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CASE-BASED UPDATE

Moyamoya syndrome as a manifestation of varicella-associated cerebral vasculopathy—case report and review of literature

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Abstract

Background Varicella-associated cerebral vasculopathy (VACV) is a serious complication of Varicella zoster virus (VZV) infection. VACV has protean manifestations, with varying clinical, radiological features and prognosis.

Case description Moyamoya syndrome (MMS) with VACV is reported in few cases in the past. All the patients were in paediatric age group, presenting with multiple episodes of transient ischemic attacks (TIAs) and infarct. Our case was a 10-year-old Indian girl with ischemic stroke due to VACV who was treated with intravenous acyclovir. She presented 11 months later with multiple episodes of TIAs. Her angiogram showed bilateral moyamoya vasculature. Acetazolamide challenge study revealed areas of hypoperfusion. Previously reported such cases had been treated medically with steroids and antiplatelets. Most of these patients had resolution of motor symptoms after long follow-up; however, this period was marred by recurrent symptoms. Our patient underwent cerebral revascularisation procedure, following which her TIAs resolved, there was improvement in her limb power and, according to her parents, her performance in school has improved at 2-year follow-up.

Conclusion MMS can be a manifestation of VACV and should be suspected in paediatric patient of non-east Asian population. These patients require treatment with intravenous acyclovir to inactivate the virus. Those with TIAs should undergo cerebral revascularisation procedures. Medical management should be reserved for patients with adequate collaterals.

Keywords Varicella-associated vasculopathy · Moyamoya · Stroke · ECA-ICA bypass

Introduction

Varicella zoster virus (VZV), a common pathogen, affects all age groups. It can manifest as vasculopathy, predominantly involving central nervous system (CNS) vessels [26].

Varicella-associated cerebral vasculopathy (VACV) has varied manifestations, ranging from encephalitis to aneurysms [23]. Currently, there are two reports of moyamoya vasculature in association with VACV [8, 36]. Recent literature suggests that VACV is more common than earlier thought [4, 15, 26]. Moyamoya syndrome, in non-East Asian population, might be one of the manifestations of VACV.

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Historical background

Earliest report of VACV probably dates back to 1959, when Cravioto and Feigin described non-infectious granulomatous angitis of the nervous system, which was later predicted to have association with varicella by Rosenblum and Hadfield in 1972. In 1974, Gordon published the first angiographic study of hemiplegia following herpes zoster ophthalmicus, showing severe stenosis at ipsilateral carotid siphon. Over the period of time, VACV has been well recognised as a cause of stroke and other manifestations [1, 26].

Clinical presentation

Varicella-associated cerebral vasculopathy

The prevalence VZV infection, in adults, reaches 90–100% [4, 15, 20]. VZV is the only virus in human beings that has been shown to replicate in cerebral arteries and in areas corresponding to ischemia or infarction [7]. Varicella-associated

vasculopathy (VAV) is mostly intracranial and causes large, small and mixed vessel vasculopathy [7, 26].

Clinical and radiological features of VACV vary according to the manifestations and are summarised in Table 1.

Varicella-associated cerebral vasculopathy and moyamoya syndrome

Moyamoya is characterised by progressive stenosis of the intracranial internal carotid arteries (ICA) and their branches with formation of collaterals from external carotid artery (ECA). It is referred to as moyamoya syndrome (MMS) when associated with predisposing factor or is unilateral, and as moyamoya disease (MMD), when bilateral with no predisposing factor [28, 31].

The aetiology of moyamoya disease (MMD) remains unclear. East Asian population has genetic predilection. No genetic predilection has been defined in the Caucasian population [19]. The genetic predilection of the Indian population to MMD is unknown [30].

