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CASE REPORT

Acute Cerebral Venous Sinus Thrombosis after Varicella Infection - Two Case Reports and Review of Literature

Sheela Mathew[1], Adarsh Aayilliath Kuttiyeri [2], Anjana Gopal[3], Akhila Arya[4], Megha S Kumar[4]

[1]Additional Professor, [2]Senior Resident, [4]Junior Resident Infectious Disease Unit, Department of Internal Medicine, Govt. Medical College Hospital, Kozhikode, Kerala, India

[3]Senior Resident, Department of Nephrology, Government Medical College, Trivandrum, Kerala

Abstract

Primary varicella infection is generally a mild disease of childhood. Nowadays it is more commonly seen in adults and sometimes associated with severe complications. The neurological manifestations are mainly in the form of encephalitis, metabolic encephalopathy, seizures and rarely arterial vasculopathy, which cause ischemic strokes, aneurysms, subarachnoid and cerebral haemorrhages. It is also associated with coagulopathy, causing DIC and Purpura fulminans, a severe autoantibody mediated coagulopathy presenting with purpuric or painful necrotizing lesions due to microthrombi in dermal capillaries. This is often associated with acquired Protein S and Protein C deficiency and micro thrombosis in arterial and venous circulation. There are few case reports of hypercoagulable states leading to DVT and other thrombo embolic sequelae following Varicella induced auto antibodies in children. Such complications are very rare in adults. We report two cases of cortical venous thrombosis; one case was associated with DVT also.

Key words: Varicella, cortical vein thrombosis, hyper coagulable state, thrombophilia, Protein S, Protein C

Introduction

Varicella zoster virus (VZV) infection causes two distinct clinical entities – varicella (chickenpox) and herpes zoster.[1] Primary varicella infection in children is generally a mild disease compared to more severe presentations in adults or immunocompromised patients of any age. Neurological complications of varicella infection include encephalitis, seizures, transient focal deficits, aseptic meningitis, transverse myelitis, vasculitis, and hemiplegia.[2] Vasculitic arterial infarctions are common but cerebral venous thrombosis (CVT) is very rare. We report two cases of cerebral vein thrombosis complicating Varicella infection in the absence of hypercoagulable states.

Case Report - 1

A 39- year- old female, with no previous comorbidities presented with severe headache, vomiting and altered sensorium. Two weeks prior to present admission she had fever, headache and malaise of 2 days duration followed by a centripetal vesicular rash over trunk, extremities and head which was diagnosed as chickenpox and subsided spontaneously. There was no history of seizures.

At the time of admission in our centre, patient was conscious but disoriented with normal vitals. She had healed chickenpox lesions over the trunk, extremities and face. Neurological examination revealed bilateral papilloedema and decreased visual acuity in both eyes (distant vision 6/10). On the second day of admission she developed an acute onset left facial palsy and weakness of left upper limb. Other systems were within normal limits. Suspecting possibility of varicella vasculopathy, a CT scan of brain was done which showed diffuse brain oedema. The next day patient developed left lateral rectus palsy and severe headache and photophobia. In view of severe headache, papilloedema and false localizing sign like lateral rectus palsy, intra cranial space occupying lesion or cortical venous thrombosis was suspected and MRI Brain was done. MRI showed acute infarct in right frontal region with diffusion restriction and MR Venogram showed filling defect in superior sagittal, right transverse and straight sinus suggestive of cerebral venous thrombosis. MR angiogram was normal. The first CT was reviewed by radiologist and reported presence of dense delta sign suggestive of superior sagittal sinus thrombosis.

Routine haematology and biochemistry were normal. Serology for HIV, HBsAg and HCV was negative. Workup for vasculitis and collagen vascular disorders was also negative. Protein C and Protein S activity was also normal.

Address for Correspondence
Dr Sheela Mathew, Additional Professor, Infectious Disease Unit, Department of Internal Medicine, Govt. Medical College Hospital, Kozhikode, Kerala, India Mob no. 9447760932
E-Mail: sheelamathewcmc@gmail.com

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Serum antiphospholipid antibody was negative. (Table1). Echo cardiogram showed no regional wall motion abnormality, LVEF-58%, no RA- RV dilatation, no vegetation and no pericardial effusion.

This patient was started on anticoagulation with unfractionated heparin followed by oral anticoagulant warfarin to optimize the INR between 2 and 3. IV Acyclovir 500mg 8hourly intravenously was also given. In the next 3-5 days patient's headache and neurological deficit improved. Her visual acuity took a longer time to improve but eventually became normal

