Hemorrhagic Stroke and Cerebral Venous Thrombosis: Rare Neurological Sequelae of Chickenpox Infection

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Abstract

Chickenpox (varicella) is primarily a disease of childhood which occurs due to infection with varicella-zoster virus (VZV). Primary VZV infection is rare in adults due to exposure in early childhood in our country. In adults, it is associated with some serious systemic and neurological complications which can follow both primary infection and reactivation of VZV. Neurological sequelae caused by primary VZV infection are rare and include encephalitis, aseptic meningitis, myelitis, acute cerebellar ataxia, Reye syndrome, Ramsay Hunt syndrome, and rarely stroke and cerebral venous thrombosis (CVT). VZV infection of cerebral vessels produces vasculopathy and hypercoagulable state, leading to complications such as stroke and CVT. We hereby report cases of two immunocompetent young adults who developed acute hemorrhagic infarction in the brain and CVT following chickenpox infection.

Keywords: Chickenpox, cerebral venous thrombosis, stroke, vasculopathy

Introduction

Chickenpox is a viral infection which presents with fever and exanthematous rash mainly in children. Causative organism is varicella-zoster virus (VZV) which is a ubiquitous, exclusively human, neurotropic DNA virus (human herpes virus 3) usually infecting children. VZV after the primary infection can remain latent in the spinal and cranial ganglia and may be reactivated at a later stage in a state of immunocompromise to present as herpes zoster. The disease is rare in adults in endemic countries like India due to early exposure to the virus. Although it is a self-limiting disease, occasionally serious systemic and neurological complications can occur. Neurological sequelae as a result of primary VZV infection are rare and estimated to be approximately 1–3/10,000 cases (0.01%–0.03%).[1] Neurological sequelae can follow both primary infection and reactivation of VZV. Neurological complications frequently encountered are cerebellitis and encephalitis. Less frequent complications are Guillain-Barré syndrome, meningoencephalitis, transverse myelitis, aseptic meningitis, optic neuritis, postherpetic neuralgia, herpes zoster ophthalmicus, peripheral motor neuropathy, and rarely stroke and cerebral venous thrombosis (CVT).[2] The more serious manifestations arise when VZV invades the spinal cord or cerebral arteries after reactivation of the virus, causing diseases such as myelitis and focal vasculopathies such as stroke. Possibly, a hypercoagulable state is produced by the infection or direct invasion of virus in venous endothelial wall with subsequent damage to endothelium, leading to CVT. We report two cases of hemorrhagic stroke and CVT in immunocompetent adults as rare neurological sequelae of primary varicella infection.

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Case Reports

Case 1

A 25-year-old unmarried female presented to the emergency department with complaints of headache followed by loss of consciousness for 1 day. It was not associated with seizure, fever, and vomiting. There was no history of preceding head trauma. She was received in intubated state owing to low Glasgow coma score (GCS), after being referred from another hospital. The patient had a history of acute febrile exanthematous rash diagnosed as chickenpox 10 days back, for which oral acyclovir for 5 days was prescribed from some private practitioner. She was nondiabetic and nonhypertensive. There was no history of chickenpox, tuberculosis, or stroke in

