Cerebral Sinus Venous Thrombosis as a Rare Complication of Primary Varicella Zoster Virus Infection

K Gayathri¹, PK Ramalingam¹, RPSP Santhakumar¹, BV Manjunath¹, N Karuppuswamy², B Vetriveran², S Selvamani², P Vishnuram², Kumar Natarajan³

Abstract
We present the case of a 23 year old with acute onset left hemiparesis and meningeal irritation, associated with recent history of chickenpox 15 days prior. Varicella-IgG and IgM was positive in the CSF and blood along with reduced serum/CSF ratios of VZV immunoglobulins. MRV showed thrombosis (CVT) of superior sagittal, transverse, right sigmoid sinuses with haemorrhagic infarct in right frontoparietal region. Patient responded well to intravenous heparin, Acyclovir and oral anticoagulant therapy.

Introduction
Varicella zoster virus (VZV) causes chicken pox after which it establishes latency and can subsequently get reactivated to cause Herpes zoster in later life. Central nervous system complications can follow both primary infection and reactivation of VZV. VZV infection can cause multifocal vasculopathy and arterial strokes. Primary Varicella infection causing venous infarct is very rare¹ and hence this case is being reported. There are only a few published reports of cerebral venous sinus thrombosis (CVST) associated with primary VZV infection.

Case Report
23 yr old male was brought to our emergency department with severe headache and altered sensorium. His illness started two weeks back with profound rash and vesicles predominantly on the trunk and limbs and to a less degree on the face. The lesions were centripetal and hence he was diagnosed to have chickenpox at local hospital. Patient did not receive any form of treatment in the interval of diagnosis of chicken pox and development of neurological complications. When patient reached our hospital, these lesions were in crusting stage. His present symptoms started with sudden onset of continuous holocranial non-throbbing headache which was associated with vomiting and fever for 2 days. Patient gradually developed altered sensorium associated with weakness of left upper limb and left lower limb. There was no history of seizures. Past history was not significant.

When patient came to emergency ward, he was drowsy and restless but responded to verbal commands. General examination revealed scabbing chicken pox lesions in trunk and limbs (Figure 1). On neurological examination he had nuchal rigidity, Kernig sign was positive. Pupils were equal and reacting to light, left eye abducent nerve palsy was present. Fundus showed bilateral papilledema. Motor examination revealed left hemiparesis with muscle power of 3/5, loss of superficial reflexes, exaggerated deep tendon reflexes and extensor plantar reflex on left side. Right side examination was normal.

His routine investigations including complete blood count, blood sugar, renal parameters, liver function tests, electrolytes, coagulation profile and blood culture were normal. Serology for Human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), Anti-HCV were negative. ANA profile, Antiphospholipid antibodies, Protein C, protein S, antithrombin III, homocysteine levels were normal. Serum IgG for varicella zoster was positive. Cerebrospinal fluid examination (Table 1) showed pleocytosis with 20 cells/mm³, mildly raised protein 60 mg/dl, and normal glucose (40 mg%). Varicella-specific IgG was positive in the cerebrospinal fluid (CSF) and the blood with reduced CSF/serum ratios of VZV IgG. CSF VZV DNA by PCR was positive.

Chest X-ray and 2D-Echo were

Table 1: Cerebrospinal fluid analysis

<table>
<thead>
<tr>
<th>Observed value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count</td>
<td>0 – 5 cells/mcL</td>
</tr>
<tr>
<td>CSF protein</td>
<td>40 – 80 mg/dl</td>
</tr>
<tr>
<td>CSF glucose</td>
<td>15 – 60 mg/dl</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>Neg &lt; 80; Borderline 80-110; Positive &gt;110</td>
</tr>
<tr>
<td>varicella zoster</td>
<td></td>
</tr>
<tr>
<td>CSF IgG</td>
<td></td>
</tr>
<tr>
<td>varicella zoster</td>
<td>74.64</td>
</tr>
<tr>
<td>Serum total IgG</td>
<td>700 – 1600 mg/dl</td>
</tr>
<tr>
<td>CSF total IgG</td>
<td>0 – 3.4 mg/dl</td>
</tr>
<tr>
<td>CSF / Serum quotient reference</td>
<td>Normal &lt; 1.3 to 1.5</td>
</tr>
<tr>
<td>CSF VZV DNA</td>
<td>Positive</td>
</tr>
</tbody>
</table>