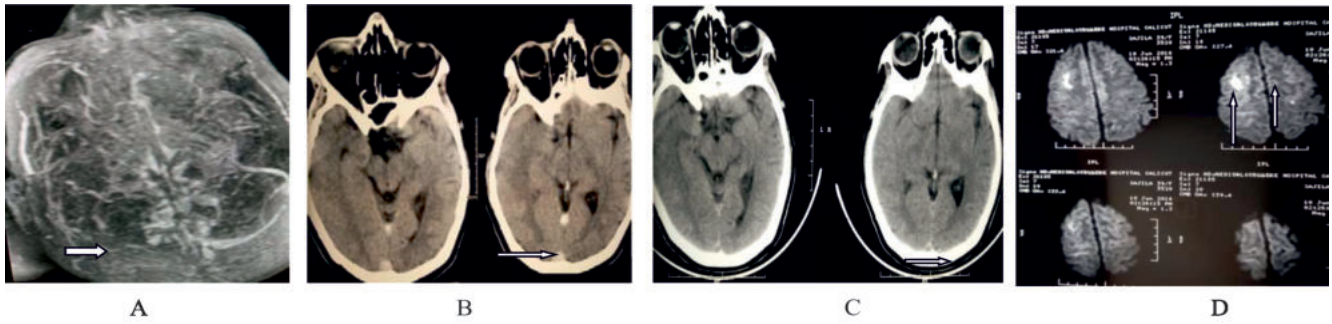
Case Report- 2

A 59 years old female who is a well-controlled hypertensive and diabetic, presented to our centre with headache, vomiting and gradually progressive altered sensorium. One week prior to present admission she had two days fever associated with myalgia and fatigue followed by centripetal vesicular polymorphic rash diagnosed as Varicella. She was treated elsewhere with acyclovir and lesions gradually began to crust.

At the time of admission in our centre she was stuporous and healed chickenpox lesions were present over her trunk, extremities and face. Neurologic examination revealed bilateral extensor plantar and adequately reacting pupils. She was moving all her limbs on painful stimulus. Initially Varicella encephalitis or metabolic encephalopathy was considered and she was investigated. CT brain revealed only cerebral oedema. Serum sodium and calcium were normal; other blood investigations were also within normal limits. She was started on IV acyclovir and mannitol. A lumbar puncture was performed which drained clear CSF at opening pressure 200 cm H2O and revealed high protein ,low sugar and lymphocytic pleocytosis. However on second day of admission she developed swelling of left lower limb and weakness of right lower limb. One episode of transient facial deviation and abnormal movements of right lower limb suggestive of focal seizure also occurred. She was started on levetiracetam. A Doppler study of left lower limb showed deep vein thrombosis of left common femoral vein, superficial femoral vein, deep femoral vein and popliteal vein. In this background suspected Varicella vasculopathy and cerebral venous thrombosis; MRI brain with contrast and MR venogram was taken. MRI showed multiple areas of hemorrhagic infarcts involving bilateral thalami, right caudate nucleus and right cerebellar hemisphere; infarcts involving deep white matter of right frontal lobe and intraventricular and subarachnoid bleed. MRV revealed hyper intensity with absent flow voids involving left

Table 1: Laboratory Values

Investigation	Case 1	Case 2	Normal
Total count	9400	6800	4000-11000 cells/mm^3
Hemoglobin	12.4	11.8	11-14 mm^3
Platelet count	2.5 l	1.9 l	1.5-4 l
ESR	15	20	0-30 mm/ hour
CRP	2.5	3.1	0-6 mg/L
RBS	98	114	70-110 mg/dL
Urea	23	34	10-40 mg/dl
Creatinine	0.6	1.0	0.4-1.3 mg/dL
SGPT	34	37	5-40 U/L
SGOT	32	42	5-45 U/L
ALP	94	88	25-120 U/L
Sodium	138	136	135-145 meq
Potassium	4.2	3.9	3.5-5 meq
Calcium	8.9	9.3	8.5-10.5 meq
TSH	1.2	1.0	0-4-4 mIU/L
Total cholesterol	218	230	<200
LDL	130	110	<130
HDL	35	42	30-60
ANA titre IF	Negative	Negative	< 1:40
Anti ds DNA IF	Negative	Negative	< 10 U/mL
Anti cardiolipin Ab	Negative	Negative	< 5 U/mL
Anti beta 2 glycoprotein Ab	Negative	Negative	< 5 U/mL
Anti phospholipid Ab	Negative	Negative	< 5 U/mL
Lupus anticoagulant	Negative	Negative	< 5 U/mL
ANCA	Negative	Negative	< 19 U/mL
Protein C	0.656	0.583	0.72-1.54 U/Ml
Protein S	0.121	0.246	0.72-1.45 U/mL
Homocysteine	8	11	< 15 micromol/L