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the past. At admission, the patient was unconscious, afebrile, and not arousable by verbal or deep painful stimulus. She was intubated and on mechanical ventilatory support. GCS was 3 E1VTM1 and both pupils were mid-dilated (4 mm) and fixed. Bilateral plantar reflex were mute. Fundus revealed papilledema. General physical examination was normal, except scars and crusting lesions on the body, indicating healing chickenpox infection. Pulse rate was 90/min, respiratory rate (ventilator) was 14 breaths/min, arterial oxygen saturation (spO2) was 98% on O_2, and electrocardiogram showed normal sinus rhythm. Mean arterial pressure was 76 mmHg and random blood sugar was 120 mg/dL. Rest of the systemic examination was unremarkable. Routine laboratory investigation revealed leukocytosis, thrombocytopenia, and deranged renal function [Table 1]. Coagulation profile at admission was normal. Serum antibody for VZV (IgM, ELISA based) was reactive. Malarial antigen and HIV were negative. Considering a diagnosis of post-varicella encephalitis, magnetic resonance imaging (MRI) of the brain was planned. After initial stabilization, MRI [Figure 1] was done on day 3 which showed acute infarction with hemorrhagic transformation involving the entire left hemisphere along with a large hematoma seen in the frontotemporal lobe, with midline shift of approximately 17 mm toward the right. A focal hyperacute to acute hematoma was also seen in the left cerebellar hemisphere with surrounding edema. Acute infarction of the right anterior cerebral artery and middle cerebral artery (MCA) territory including parasagittal right frontal and the anterior right temporal lobe along with acute infarction of the midbrain and the pons was also seen. Thus, a diagnosis of post-varicella hemorrhagic stroke with raised intracranial pressure (ICP) was made and the patient was managed with intravenous (IV) antibiotics (ceftriaxone 2 g BD), antivirals (acyclovir 500 mg thrice a day (TDS)), inotropes (noradrenaline 0.1–1 ug/kg/min), corticosteroids (dexamethasone 8 mg TDS) fluids, and mechanical ventilatory support; however, unfortunately, the patient could not survive and expired on day 4 of hospital stay. The cause of death was raised ICP due to hemorrhage into the infarcted brain. Cerebral angiography or autopsy analysis could not be done.

Table 1: Laboratory parameters at admission in case 1

Parameter	Normal range	At admission
Hb (g/dl)	12-15	12.1
TLC (cells/mm^3)	4000-11,000	13,900
DLC (N/L/E/M) (%)	50-73/20-40/2-5/5-10	80/18/1/1
Platelets (1000×mm^3)	150-450	20
Bilirubin (T/D) mg/dl	0.1-1/0.0-0.3	0.5/0.3
AST/ALT (IU/L)	<40	98/30
SAP (IU/L)	<92	63
Protein/albumin (g/dl)	6.0-7.5/3.5-5.5	7/4.1
INR	<1.2	1.1
Blood urea/creatinine (mg/dl)	15-40/0.1-1	69/2.4
Na/K (Meq/L)	135-145/3.5-5	159/4.1
Serum anti VZV IgM		1:128 positive

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, Hb = Hemoglobin, N/L/E/M = Neutrophils/Lymphocytes/Eosinophils/Monocytes, SAP = Serum alkaline phosphatase, T/D = Total/Direct, TLC = Total leukocyte count, JE = Japanese encephalitis, VZV = Varicella-zoster virus, INR = International normalized ratio DLC = Differential leucocyte count

Case 2

A 20-year-old male was brought to emergency with altered sensorium for 4 days, which was preceded by headache for 2 weeks following chickenpox infection. The fever had subsided and there was no history of vomiting, seizures, or head injury. There were no addictions and history was insignificant. On admission, he was conscious but appeared confused. On examination, the skin showed multiple small scars, some with scabs, a manifestation of recent varicella infection. There were no new lesions. These lesions were mainly on chest wall and neck. The general physical examination including blood pressure, pulse rate, and respiratory rate was found to be within normal limits. Higher mental functions were abnormal as the patient was aphasic and could not follow verbal commands. Memory could not be tested. Cranial nerve could not be tested in the patient. Pupils were bilateral equal in size and showed prompt reaction to light. Fundus was normal. The patient was aggressively moving all the four limbs. Deep tendon jerks were elicited bilaterally in all four limbs. Plantar responses were extensor bilaterally. He had nuchal rigidity. Gait could not be tested. There were no involuntary movements. Cerebellar signs and sensory examination could not be tested. Rest of the systemic examination was normal. His routine investigations were normal [Table 2]. Serology for anti-VZV antibody was positive. Considering a diagnosis of post-varicella meningoencephalitis, a cerebrospinal fluid (CSF) analysis and MRI of the brain were planned on day 2. CSF was clear and the opening pressure was normal. CSF report showed normal leukocyte count of 5 cells/mm^3, all lymphocytes with mildly raised CSF protein (62.1 mg/

