From the Case Records of Kanchi Kamakoti CHILDS Trust Hospital: An Infant with Post-varicella Angiopathy (Stroke)

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Dr Sumanth Amperayani

Varicella in children is a common and highly contagious viral illness, which is usually self-limiting but morbidity and mortality can be higher in infants and immunocompromised.[1]

We would like to discuss with you an infant with varicella-related neurological complication.

A 6½-month-old female second born to a third-degree consanguineous parentage is brought for paucity of movements on right side and deviation of angle of mouth toward left for 4 days. There is also history of intermittent right facial deviation lasting for few seconds, suggestive of focal seizures. She was born preterm (28 weeks) with a birth weight of 1.7 kg and was hospitalized for respiratory distress for 5 days. Since then she has been growing well and her development was appropriate. The infant's mother and elder sibling had varicella 3 weeks prior to this case and recovered. This infant had mild varicella 2 weeks prior to this illness. She had not received medications for varicella. She is consciously alert and her vitals are stable. On her face and trunk, the old healed lesions of varicella infection could be seen. The angle of mouth deviated to the left with hemiparesis on right upper and lower limb with brisk reflexes. I have asked for complete blood count (CBC), renal function test (RFT), liver function test (LFT), prothrombin time/activated partial thromboplastin time, and international normalized ratio. Considering her young age and preterm birth, I would also like to consider late hemolytic disease of newborn. Hence, I would like to start her on injection levetiracetam for control of seizures and also vitamin K till we await preliminary labs. Is varicella the trigger or cause for stroke in this infant?

Dr S Balasubramanian

Infants with varicella are more prone than older children for complications.[2] This infant has acute onset weakness and is hemodynamically stable and most probably has developed an arterial ischemic stroke (AIS). Although the most common cause of ischemic stroke in children is transient cerebral arteriopathy of idiopathic cause, post-varicella angiopathy (PVA)/viral angiopathy is the second most common cause.[2] In this case, PVA is likely to be the cause of stroke.

Dr Dhanalakshmi K

There are several possible causes of AIS in pediatric age-group (Table 1). It has been stated that PVA is a form of transient arteriopathy and one of the important causes of pediatric stroke accounting for 30–40% of AIS. It should be suspected in a child with acute hemiparesis and basal ganglia infarction, and the risk period can be from days up to 20 months after the onset of rash, though highest risk period is after the first 6 months.[3] Once the seizures are controlled, we will do magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) of the child to confirm the nature of illness. We will also evaluate for other likely causes of stroke—hematologic and cardioembolic.

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Dr Lakshan

The investigations obtained show that CBC/RFT/LFT, coagulation profile, and echocardiogram (ECHO) are normal. To understand the prothrombotic status, the serum has to be tested. As the seizures are now under control, the child was shifted for MRI/MRA. The neurologic complications of varicella have to be reviewed, considering the child has significant history of varicella in the recent past.

Dr Silky

Encephalitis—acute cerebellar ataxia and diffuse encephalitis—and Reye's syndrome in past are the most common neurologic complications of varicella. The other less common complications being transient focal deficit, aseptic meningitis, transverse myelitis, vasculitis, and hemiplegia.[4]

The MRI/MRA (Fig. 1) findings are suggestive of acute infarct in the left inferior parietal gyrus, left corona radiata, left insula, basal ganglia, and left superior and middle temporal gyrus. No hemorrhagic transformation or mass effect was observed. The MRA is suggestive of arteriopathy in the form of diffuse narrowing of petrous, cavernous, supraclinoid segment of left internal carotid artery (ICA), proximal segment of left middle cerebral artery, and peripheral enhancement noted along the left ICA adjacent to cistern. Eventually she was started on aspirin and right hemiparesis did not progress. Prothrombotic workup is normal. Therefore, based on the history/clinical findings and imaging features, we need to consider whether any specific therapy is required.

