

*Case Report***Primary Varicella Zoster Infection Presented with Cerebral Venous Sinus Thrombosis in Adult**Upasana Patel¹, Rajeev Ranjan², Chandrashekhar Agrawal³, Nirajkumar Patel⁴¹DNB Neurology, Ganga Ram Hospital, New Delhi, India.²DNB Neurology, Consultant, Sir Ganga Ram Hospital, New Delhi, India.³DM Neurology, Senior Consultant, Sir Ganga Ram Hospital, New Delhi, India.⁴MD Medicine, Sir Ganga Ram Hospital, New Delhi, India.

Corresponding Author: Upasana Patel

*Received: 14/07/2015**Revised: 08/08/2015**Accepted: 14/08/2015***ABSTRACT**

Varicella zoster virus (VZV) is well known to produce a benign self-limiting exanthematous illness in pediatric population with fewer neurological complications. Adult patients with chicken pox however can have more severe manifestations including neurological one. We hereby report a case of cerebral venous sinus thrombosis (CVST) as a part of primary VZV infection in an adult male, which is a rare association. The temporal relationship of VZV rash and CVST as well as detection of VZV antibody in cerebrospinal fluid (CSF) and reduced ratios of the concentration of anti-VZV IgG in serum to that in CSF, as compared to normal ratios for total IgG and albumin, corroborated with the viral etiology of the illness. Moreover, he was also found to have moderate hyperhomocysteinemia as a pre-existing hypercoagulable state, which made him prone for the development of VZV - induced vasculopathy.

Key words: Chicken pox, cerebral venous thrombosis, intracranial sinus thrombosis.

INTRODUCTION

Over the past few decades, increasing recognition and case reports about the varicella zoster virus (VZV)-associated vasculopathy has broadened the range of manifestations, including large-artery disease, transient ischemic attacks, protracted illness involving both small and large arteries, aneurysm, cerebral and subarachnoid haemorrhage, arterial ectasia, and carotid dissection as well as peripheral arterial disease. [1-3] The association of coagulopathy with VZV has also become evident due to its temporal relationship with purpura fulminans, a form of severe

autoantibody-mediated coagulopathy, [4,5] often accompanied by the acquired deficiency of proteins C and S, leading to disseminated intravascular coagulation with micro- or macrothrombosis in both arterial and venous circulation. [4-7] However, cerebral venous sinus thrombosis (CVST) as a complication of primary VZV infection is described as a rare entity with fewer case reports.

CASE PRESENTATION

A 25 year old previously healthy male, with history of exposure to a case of chicken pox in his family in the recent past,

developed copious rashes predominantly over trunk as well as limbs and to a lesser degree on the face, clinically diagnosed to be chicken pox.[Figure-1] Initially, he was treated conservatively with antipyretics, to which he responded. Ten days later, he started having high grade fever with severe throbbing headache. After total two weeks of illness, he presented to our emergency ward in status epilepticus. The lesions were in crusting stage when the patient developed neurological complaints. He was managed with intravenous (IV) lorazepam, followed by loading with IV fosphenytoin as an emergency measure. After the control of seizures, his sensorium gradually improved on the next day. He did not have any focal neurological signs except mild bilateral papilloedema on examination.



Figure-1: Rash in crusting stage over chest, back and few over face, characteristic of chicken pox

Investigations: Routine investigations including hemogram and blood biochemistry were within normal limits. His initial plain computerized tomography (CT) head revealed haemorrhagic infarct in the left temporo parietal region with edema and mass effect over the ipsilateral lateral ventricle. Considering the possibility of CVST, his magnetic resonance imaging (MRI) of brain with gadolinium contrast and venography was done, which showed significant thrombosis in left transverse,

straight and sigmoid sinuses, extending into left internal jugular vein, thus confirming the diagnosis. [Figure-2] Serology for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), vasculitic markers were negative. Thrombophilia panel including antiphospholipid antibodies, protein C, protein S, antithrombin III, factor V Leiden were normal; however, homocysteine levels were found to be moderately elevated (37.43micromol/L). Cerebrospinal fluid (CSF) analysis revealed pleocytosis (38 cells/mm³), with few red blood cells, mildly raised protein (55.5 mg %), and normal glucose. Although CSF VZV- IgG antibody was positive, CSF VZV PCR (Polymerase chain reaction) was found to be negative. Other tests including PCR for Mycobacterium tuberculosis, adenosine deaminase, bacterial culture, India ink stain, cryptococcal antigen and herpes simplex virus (HSV) serology in CSF were negative.