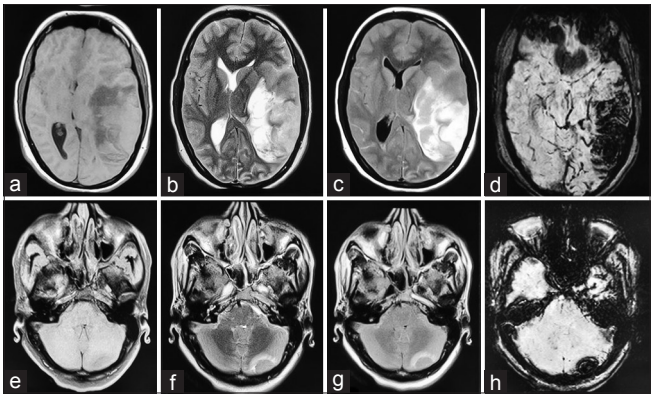

Figure 1: Axial magnetic resonance imaging of the brain showing (a) a large area of altered mixed signal intensity involving left fronto-temporo-parietal region causing mass effect in form of effacement of surrounding sulcal spaces, compression of ipsilateral lateral ventricle and mid line shift of 1.7 cm to the right. (b) The lesion was iso- to hyper-intense on T1-weighted and T2-weighted images. (c) Extensive surrounding edema (fluid ATTENUATED inversion recovery image). (d) Blooming on susceptibility-weighted imaging, but no postcontrast enhancement (not shown). (e-h) Similar morphology small lesions were noted in left cerebellar and left frontal parasagittal region (not shown)

dL) and with normal sugar (79 mg/dl). CSF IgM for VZV was positive. Acid-fast bacilli stain of CSF was negative. Adenosine deaminase (ADA = 4) in CSF was negative. MRI showed a T2 fluid attenuated inversion recovery (FLAIR) hyperintense area in the left tempo-parieto-occipital area, suggestive of subacute infarct (left MCA and posterior cerebral artery territory) with effacement of cortical sulci seen on the left side, suggestive of edema [Figure 2]. Serum homocysteine B12, folic acid, thyroid function coagulation profile, and lipid profile were normal. HIV serology was nonreactive. Chest X-ray was normal. The patient was started on IV acyclovir (500 mg TDS), ceftriaxone (2 g BD), mannitol 20% (100 ml TDS), and corticosteroids (dexamethasone 8 mg TDS). On day 8 of hospital stay, patient's headache persisted and he developed left lateral rectus palsy. Fundus showed signs of early papilledema. In view of massive infarct and edema, a possibility of venous sinus thrombosis was considered and a magnetic resonance venogram of brain was done. It showed features suggestive of dural sinus thrombosis, involving left transverse, sigmoid sinuses, and internal jugular vein (IJV) with subacute infarct with hemorrhagic transformation in left temporo-parieto-occipital lobes, with mass effect and midline shift to right with subfalcine herniation and midbrain rotation to right. Venography showed luminal hyperintense signal (loss of flow void) in left transverse sinus, sigmoid sinus, and IJV on T1/T2/FLAIR sequences with peripheral blooming on fast field echo (FFE) and enhancement of wall on postcontrast scan [Figure 3]. Dose of mannitol was increased to 150 ml TDS and started on anticoagulation (low-molecular-weight heparin and acitrom 2 mg OD) to maintain therapeutic international normalized ratio (INR) of 2–3. Headache and papilledema resolved by day 11. By day 14, he started conversing and accepting orally. Repeat fundus examination was normal. The patient was discharged on acitrom 2 mg and oral steroids tapered over next 4 weeks. On discharge, his INR was 2.5 and he was asked to follow-up with monitoring of coagulation parameters. At 12 weeks, the patient showed complete clinical recovery and oral anticoagulants were stopped.

