitis was normal. The child was started on tab Aspirin at 4mg/kg/day along with oral sodium valproate at 20 mg/kg/day as seizure prophylaxis. Throughout the patient's ward stay of 5 days, he showed some clinical improvement quantified by improving grades of power and hypotonia. Considering a rare possibility of PIMS-TS, COVID IgG antibody titers and inflammatory markers were sent of which COVID19 IgG antibodies came positive with significant titers. As no other cause was attributed, COVID19 IgG antibodies was considered to have caused the stroke.

Patient 2: 7 years old male child was brought to our hospital with complaints of fever, intermittent headache and multiple episodes of non-projectile vomiting which was followed by acute onset slurring of speech and weakness of right sided upper limb and lower limb. He was vitally stable and his CNS examination showed right sided hypotonia with brisk reflexes while cranial nerve examination showed right sided facial nerve palsy (UMN type). Haemogram, ESR, PT-INR and serum electrolytes done were normal. Suspecting stroke, MRI Brain with MR Angiography done showed an acute non hemorrhagic infarct in the left fronto-parietal lobe and left posterior insular cortex and white matter along with severe narrowing of supraclinoid segment of left internal carotid artery and complete occlusion artery of left middle cerebral artery. He was started on Low molecular weight Heparin and Tab Aspirin in view of ischemic stroke. LMWH was omitted after ruling out a venous thrombosis. Further workup to look for cause of the stroke showed normal homocysteine levels, ferritin levels, negative sickling test. As the father of the child had COVID infection 15 days back, Covid antibodies sent were positive. Reports of Factor V Leiden deficiency and Prothrombin mutation 20210-A and APLA profile were negative. 2D Echo done showed normal study. Ophthalmology review done to look for any fundus changes was normal. His power gradually improved in the right upper and lower limb along with resolving dysarthria. Gradually the power in the right upper and lower limb improved along with improving facial palsy and improving speech. He was discharged after 5 days of hospital stay. As no other cause was attributed, COVID19 IgG antibodies was considered to have caused the stroke.

Investigation	Patient 1	Patient 2
MRI Brain	Acute lacunar infarct in the subcortical white matter of right occipital lobe. Moderate narrowing of cavernous segment of bilateral internal carotid arteries.	Acute non hemorrhagic infarct in the left fronto-parietal lobe and left posterior insular cortex and white matter along with severe narrowing of supraclinoid segment of left internal carotid artery and complete occlusion artery of left middle cerebral artery.
ANA Anti- nuclear antibody by IFA	Negative	Negative
ASO	Negative	Negative
ESR	07 mm	08mm

HAEMOGRAM	Hb-11.9 g/dl TLC-10000/cumm Neutrophils-44% Lymphocyte-42% Platelet count-1.96/cumm	Hb-13.4 g/dl TLC-13600/cumm Neutrophils-86% Lymphocyte-12% Platelet count-4.44/cumm
HOMOCYSTEINE	8.11 mmol/L	13.2 mmol/L
LIPID PROFILE TEST	Serum Cholesterol (total): 151 Serum triglycerides; 73 Serum HDL:43 Serum VLDL:14.60 Serum LDL:93.40 Total: HDL:3.51 LDL:HDL:2.17	Serum Cholesterol (total): 135 Serum triglycerides; 106 Serum HDL: 29 Serum VLDL:21.2 Serum LDL: 84.80 Total: HDL: 4.66 LDL:HDL:2.92
PT APTT INR	12.9 s 34.2 s 1.09	14.7 40 1.23
SERUM ELECTROLYTES	Na-137 mEq/l K-3.6 mEq/l Ca-1.12 mmol/l	Na-135 mEq/l K-4.6 mEq/l Ca-1.19 mmol/l
SICKLING TEST	Negative	Negative
Covid -19 antibody IgG	Positive (2.23)	Positive (4.3)
CRP QUANTITATIVE	1.80	8.7
D-DIMER	<137	258
FERRITIN	49.89 ng/ml	82.74
Serum Ceruloplasmin	negative	
APLA profile(lupus anticoag)	negative	negative
Anti cardiolipin IgG, IgM, IgA	negative	negative
Anti-beta 2 glycoprotein igG, IgM	negative	negative

Conclusion

Most etiologies of pediatric stroke were ruled out in both of our cases. As no cause was attributed, COVID19 IgG antibodies was considered to have caused the stroke.