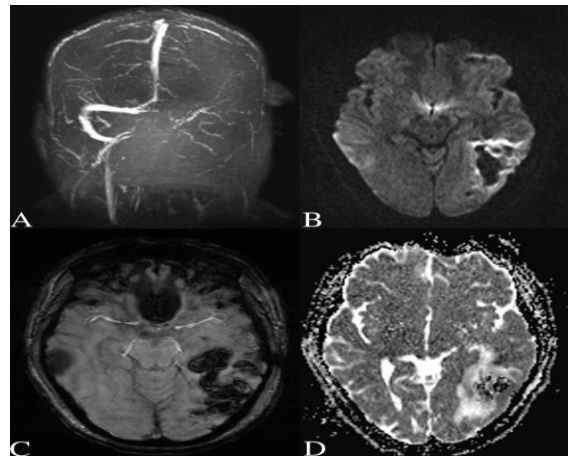


Figure-2: Magnetic resonance imaging (MRI) of brain with gadolinium contrast and venography. A. Significant thrombosis in left transverse, straight and sigmoid sinuses, extending into left internal jugular vein. B-D. Diffusion weighted, susceptibility weighted, apparent Diffusion Coefficient imaging respectively, showing haemorrhagic infarct in the left temporo parietal region with perilesional edema and mass effect over the ipsilateral lateral ventricle.

Differential Diagnosis: In view of straight forward clinical history of chicken pox rash followed by development of CVST along

with virological evidence of VZV in CSF, the etiology seems to be viral (VZV) only. However, moderately elevated homocysteine level confounds the picture suggesting its additional role in the causation of CVST in this case.

Treatment: He was treated with low molecular weight heparin, IV acyclovir, anti-edema measures consisting of IV 20% mannitol and dexamethasone (short term with rapid tapering) along with adequate hydration.

Outcome and Follow-Up: He gradually showed clinical improvement, in terms of absence of fever, headache and seizure recurrence. He was continued on oral anticoagulation for 3 months and follow up visits were unremarkable.

DISCUSSION

With increasing incidence of chicken pox in adults, VZV has been reported to cause more severe complications in this population in contrast to the pediatric one. Common neurological complications associated with VZV infection are cerebellar ataxia and encephalitis. [8] However the list of complications involving nervous system stretches to include aseptic meningitis, Guillian-Barré syndrome, and transverse myelitis, although rarely encountered. [9] Our patient had primary VZV - associated CVST, again a rarer one to add to the list.

In addition to the above mentioned neurological complications, VZV infection is also associated with cerebral vasculopathy. [10] The pathogenesis behind this is considered to be a productive viral infection in the cerebral arteries, as evident by the histologic evidence of granulomatous inflammation and the presence of VZV DNA and VZV-specific antigen in the media of the involved arteries, anti-VZV IgG with or without positive VZV PCR studies of the CSF, and stenosis of the involved cerebral arteries. [1,10-11] Purpura fulminans, being a

form of severe autoantibody-mediated coagulopathy, is found to be commonly associated with VZV vasculopathy, but it was not found in our case.

The exact pathogenesis of varicella CVST is still not known but presumed to be similar to VZV arteriopathy. Afferent fibers from trigeminal and other ganglia to both intracranial and extracranial blood vessels provide an anatomical pathway for the transaxonal spread of virus, thereby giving the virus an opportunity to infect meninges and venous sinuses of brain. [1] The damage to venous sinus and consequent CVST can be due to direct endothelial damage by virus, by provoking thrombosis secondary to acquired protein S deficiency, by producing local form of vasculitis as a part of immunologic reaction, and/or an underlying hypercoagulable state. [7, 10] The latter two possibilities seem to be the underlying mechanism of CVST in our patient. Homocysteinemia, in particular, is found to be an independent and strong risk factor for CVST. [12-14] Moreover, people with prothrombotic conditions are shown to be prone to develop thrombosis after having any systemic infection, especially in children. [15] Although there can be a confounding effect of hyperhomocysteinemia in causing CVST, the temporal relationship of VZV rash followed by development of CVST and detection of VZV IgG in CSF point towards an unrevealed association of VZV with CVST.

Virological confirmation of VZV – associated cerebral vasculopathy includes CSF analysis for both VZV DNA and anti-VZV IgG antibody although the diagnostic value of detecting anti-VZV IgG antibody in the CSF is greater than that of detecting VZV DNA. [16] Although a positive PCR for VZV DNA in CSF is helpful, a negative PCR does not exclude the diagnosis; only negative results in both VZV PCR and anti-

VZV IgG antibody tests in the CSF can reliably exclude the diagnosis of VZV vasculopathy. [1]

IV acyclovir is being traditionally used in treatment of virus-associated cerebral vasculopathy. Regarding the role of concurrent steroid therapy, the largest study so far consists of 30 patients. Of all the patients treated with acyclovir alone, 20 improved or stabilised, compared with 23 who improved or stabilised when treated with both acyclovir and steroids. [17] Due to lack of uniformity in steroid regimen, dose and duration of acyclovir, in an uncontrolled setting, the established protocol using steroids in this condition still needs to be defined and awaits prospective studies with larger case numbers. In our case, we gave both IV acyclovir as well as parenteral steroid with short-term rapidly tapering dose considering the inflammatory response in cerebral vessels as an underlying mechanism, along with initial injectable later followed by oral anticoagulation for total duration of 3 months. The patient improved clinically with this regimen.