¹Postgraduate, ²Assistant Professor, ³Professor and Head of Medicine, Department of General Medicine, Coimbatore Medical College Hospital, Coimbatore, Tamil Nadu
Received: 12.12.2014; Revised: 09.04.2015; Accepted: 28.07.2015
normal. A plain Computed Tomography of brain showed diffuse cerebral edema and hyperdense superior sagittal, straight sinus and right transverse sinuses (Figures 2, 3). A possibility of venous sinus thrombosis was considered and a Magnetic Resonance Venography with gadolinium enhancement was done. MRI brain with MRV showed (Figures 4, 5, 6 and 7) thrombosis in superior sagittal, bilateral transverse and right sigmoid sinuses which extends into the straight sinus. There was no flow in the internal cerebral veins. Venous haemorrhagic infarcts were seen in right frontoparietal cerebral parenchyma (largest 4 cm in length) and in right thalamus.

Multiple lacunar infarcts in bilateral frontoparietal white matter (Figures 8, 9) were also seen.

Patient was treated with cerebral decongestants, intravenous Acyclovir 500 mg three times daily and low molecular weight heparin for one week. Patient started improving gradually over the next few days with improvement in sensorium and limbs weakness. At the time of discharge, physiotherapy and oral anticoagulant was advised. Tab. Acitrom 2 mg orally once daily was continued for next 12 weeks to maintain INR between 1.5 to 2.5. There was no history of worsening of symptoms or any bleeding manifestations. Tab. Aspirin 150 mg once daily was started and continued for next 12 weeks. After 6 months of treatment, patient improved well and he is on regular follow up.

Discussion

Varicella-related neurological complications are seen in less than 1% cases of chickenpox. Neurological complications frequently encountered are cerebellitis and encephalitis. It can cause unifocal or multifocal vasculopathy. However several rare complications related to central nervous system involvement have been reported like aseptic meningitis, Guillain-Barre syndrome and transverse myelitis. Our patient had post-varicella CVST.

Primary VZV infection can cause vascular thrombosis approximately 6 weeks after primary infection. In elderly immunocompetent patients it occurs as a large-vessel vasculopathy i.e. a granulomatous arteritis involving single vessel (unifocal), whereas in immunocompromised hosts, it presents as multivessel involvement (multifocal vasculopathy). Unifocal large-vessel infarcts may occur in either anterior or posterior circulation. These infarcts are believed to result from transaxonal transport of varicella zoster virus from cervical or trigeminal afferent fibers to the cerebral blood vessels and their smaller branches. The occurrence of venous thrombosis following primary Varicella Zoster infection is very rare, though it can occur secondary to reactivation and due to herpes zoster infection. Our case developed CVST in the stage of primary infection itself (that is, in 2 weeks of primary varicella infection).
Figs. 8 and 9: Venous haemorrhagic infarcts in right frontoparietal cerebral parenchyma (largest 4 cm in length) and infarcts in right thalamus and right frontal region

The causal association in this particular case was evidenced by positive varicella antibodies in serum and CSF. VZV vasculopathy patients do not always have VZV DNA in CSF, but the diagnosis can be confirmed by anti-VZV antibody in CSF, along with reduced serum/CSF ratios of VZV IgG. Serum and CSF IgG was positive in our patient with reduced CSF/serum ratios of VZV IgG and VZV DNA was positive.

The exact pathogenesis of varicella venous thrombosis is not known but similar to VZV arterial strokes, activated varicella virus may migrate transaxionally to infect the meninges and venous sinuses of brain. The mechanisms underlying cerebral vascular events after VZV infection could be vasculitis, thrombosis due to direct endothelial damage, and acquired protein S deficiency. Our patient developed thrombosis during primary varicella infection and not as a delayed complication. He had no other risk factors for cerebral venous thrombosis. Probably, the same pathogenic mechanisms underlying arteriopathy may have played a role in the development of CVST in our patient. These patients require antiviral treatment and symptomatic treatment with heparin and oral anticoagulants. Our patient improved with above treatments.

**Conclusion**

Our case demonstrates that CVST is one of the rare neurological complications of primary varicella zoster infection and early diagnosis of this is essential for the proper management of the patient.

**References**