Houkin et al. proposed double hit theory for MMS. According to him, in predisposed individuals, moyamoya vasculature develops after some initial trigger like infection or immune disorder, causing inflammation, leading to narrowing of cerebral vessels [10]. Studies have shown that ICA in MMS patient has lower wall shear stress, which promotes stenosis of distal ICA, when triggered by inflammation [11, 12, 32, 33]. Hence, once triggered, ICA stenosis may persist in these individuals and vessel remodelling may continue even after removal of triggering factor [27]. The vessels in both VACV and MMS show fibrocellular intimal thickening and luminal stenosis [14, 21, 38]. While luminal narrowing resolves in most of the patients treated for VACV, in susceptible individuals, ICA stenosis may persist with remodelling into moyamoya vasculature [10, 17].

Diagnosis

The diagnosis of VACV is confirmed by the presence of anti-VZV IgG antibody or VZV DNA in cerebrospinal fluid [26, 34]. Anti-VZV IgG antibody in CSF is positive in > 90% of cases [24].

However, MMS as a manifestation of VACV may get missed, if there is no recent history of VZV infection. VACV should be suspected in paediatric patients, from non-east Asian population, with history of VZV infection or who have extracranial vasculopathy along with moyamoya vasculature [37]. There are also reports of development of MMS in patients with recent history of VZV where CSF-based diagnosis was not performed [6, 16] (Table 2).

Management

VACV should be treated with acyclovir (10–15 mg/kg given three times daily for 14 days). Immunocompromised individuals may need a longer course of treatment [23]. In cases of severe vessel wall inflammation, which can predispose to thrombosis and segmental wall weakness, steroids may be considered. However, steroid administration should be limited to 7 days because it carries the risk of increased viral replication and persistence of chronic infection [25, 26].

There are no definite guidelines for MMS associated with VACV. In previous reported cases, patients were treated with steroids, aspirin and follow-up. None of them underwent neurosurgical procedure. Steroids may help in acute phases of VACV but prolonged use is not advised [26]. The role of antiplatelet is controversial. Ischemia in MMS is because of hemodynamic changes; however, some authors suggest aspirin in acute phases of VACV due to increased markers of thrombogenesis and platelet activation [3, 9, 13, 29]. Aspirin can be given in dose of 1–5 mg/kg/day [22]. Patient with recurrent TIAs should undergo revascularisation procedure.

Prognosis and outcomes

In general, prognosis of VACV with MMS is favourable. Lanthier et al. found that vascular stenosis in VACV generally takes a monophasic course, with subsequent stenosis regression [17]. However, occasionally, stenosis progression can occur. In Table 2, four patients were conservatively treated with three having long term follow up, of which one improved fully and two had deficits along with TIAs. Patients with recurrent TIAs should undergo revascularisation surgery.

Exemplary CASE description

A 10-year-old girl presented with 5-day history of high-grade fever with itching, vesicular rash and myalgia followed by right hand and then left leg weakness. MRI brain revealed multiple areas of infarct with focal narrowing of bilateral supraclinoid ICA (Fig. 1). Cerebrospinal fluid (CSF) was positive anti-VZV IgG antibody. She was treated with intravenous acyclovir and aspirin. Subsequent imaging, 2 months later, revealed further progression of narrowing and areas of CLN (Fig. 1). She improved and was discharged with residual right hand weakness.

Eleven months later, she presented with episodes of right facial focal motor seizures and speech arrest 3–4 times in a day. She also had drop in her school performance. Acetazolamide challenge study revealed hypoperfusion in bilateral inferior prefrontal cortices, orbitofrontal cortices,

Table 1 VACV—manifestations, clinical and radiological features, treatment and prognosis