Till now, there are four cases reported to have co-occurrence of CVST with primary VZV infection. [18-20] two of them showed decreased protein C and S levels. [20] However, raised homocysteine present in our case was reported in none.

Learning Points: Cerebral venous sinus thrombosis (CVST) is a rare neurological complication associated with primary VZV infection.

- Evaluation of VZV - associated cerebral vasculopathy includes CSF analysis for both VZV DNA by PCR method and anti-VZV IgG antibody measurement, although the diagnostic value of the later is greater than that of the former.
- Search for the underlying hypercoagulable state should be made as such conditions make the patient prone

for development of CVST in presence of infection.

- In contrast to traditionally used intravenous acyclovir and anticoagulation in this condition, the role of steroids still needs to be defined and awaits larger studies.

REFERENCES

1. Gildea D, Cohrs RJ, Mahalingam R, et al. Varicella zoster virus vasculopathies: Diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol* 2009; 8:731-740.
2. Takeoka M, Takahashi T. Infectious and inflammatory disorders of the circulatory system and stroke in childhood. *Curr Opin Neurol* 2002; 15:159-164.
3. Massano J, Ferreira D, Toledo T, et al. Stroke and multiple peripheral thrombotic events in an adult with varicella. *Eur J Neurol* 2008; 15:e90-e91.
4. Dogan M, Acikgoz M, Bora A, et al. Varicella-associated purpura fulminans and multiple deep vein thromboses: A case report. *J Nippon Med Sch* 2009; 76:165-168.
5. Regnault V, Boehlen F, Ozsahin H, et al. Anti-protein S antibodies following a varicella infection: Detection, characterization and influence on thrombin generation. *J Thromb Haemost* 2005; 3:1243-1249.
6. Limb J, Binning A. Thrombosis associated with varicella zoster in an adult. *Int J Infect Dis* 2009; 13:e498-e500.
7. Nguyen P, Reynaud J, Pouzol P, et al. Varicella and thrombotic complications associated with transient protein C and protein S deficiencies in children. *Eur J Pediatr* 1994; 153:646-649.
8. Johnson RT. *Viral infections of the nervous system*. New York: Raven Press; 1998; 133-168.

9. Caheid Y, Husein C. Severe neurological complications of chickenpox: Report of four cases. *Eur J Gen Med* 2005; 2:177-9.
10. Nagel MA, Traktinskiy I, Azarkh Y, et al. Varicella zoster virus vasculopathy: Analysis of virus-infected arteries. *Neurology* 2011; 77:364-70.
11. Linnemann CC Jr, Alvira MM. Pathogenesis of varicellazoster angiitis in the CNS. *Arch Neurol* 1980; 37:239-240.
12. Martinelli I, Battaglioli T, Pedotti P, et al. Hyperhomocysteinemia in cerebral vein thrombosis. *Blood* 2003; 102: 1363-66.
13. Cantu C, Alonso E, Jara A, et al. Hyperhomocysteinemia, low folate and vitamin B12 concentrations, and methylene tetrahydrofolate reductase mutation in cerebral venous thrombosis. *Stroke* 2004; 35: 1790-94.
14. Ventura P, Cobelli M, Marietta M, et al. Hyperhomocysteinemia and other newly recognized inherited coagulation disorders (factor V leiden and prothrombin gene mutation) in patients with idiopathic cerebral vein thrombosis. *Cerebrovasc Dis* 2004; 17: 153-59.
15. Sebire G, Tabarki B, Saunders DE, et al. Cerebral venous sinus thrombosis in children: Risk factors, presentation, diagnosis and outcome. *Brain* 2005; 128:477-489.
16. Nagel MA, Forghani B, Mahalingam R, et al. The value of detecting anti-VZV antibody in CSF to diagnose VZV vasculopathy. *Neurology* 2007; 68:1069-73. [PubMed: 17287447]
17. Nagel MA, Cohrs RJ, Mahalingam R, et al. The varicella zoster virus vasculopathies. Clinical, CSF, imaging, and virologic features. *Neurology* 2008; 70:853-60. [PubMed: 18332343]
18. Menon B, Goyal R. Cerebral venous thrombosis as a complication of chicken pox. *Ann Trop Med Health* 2012;5:520-522
19. Sada S, Kammineni A, Kanikannan MA, et al. Cerebral sinus venous thrombosis: A rare complication of primary Varicella zoster virus. *Neurol India* 2012; 60:645-646
20. Siddiqi SA, Nishat S, Kanwar D, et al. Cerebral Venous Sinus Thrombosis: Association with Primary Varicella Zoster Virus Infection. *J Stroke Cerebrovasc Dis* 2012 Nov; 21(8): 917.e1-4.

How to cite this article: Patel U, Ranjan R, Agrawal C et. al. Primary varicella zoster infection presented with cerebral venous sinus thrombosis in adult. *Int J Health Sci Res.* 2015; 5(9):568-572.