Table 1: Etiology of stroke

Arteriopathy	Transient cerebral arteriopathy (TCA) (synonyms: childhood primary angiitis of the central nervous system [cPACNS]; focal cerebral arteriopathy [FCA])
	Post-varicella and other viruses angiopathy (PVA)
	Systemic/secondary vasculitis (e.g., Takayasu arteritis)
	Moyamoya disease/syndrome
	Arterial infection (e.g., bacterial meningitis, tuberculosis)
	Fibromuscular dysplasia
	Traumatic or spontaneous carotid or vertebral artery dissection
	Vasospasm (e.g., Call–Fleming syndrome)
	Migraine (migrainous infarction?)
	Congenital arterial hypoplasia (e.g., PHACES syndrome)
Cardiac	Complex congenital heart diseases (cyanotic ≫ acyanotic)
	Cardiac catheterization/procedure (e.g., balloon atrial septostomy)
	Ventricular-assistive device use
	Cardiac surgery
	Arrhythmia
	Valvular heart disease
	Endocarditis
	Cardiomyopathy, severe ventricular dysfunction
	Intracardiac lesions (e.g., atrial myxoma)
	Septal defects (atrial septal defect, ventricular septal defect, patent foramen ovale [possible paradoxical emboli])
Hematologic	Sickle cell anemia
	Iron-deficiency anemia
	Inherited prothrombotic (e.g., factor V Leiden, prothrombin gene mutation 20210A)
	Acquired prothrombotic (e.g., protein C/S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies, oral contraceptives, pregnancy)
Other including metabolic/ genetic etiologies	Acute systemic illness (e.g., dehydration, sepsis, diabetic ketoacidosis)
	Chronic systemic illness (e.g., systemic lupus erythematosus, leukemia)
	Illicit drugs and toxins (e.g., cocaine)
	Extracorporeal membrane oxygenation (ECMO)
	Hereditary dyslipoproteinemia
	Familial hypoalphalipoproteinemia
	Familial hypercholesterolemia
	Type IV, type III hyperlipoproteinemia
	Tangier disease
	Progeria
	Fabry disease (α-galactosidase A deficiency)
	Subacute necrotizing encephalomyelopathy (Leigh disease)
	Sulfite oxidase deficiency
	11β-Ketoreductase deficiency
	17α-Hydroxylase deficiency
	Purine nucleoside phosphorylase deficiency
	Ornithine transcarbamylase deficiency
	Neurofibromatosis type I
	HERNS
	Heritable disorders of connective tissue
	Ehlers-Danlos syndrome (type IV)
	Marfan syndrome
	Pseudoxanthoma elasticum
	Homocystinuria (cystathionine β-synthase deficiency, or 5,20-methylenetetrahydrofolate reductase)
	Menkes' syndrome
	Organic acidemia

Contd…

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	Methylmalonic academia
	Propionic academia
	Isovaleric academia
	Glutaric aciduria type II
	Mitochondrial encephalomyopathies
	MELAS
	MERRF
	MERRF/MELAS overlap syndrome
	Kearns-Sayre syndrome

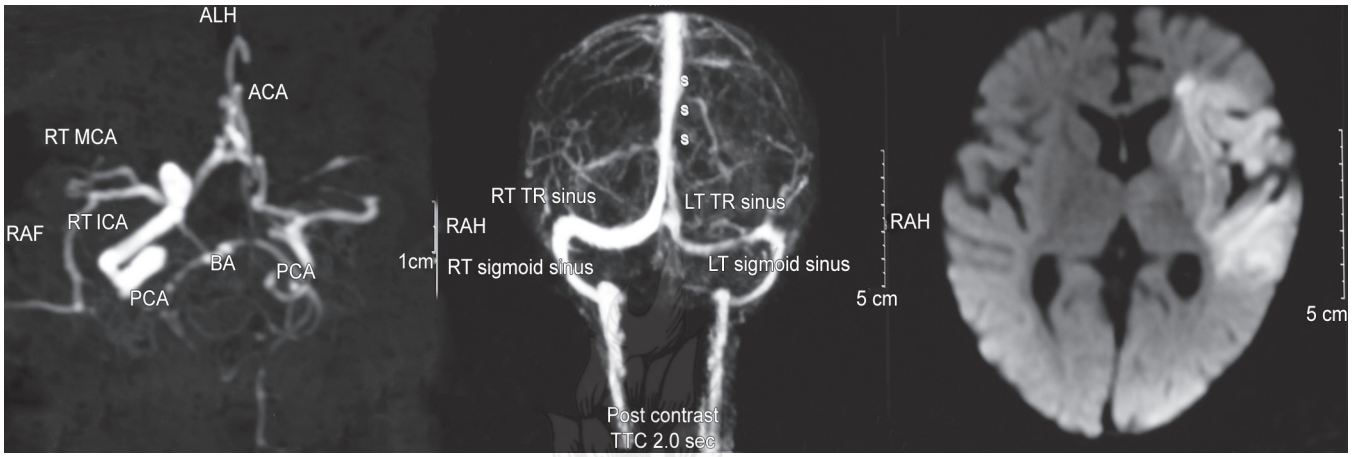

Fig. 1: Magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA): acute infarct in left inferior parietal gyrus, left corona radiata, left insula, and basal ganglia, also left superior and middle temporal gyrus