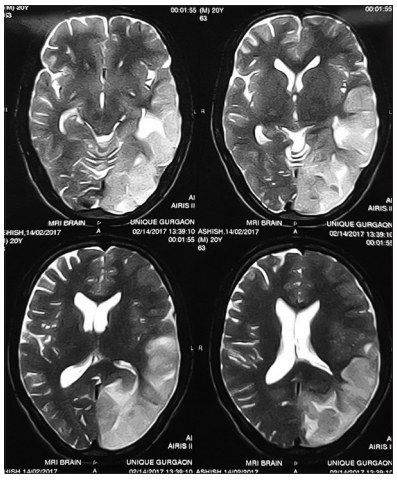

Figure 2: Magnetic resonance imaging of the brain showing infarct in the left temporoparietal and occipital lobes with significant perilesional edema

Discussion

VZV is a neurotropic alpha herpes virus whose infection causes two clinically distinct forms of disease. Primary infection with VZV results in varicella (chickenpox) characterized by vesicular lesions in different stages of development on the face, trunk, and extremities. Herpes zoster (shingles) results from reactivation of endogenous latent VZV infection within the sensory ganglia.

Neurological complications caused by primary VZV infection are rare and estimated to be approximately 0.01%–0.03%.[1] In children, it is usually a self-limiting disease, with cerebellitis being the most common neurological complication.[2] However, in adults, even though infection is rare in endemic countries like ours, VZV can cause serious neurological complications which include encephalitis, aseptic meningitis, myelitis, acute cerebellar ataxia, Reye syndrome, Ramsay Hunt syndrome, and rarely stroke and CVT. The mechanisms responsible have been attributed to direct neurological damage, immune mediated

Table 2: Laboratory parameters at admission in case 2

Parameter	Normal range	At admission
Hb (g/dl)	12-15	12.8
TLC (cells/mm^3)	4000-11,000	10,200
DLC (N/L/E/M) (%)	50-73/20-40/2-5/5-10	80/18/1/1
Platelets (1000×mm^3)	150-450	238
Bilirubin (T/D) mg/dl	0.1-1/0.0-0.3	0.5/0.3
AST/ALT (IU/L)	<40	33/17
SAP (IU/L)	<92	60
Protein/albumin (g/dl)	6.0-7.5/3.5-5.5	7.2/4.2
INR (baseline)	<1.2	1.4
Blood urea/creatinine (mg/dl)	15-40/0.1-1	34/0.5
Na/K (Meq/L)	135-145/3.5-5	136/4.0
B12 (pg/ml)/folic acid (ng/ml)	187-883/3.1-20.5	237/5.1
Homocysteine (μmol/L)	5.46-16.20	15
Serum anti-VZV IgM (ELISA)		1:256 positive
CSF anti-VZV IgM (ELISA)		1:16 positive
CSF anti-JE IgM (ELISA)		Negative

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, Hb = Hemoglobin, N/L/E/M = Neutrophils/Lymphocytes/Eosinophils/Monocytes, SAP = Serum alkaline Phosphatase, T/D = Total/Direct, TLC = Total leukocyte count, JE = Japanese encephalitis, ELISA = Enzyme-linked immunosorbent assay, INR = International normalized ratio, CSF = Cerebrospinal fluid, VZV = Varicella-zoster virus, DLC = Differential leucocyte count

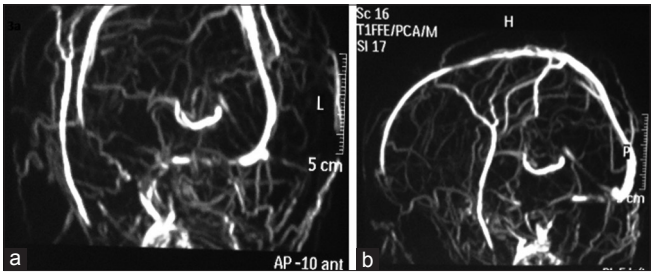

Figure 3: (a and b) Magnetic resonance venogram of the brain showing loss of normal signal intensity in left transverse sinus, sigmoid sinus, and internal jugular vein (red arrows, (a) coronal view, (b) sagittal view)

and recently also due to infection of the small and large blood vessels by VZV causing vasculopathy.[3] VZV is the only virus in human beings which has been shown to replicate in vessels and produce vasculopathy.