Manifestations	Clinical features	Radiological features	Diagnosis/treatment	Prognosis
Encephalitis/ischemic stroke	Susceptibility: all age group.	MRI brain—early stages—normal.	Diagnosis: anti-VZV IgG antibody (> 90% of times)	Irreversible changes due to infarction do not revert back.
	Past history: VZV infection (within 6 months to years ago), rarely no history of VZV infection	Multiple area of cortical, subcortical demyelination/infarction. It can also involve deep nuclei, cranial nerve. Rarely, involves infratentorial region	CSF positive for VZV DNA	Patients treated with IV acyclovir do good cognitively [34, 35].
	Recent history: constitutional symptoms ±, rash ±	Angiogram—focal or diffuse stenosis involving both large and small vessel, can involve either of them alone.	Treatment: oral acyclovir may not be of much help.	
	Clinical features: progressive drowsiness, weakness or other neurological deficits which worsens over a period of days to few weeks	Rarely beading of vessel can be seen or can be normal	IV Acyclovir (10–15 mg/kg given three times daily for 14 days)	
	CSF may show pleocytosis		Steroids may be given in case of severe vasculitis for initial period.	
			Role of antiplatelet is controversial [2, 5, 6, 9]	
Aneurysm/subarachnoid haemorrhage (SAH)/arterial dissection	Susceptibility, past history and recent history: same as above	MRI can show T2 hyperintesities due to vasculitis. Subarachnoid haemorrhage.	Diagnosis—same as above	Prognosis depends on natural history of infectious aneurysm and arterial dissection.
	Clinical features: asymptomatic—diagnosed while evaluating for other manifestation of VZV. Headache.	Angiogram: multiple aneurysms can be seen in immunocompromised.	Treatment—no clear guidelines. IV acyclovir reported to decrease size of aneurysm [18]	Acyclovir stops disease progression and reverts vasculopathy changes
	Arterial dissection patient with no history of trauma	Arterial dissection	SAH, aneurysm, arterial dissection management as per hospital protocol.	
	CSF may show pleocytosis			
Haemorrhagic stroke/cortical venous infarct	Susceptibility, past history and recent history: same as above	MRI brain—changes similar to venous infarct, VACV encephalitis, along with areas of haemorrhagic transformation.	Diagnosis—same as above	Depends on the initial condition of patient. Prognosis can be poor in cases of progressive disease.
	Occurs due to haemorrhagic transformation of ischemic stroke or venous infarct.		Treatment—IV acyclovir prevents vasculopathy progression.	
	Presentation similar to that of encephalitis		Haemorrhagic stroke/venous infarct management as per hospital protocol	
Moyamoya vasculature	Reported in immunocompetent, paediatric population.	Angiogram—moyamoya pattern of vasculature.	Diagnosis—same as above	Good outcome. Symptomatic cases should undergo revascularisation surgery
	History of VZV infection.	MRI—multiple perforators in deep nuclei. Areas of cortical laminar necrosis (CLN).	Treatment—no clear guidelines.	
	Presents with transient ischaemic attacks (TIAs)/stroke/seizure.		IV acyclovir to prevent progression of disease.	
			Revascularisation surgery in symptomatic cases.	

Table 2 Moyamoya and VACV

Author	Age/gender	Time interval between MMS and VZV infection (months)	VACV-CSF confirmed	Side of moyamoya vasculature	Treatment	Prognosis
Ganeshan et al. (1997)	3.5 y/m	6	No	Bilateral	Long-term low-dose aspirin.	Multiple TIAs after the initial stroke with persistent difficulties with coordination and language at 16 months.
Häusler M G et al. (1998)	16 y/f	48	Yes	Bilateral	Prednisolone, heparin followed by aspirin.	Hemiparesis recovered but cognitive function impaired
Ueno M et al. (2002)	4 y/m	6	Yes	Right	Because of the well-developed collateral circulation, no neurosurgical procedure	One year later, neurological deficits had disappeared completely.
Kundu et al. (2016)	5 y/m	1	No	Bilateral	Steroids, aspirin	Improved and discharged. Long-term follow-up unavailable
Current Case	10 y/f	11	Yes	Bilateral	IV acyclovir, aspirin. Later underwent revascularisation procedure	TIAs resolved after surgery. Improvement in limb power and cognition.