Dr S Balasubramanian

Although the infant completely recovered from acute varicella infection, the risk of PVA and stroke is maximum up to 6 months' post acute illness.[5] Before deciding on further management, the definition of PVA has to be reviewed.

Dr Silky

Perusing the available literature, following are mentioned as the imaging criterion for PVA.

Post-varicella angiopathy is an AIS that (1) followed a verified varicella infection within 12 months; (2) has an accompanying evidence of a vascular disease affecting the supraclinoid internal carotid artery, A1 or A2 segments of the anterior cerebral artery, or M1 or M2 segments of the middle cerebral artery; and (3) does not have any other possible etiologies.[6] Coagulation defects, metabolic and hematological risk factors, and cardiac disorders were excluded by the diagnostic evaluation.

This infant is likely diagnosed with PVA after excluding other possible hematologic and emboli cause and consistent with imaging findings.

Dr S Balasubramanian

Now that it is concluded that this infant is having PVA, let us review the prevention and management strategies.

Varicella is a live attenuated vaccine against moderate to severe disease, with 90% efficacy with one dose and 99% efficacy with two doses.[14] Vaccination helps in preventing the disease in at-risk population who experience severe disease and higher rate of complication. It has considerable herd protection and has shown to reduce the incidence of varicella even in noneligible vaccine group.[7,8] The vaccine is very safe with excellent safety profile. Considering the efficacy and safety of the available vaccine, serious consideration for routine immunization in public- and private-sector settings is needed, keeping in mind the long list of neurological and other systemic complications of varicella.

We will administer low-dose aspirin (3 mg/kg/od) for prevention of stroke recurrence as in general for any arteriopathy. Specific treatment guidelines for varicella angiopathy are yet to emerge owing to a lack of prospective randomized controlled trials and diverse expert opinion on diagnostic criteria, prognosis, and management. Most reports favor the use of acyclovir and steroids.[9] It has been observed that intravenous (IV) acyclovir for 14 days at a dosage of 30–45 mg/kg/day and a short course of immunosuppressive prednisolone at a dosage of 1 mg/kg/day are beneficial.[10,11] The pathogenesis is related to granulomatous angitis and endothelial damage owing to viral invasion of arteries especially in the immunocompromised. It can also be an immune-mediated vascular reaction secondary to distant infection. The histological specimens have often demonstrated arterial inflammation, so short course of steroid has been observed to be useful.[12] Based on the existing data, we shall start the child on IV acyclovir and steroids.

Considering the risk and benefit ratio, IV acyclovir and steroids can be started. We need to find out whether analysis of cerebrospinal fluid (CSF) be of any help?

Dr Lakshan

Review of literature suggests that CSF analysis for varicella markers [varicella zoster virus (VZV) DNA and VZV immunoglobulin (Ig)]

along with imaging characteristics are adjuncts for diagnosis of PVA. However, data on the timing of lumbar puncture for diagnosis and pediatric data on CSF studies are deficient. The yield for viral DNA/immunoglobulin G/immunoglobulin M (IgG/M) in adults is up to 30% and 97%, respectively.[12] Moreover, the yield of CSF analysis for viral markers is low for pediatric population, and data are limited.

Dr S Balasubramanian

The crucial bottom line is that PVA diagnosis can usually be made based on the characteristic neuroimaging findings of stroke related to intracranial arteriopathy and a contemporary anamnestic evidence of a varicella rash in a time frame of 12 months before stroke onset. Confirmation of PVA using CSF analysis is needed only if there is absence of varicella rash.[6]

Dr Lakshan

On day 4 of acyclovir and steroids, the child has been observed to show improvement in the power of right upper limb and lower limb. Also no new seizures were reported. Hence, IV acyclovir was continued for 2 weeks along with short course of oral steroids—tablet prednisolone 1 mg/kg (7 days)—and the child discharged from the hospital.