Vasculopathy can occur after either primary infection with VZV (chickenpox) or after viral reactivation (herpes zoster). The exact incidence and prevalence of stroke caused by VZV are still unknown. The pathogenesis of VZV vasculopathy is still debatable. It is considered that VZV spreads directly along the intracranial branches of the trigeminal nerve to the ipsilateral arterial walls, through hematogenous seeding or spreading via the sympathetic nervous system.[4] Various histopathological studies of patients with varicella vasculitis have demonstrated the virus and the antigen within the vessel wall. The virus induces a noncytolytic infection of the smooth muscle cells in the media which causes functional damage to the vascular endothelium (vascular remodeling) and may thus result in thrombosis and promote subendothelial proliferation of smooth muscle cells, fibroblasts, and collagen, leading to areas of stenosis and occlusion.[5] However, pathologic findings may differ depending on stage of the disease whether acute or chronic and are also influenced by the host immune response.[6,7] However, in children, it is estimated that varicella accounts for 7%–31% of arterial ischemic stroke,[8-10] with 1 in 15,000 cases of varicella associated with stroke.[8] A potential cofactor that has emerged in VZV-associated ischemic stroke is the role of transient autoantibodies to phospholipids and coagulation proteins during or after varicella infection.[11,12] The role of these autoantibodies in thrombus formation in cerebral vessels during VZV infection requires further study.

In immunocompetent individuals, a spectrum of vascular involvement exists, ranging from necrotizing arteritis to moderate, chronic vascular inflammation, thrombosis without inflammation, remote vascular occlusion resembling atherosclerosis of the small vessels of the nervous system, and stenosis or thrombotic occlusion of large vessels in the circle of Willis. VZV penetrates to a greater extent in immunocompromised patients, resulting in small vessel angiopathy (multifocal leukoencephalopathy) or ependymitis (ventriculitis). An increasing disease spectrum of this condition now includes ischemic and hemorrhagic stroke, transient ischemic attacks, arterial dissection, temporal artery infection, ischemic cranial neuropathies, CVT, peripheral thrombotic disease, and spinal cord infarction.[13]

Because not all patients with VZV vasculopathy have a history of zoster or varicella rash, the CSF of all patients with uni- or multi-focal vasculopathy, as well as central nervous system angiitis of unknown etiology, should be studied for the presence of both VZV DNA and anti-VZV IgG antibody. However, studies have shown, perhaps somewhat surprisingly, that this latter serological method is a more sensitive diagnostic marker of this condition than polymerase chain reaction analysis.[14]

In our first patient, CSF examination could not be done due to sick status, but the stroke could be attributed to chickenpox infection as it had occurred within 2 weeks of chickenpox and no other etiological factors could be identified. Another important finding in our patient was thrombocytopenia. It was severe which may be attributed to the septicemia that complicated chickenpox infection in our patient. Thrombocytopenia is a well-known complication of chickenpox and can occur in up to 1% cases.[15] It usually occurs early and is immune mediated and mild. In our second case, CSF was done and anti-VZV IgG was positive. The current recommended treatment of VZV vasculopathy in immunocompetent individuals is 14 days of IV aciclovir and 5–7 days of corticosteroids, though immunocompromised individuals or those relapsing with recurrent VZV vasculopathy may need a longer course of aciclovir and corticosteroids.[16]

Conclusion

Thus, keeping in mind the varied neurological sequelae of chickenpox and VZV vasculopathy being responsible for the same, one should be highly suspicious in cases with post-varicella neurological manifestations. Rapid and accurate diagnosis can lead to effective antiviral treatment of VZV vasculopathy disease spectrum.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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