Broca's area and left temporal cortex (Fig. 2), which along with CLN can explain her seizures.

Angiogram revealed severe narrowing of bilateral supraclinoid ICA and distal branches, with extensive collaterals via ECA, akin to MMS (Fig. 1), due to vascular remodelling.

She then underwent left STA-MCA bypass along with encephalo-duro-arterio-myo-pericranial-synangiosis

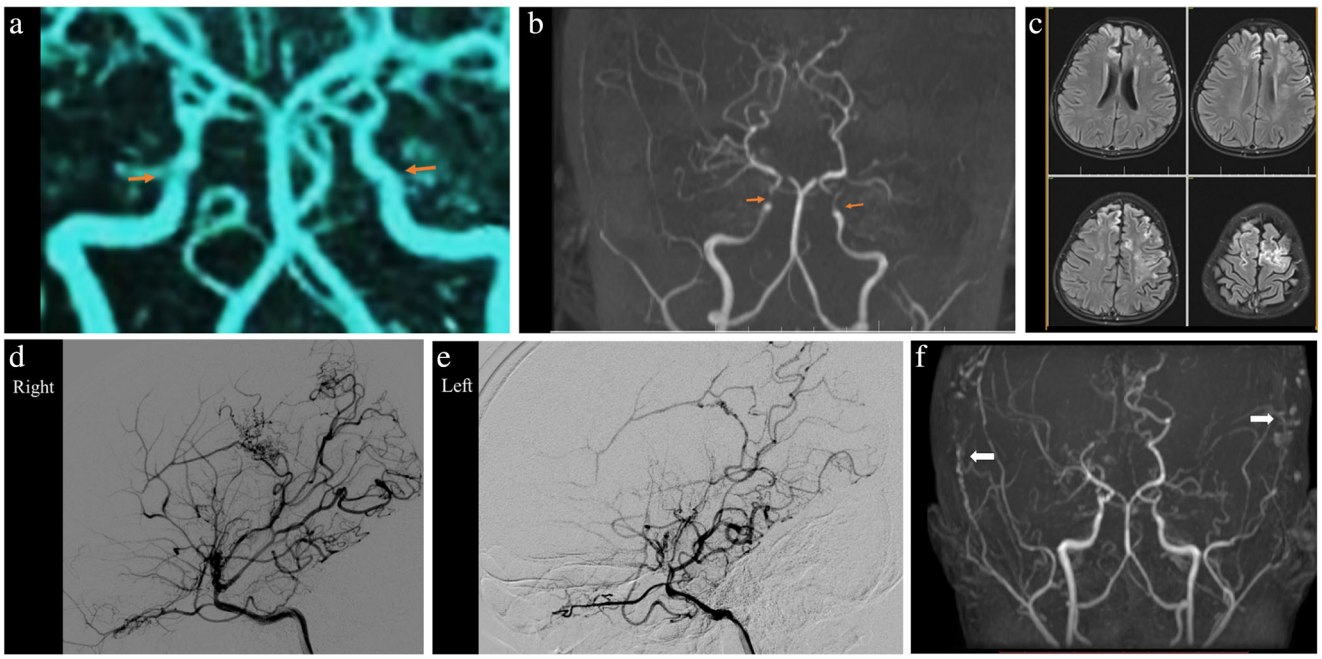

Fig. 1 (**a**) MRA at time of initial stroke showing narrowing of bilateral ICA. (**b**) MRA, done 2 months later, showing narrowing of ICA, the ICA bifurcation and distal branches. The cortical branches were not visible. Basal perforators were indistinctly made out. (**c**) MRI brain, done 2 months later, revealed areas of CLN. (**d**) and (**e**) Preoperative angiogram, done 11 months later, showing development of moyamoya vasculature. (**f**) Postoperative MRA, done 1.5 years after surgery, showing normal flow along bilateral superficial temporal artery (STA) to middle cerebral artery (MCA) bypasses