Dr Sumanth Amperayani

At 1-week follow-up post discharge, the child was doing well and was advised to continue aspirin and levetiracetam. It was also observed that the child showed improved power on right upper and lower limb and did not develop seizures again.

Dr Lakshan

The infant was readmitted with incessant crying and status epilepticus 4 weeks after the initial presentation. She had left focal seizures with secondary generalization. The child is currently encephalopathic with paucity of movements on the left side and the angle of mouth deviated toward right. The child continued to have seizures even after administering IV levetiracetam, so fosphenytoin was added for controlling seizures. What might be the cause of this recurrent stroke? Can Moyamoya disease be an alternative diagnosis?

Dr S Balasubramanian

Of all the causes of AIS, arteriopathy is most prone for recurrence.[13] Varicella has found to be associated with a twofold increase in recurrent AIS and transient ischemic attacks.[6] So PVA can still be the cause of recurrent stroke in this child. Although Moyamoya disease can present as recurrent and ischaemic stroke, imaging characteristic last done were not suggestive of collateral circulation, and child does not have any associated predisposing condition. Once the child is stable, repeat neuroimaging and CSF analysis need to be performed for confirmation. For now, we need to proceed with repeat MRI and lumbar puncture.

Dr Silky

The MRI reports are suggestive of acute infarct in the right inferior parietal gyrus, right corona radiata, right insula, and basal ganglia. The CSF analysis has been also suggestive of aseptic meningitis [moderate pleocytosis white blood cell (WBC) 350 (N21%, L88%); red blood cell (RBC) 4; protein 172 mg/dL, sugar 31 CSF C/S no growth]. However, varicella polymerase chain reaction (PCR) and IgG antibodies to varicella are negative.

Dr S Balasubramanian

So this child had recurrent stroke affecting the opposite side almost 4 weeks after the last event. It has been observed that in pediatric population, the diagnostic yield of CSF analysis is likely to be low. Positive CSF VZV markers in pediatric population have been found in only 50% of the patients.[6] As the pathogenesis is related to invasion of arteries in immunocompromised child, we need to do immunodeficiency workup for this child and restart the child on IV acyclovir and steroids.

Dr Lakshan

The immunoglobulin profile and flow cytometry reports are normal, and the HIV serology is negative. Seizures are well controlled in this child, and we have started the child on IV acyclovir with IV dexamethasone (0.6 mg/kg/day). Child is currently doing well with improvement in the power of left upper and lower limbs, with no further seizures. How long should we continue the antiviral as this is a recurrent stroke?

Dr Dhanalakshmi

For recurrent disease, a second course of oral antiviral is required for several months particularly in the immunocompromised patients.[6] Steroids will be given for 1 week and valacyclovir and aspirin with antiepileptics will be continued and child will be followed up periodically (Figs 2 and 3).

Dr Balasubramanian

The infant received oral valacyclovir for 3 months; and on follow-up (10 months of age), it was observed that child is able to move all the four limbs well, and the cranial nerve examination also did not reveal any abnormalities. Now the infant is able to sit with support and babbling and playing with the mother, indicating excellent recovery.

Dr Dhanalakshmi

Looking back, this was a young infant with a history of varicella in the recent past, but who recovered without any definitive treatment, though the infant developed late onset complication of varicella angiopathy. The CSF varicella markers, the gold standard for diagnosis of varicella angiopathy, were negative in this infant. There was recurrence of stroke and the child required prolonged antiviral therapy after which the hemiparesis improved and no recurrence occurred during the 6-month follow-up. Immunodeficiency was ruled out as a predisposing factor. Young age and a probable immature immune system can be risk factors for this rare neurological complication of varicella angiopathy. High index of suspicion in pediatric stroke and administration of acyclovir with short-course steroids may prevent the recurrence of stroke.

HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; PHACES, posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities.