A B C D

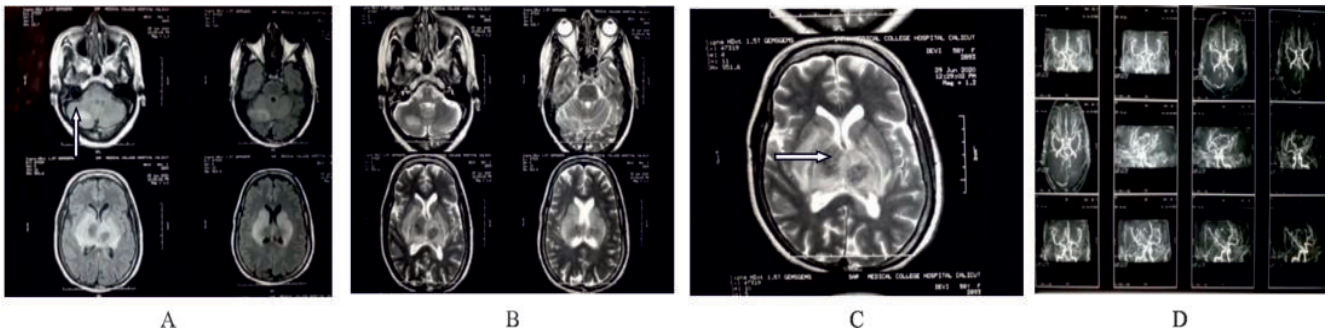
Figure 1 :

A : MR Venogram showing non visualization of right transverse and superior sagittal sinus suggestive of acute venous sinus thrombosis.

B: Non contrast CT scan showing dense delta sign suggesting thrombosis of superior sagittal sinus thrombosis.

C: Non contrast CT scan after anticoagulation showing recanalization of superior sagittal sinus.

D: Diffusion weighted image showing diffusion restriction in right frontal lobe suggestive of venous infarct due to CVT.



A B C D

Figure 2

A: MRI Flair sequences showing hyper intensity in right cerebellar hemisphere, bilateral thalami (appears bulky) and right caudate nucleus suggestive of haemorrhagic infarcts

B: MRI T2 images showing hyper intense areas in right cerebellar hemisphere, bilateral thalamus and right caudate nucleus suggestive of haemorrhagic infarcts

C: MRI T2WI showing bilateral bulky thalami with surrounding hyper intense areas indicative of haemorrhagic infarcts

D: MR venogram showing absent flow voids in Great vein of Galen, internal cerebral veins and left superior ophthalmic vein suggestive of venous thrombosis

superior ophthalmic vein, inferior cerebral veins and great vein of Galen; features suggestive of venous thrombosis with hemorrhagic infarcts.

Routine haematology and biochemistry was normal. Serology for HIV, HBsAg and HCV was negative. Workup for vasculitis and collagen vascular disorders was also negative. Serum antiphospholipid antibody was negative. Serum homocysteine, Protein C and Protein S activity were also normal (Table1).Echo cardiogram showed no regional wall motion abnormality,LVEF-50%,no RA-RV dilatation, no vegetation and no pericardial effusion

She was started on anticoagulation with unfractionated heparin followed by oral anticoagulant warfarin to optimize the INR between 2 and 3. In the next few days her weakness gradually improved, she was responding to verbal stimulus and there was no further episode of seizure.

Discussion

Primary Varicella infection is generally a mild disease of childhood. When it occurs in adults, complications are more common. Complications seen in adults include varicella pneumonia, myocarditis, pancreatitis, hepatitis, DIC, Purpura fulminans, encephalitis, metabolic encephalopathy, seizures and vasculopathy.The cause of cerebral vascular events after VZV infection could be vasculitis, thrombosis due to direct endothelial damage, or acquired protein S, protein C deficiency.

Varicella virus can multiply in arterial wall, invading the smooth muscle cells in the media and cause functional damage to the vascular endothelium, promoting thrombosis and sub endothelial proliferation of smooth muscle cells, fibroblasts, and collagen, leading to areas of stenosis and occlusion [3-5]. leading to ischemic strokes, aneurysms

or subarachnoid and cerebral haemorrhages[6-9]. DIC and Purpura fulminans are due to severe autoantibody mediated coagulopathy presenting with purpuric or painful necrotizing lesions due to micro thrombi in dermal capillaries [10,11]. This is often associated with acquired Protein S and Protein C deficiency and micro thrombosis in arterial and venous circulation.

Cerebral venous sinus thrombosis in primary Varicella infection is reported, yet uncommon. The exact pathogenesis of Varicella venous thrombosis is not known; however it is suggested that thrombosis can occur due to virus migrating transaxonally to infect meninges and venous sinuses of brain in the vessel wall similar to VZV arteriopathy. Searching the literature there are only few case reports of cerebral venous sinus thrombosis in primary Varicella infection. Acquired Protein S deficiency is the reason for CVT in few reported cases.

In our two patients, the temporal relationship of vesicular rash followed by cerebral venous sinus thrombosis establishes varicella infection to be the cause for cerebral venous sinus thrombosis. Workup for procoagulable state was negative in both patients. The direct virus invasion of endothelium of venous sinuses may be the causative factor for cerebral venous sinus thrombosis in our cases.

The presence of headache with papilloedema made us consider the possibility of cerebral venous thrombosis in our first patient. The concomitant lower extremity deep vein thrombosis and worsening neurologic status despite treatment of encephalitis prompted considering possibility of CVT in the second patient. Early detection of venous thrombosis by MR venogram and prompt treatment led to excellent recovery in both patients. In acute varicella infection with focal neurological signs, in addition to arteriopathy, cerebral venous thrombosis should also be considered. Early diagnosis and management is crucial to prevent morbidity and mortality.

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