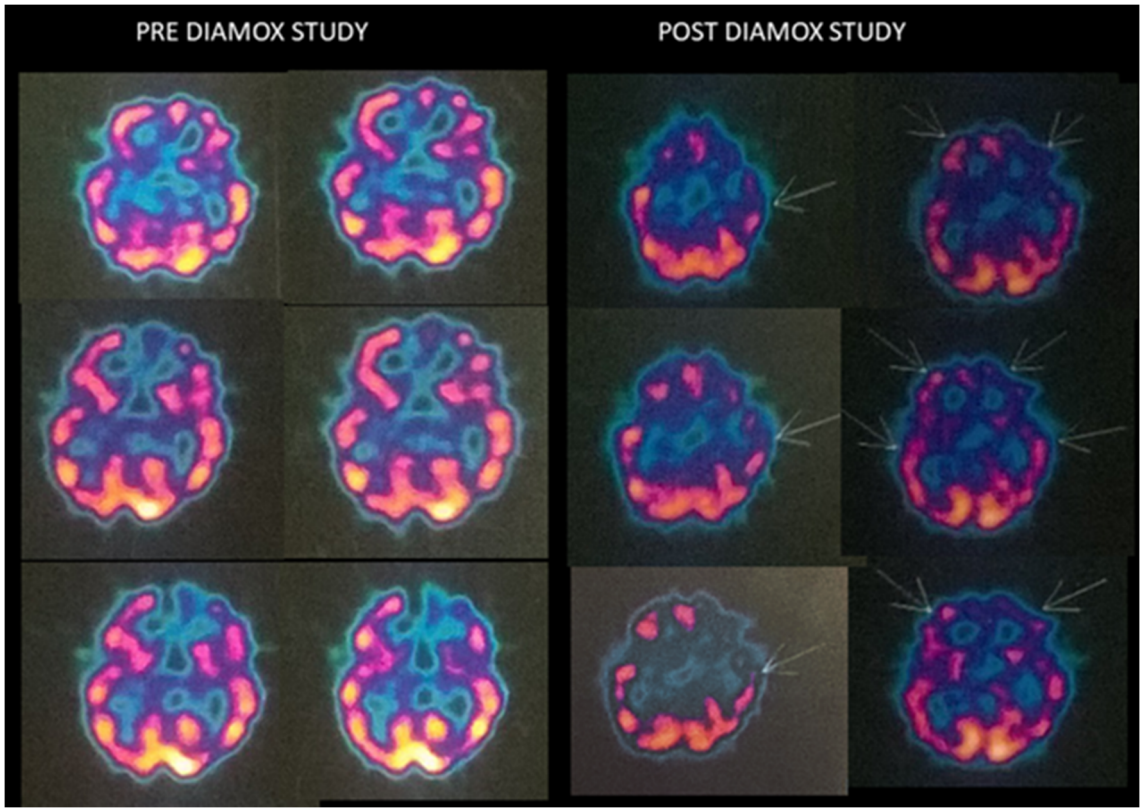

Fig. 2 Acetazolamide challenge study showing area of decreased perfusion

(EDAMPS) which was followed by right STA-MCA bypass along with EDAMPS 5 months later.

Follow-up MRA, done 1.5 years after surgery, demonstrated normal flow along bilateral STA-MCA bypasses (Fig. 1).

Her seizures and speech arrest had resolved after the first surgery. At 2-year follow-up, there was improvement in her limb power. According to her parents, her rank in her class has improved post surgery.

Conclusions

VACV is a serious complication of VZV infection. It may manifest as MMS and can be a cause of moyamoya in non-East Asian population. VACV should be sought in MMS patient with recent history of fever and rash. When treated with intravenous acyclovir and revascularisation in symptomatic patients, prognosis is good.

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Compliance with ethical standards

Conflict of interest No conflict of interest.

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