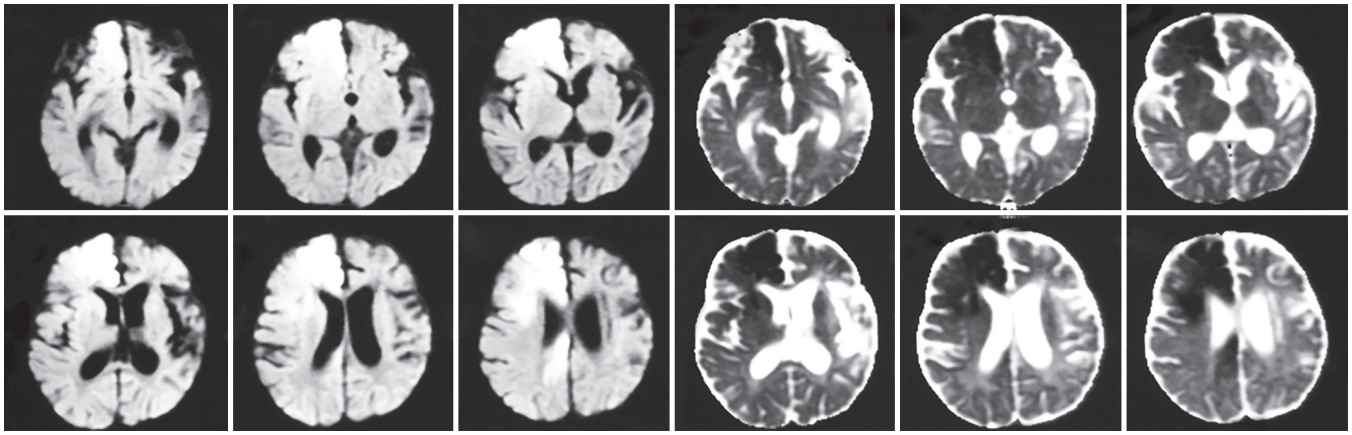

Fig. 2: Magnetic resonance imaging (MRI): acute infarct in right inferior parietal gyrus, right corona radiata, right insula, and basal ganglia

Fig. 3: Old healed varicella lesions over trunk of the baby and in the face of the mother

Summary

- Varicella is mostly a benign illness in immuocompetent children but can cause serious neurological and systemic life-threatening complication.
- Varicella vaccination is a reasonable and rational preventive option for prevention of pediatric stroke.
- Diagnosis of varicella angiopathy is essentially clinical.
- Confirmation of varicella angiopathy by CSF PCR and antibody tests is less often made in infants and young children.
- Acyclovir in combination with short-course steroid therapy is recommended for treatment of varicella angiopathy.
- Recurrence of stroke due to varicella angiopathy is a rare occurrence.
- Prolonged antiviral therapy may be considered for varicella angiopathy.

References

1. https://www.who.int/immunization/diseases/varicella/en/.
2. Nelson text book of pediatrics. 20th ed. In: Kleigman R, Stanton B, St.Geme J, Schor N ed., Elsevier: Philadelphia; 2016.
3. Thomas SL, Minassian C, Ganesan V, et al. Chickenpox and risk of stroke: a self controlled case series analysis. Clin Infect Dis 2014;58(1):61–68.
4. Straus SE. Varicella-Zoster Virus Infections Biology, Natural History, Treatment, and Prevention Moderator. Ann Intern Med 1988;108(2):221–237.
5. Dunkhase-Heinl U, Stausbøl-Grøn B, Christensen J, et al. Pediatr Neurol 2014;50(6):581e585.
6. Amlie-Lefond C, Gilden D. Varicella Zoster Virus: A Common Cause of Stroke in Children and Adults. J Stroke Cerebrovasc Dis 2016;25(7):1561–1569.
7. Gershon AA, Takahashi M, Seward JF. Varicella vaccine Plotkin S, Orenstein W, Offit P. Vaccines, 6th ed., Saunders Elsevier; 2013. pp. 836–869.
8. Background paper on varicella vaccines-SAGE working group. Available at http://www.who.int/immunization/sage/meetings/2014/april/presentations_background_docs/en/; accessed April 2014.
9. Nagel MA, Bubak AN. J Infect Dis 2018;218(S2):S107–S112.
10. Braun KPJ, Bulder MMM, Chabrier S, et al. The course and outcome of unilateral intracranial arteriopathy in 79 children with ischaemic stroke. Brain 2009;132(2):544–557.
11. Gilden D, Cohrs RJ, Mahalingam R, et al. Varicella zoster vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis and treatment. Lancet Neurol 2009;8(8):731–740.
12. Askalan R, Laughlin S, Mayank S, et al. Chickenpox and stroke in childhood: a study of frequency and causation. Stroke 2001;32(6):1257–1262.
13. Fullerton HJ, Wintermark M, Hills NK, et al. Risk of recurrent arterial ischemic stroke in childhood: a prospective international study. Stroke 2016;47(1):53–59.
14. Red book 2018–2021.