Discussion

The differential diagnosis of stroke in children is broad. It can be caused by multiple causes such as intracranial infection such as meningitis, meningoencephalitis or viral encephalitis. It can be caused by non-infectious causes such as intracranial bleeds and thromboembolisms. Rare causes of stroke include intracranial neoplasms, alternating hemiplegia and metabolic disorder such as MELAS. Various pathologies also mimic a stroke. Such pathologies include

complicated migraines causing focal neurological symptoms, post seizure Todd's paresis. But such mimics typically resolve within 24 hours.

The clinical presentation of AIS is extremely various, depending on age, cause, and involved vascular territory[3]. Focal neurological deficits is the most common presentation of strokes. Hemiplegia is the most common focal manifestation, occurring in up to 94% of cases [4]. The younger the child, the more nonspecific their symptoms may be.

The majority of signs and symptoms of stroke are nonspecific, and can be easily attributed to other causes. Hence to avoid misdiagnosis identification of various risk factors along with aggressive and timely investigations are advised.

Chorea is a no patterned, involuntary, hyperkinetic movement disorder. It is continuous, variable in speed, unpredictable in timing and direction, and flowing or jerky in appearance[5]. Because of the vulnerability of the basal ganglia and its connections to a wide variety of pathologies, the differential diagnosis of acute and chronic chorea is very large. While the most common etiology is autoimmune and poststreptococcal; ischemic or hypoxic insults to the brain in form of stroke also is a significant etiological factor for acute chorea in children.

Key points in the diagnosis of childhood stroke are causal investigation, laboratory tests, and imaging studies. Integration of diffusion weighted (DWI) and perfusion-weighted (PWI) imaging, is optimal for diagnosing stroke in acutely ill child. Although neuroimaging is the diagnosis of choice for stroke, screening for risk factors is quintessential.

Cardiac disease is the most common cause of stroke in childhood, accounting for up to a third of all Acute Ischemic Stroke[6]. Congenital cyanotic heart disease, polycythemia and anemia needs to be ruled out.

Sickle cell disease (SCD) is a very common cause of pediatric stroke, occurring in 285 cases per 100,000 affected children[7]. SCD causing stroke can present as early as 18 months of age but most children present after 5 years of age. Prothrombic disorders secondary to Protein C And Protein S deficiency as well as bleeding disorders such as factor VII, factor VIII deficiency need to be ruled out.

Infections typically present with fever. Varicella infection within past 1 year results in basal ganglia infarction. HIV/ HIV related vasculitis can cause cerebral aneurisms and hemorrhagic stroke. Other common infections include tuberculosis, mycoplasma, chlamydia, rickettsia infections including scrub typhus etc.

Vascular causes include Arterio-venous malformations secondary to neurocutaneous syndromes such as Sturge-Weber disease, neurofibromatosis, or von Hippel-Lindau syndrome. Moyamoya is another important vascular cause of childhood stroke and is associated with conditions such as Down syndrome, neurofibromatosis, and sickle cell disease.[8]

Nutritional deficiencies of folic acid or vitamin B12 may also cause hyperhomocysteinemia, leading to stroke. Vasculitis caused by disorders such as Kawaski disease, Henoch-Schonlein ¨Purpura (HSP), polyarteritis nodosa, Takayasu's arteritis, juvenile rheumatoid arthritis, systemic lupus erythematosus also cause stroke but it is more common in children above 14 years of age. Other causes include malignancies such as leukaemias, treatment with L-Asparginase, intracranial tumors, trauma, illicit drugs (amphetamines, cocaine, ecstasy)

and prescribed drugs (ergot derivatives for migraine, oral contraceptive pills etc)

Active COVID -19 infections with stroke has been described in literature. MIS-C causing neurological symptoms including stroke is also described in Paediatrics. Possible pathophysiology for it includes immune mediated or Para-infectious events, a hypercoagulable state from systemic inflammation and cytokine storm, viral mimicry of the host resulting in autoantibodies, viral super antigen sequences, antibody or T-cell recognition of viral antigens, or formation of immune complexes [9]

But the cases described in this report do not fit into clinical definition of MIS-C as described by CDC and WHO as there was neither fever nor multi-system involvement. Both the children were vitally stable and not acutely sick. As screening for risk factors were negative for both the patients, possible association of COVID-19 antibodies and stroke was thought and explored. Further studies are required to understand the pathogenesis of ischemic stroke with presence of COVID-19 antibodies.

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