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# Acute severe headache: Association of herpes zoster meningitis and sinus vein thrombosis

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**Informed Consent**
The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

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## Abstract

The development of neurological complications related to varicella zoster virus (VZV) is rare, especially in immunocompetent children. We report a case of a 14-year-old male patient who presented with severe headache and diagnosed with acute aseptic meningitis and sinus vein thrombosis caused by reactivated VZV infection. Magnetic resonance (MR) venography identified limited flow, consistent with a thrombus in the right sigmoid sinus. Pressure of cerebrospinal fluid (CSF) was measured as high, with the PCR meningitis panel positive for VZV. These results show an association of VZV meningitis and sinus vein thrombus. Pediatric cases associated with aseptic meningitis and cerebral venous sinus thrombosis to varicella zoster reactivation have not yet been reported in the literature.

**Keywords:** Children, Headache, Herpes zoster meningitis, Immunocompetent, Sinus vein thrombosis

## Introduction

Varicella zoster virus (VZV) is a virus of the herpes family, primarily causing chickenpox, which may remain latent in cranial nerves and dorsal root ganglia after primary infection and then lead to shingles [1]. One of the rarest neurological complications linked to VZV is VZV aseptic meningitis (5-10%), which is an infection of the brain membranes and clinically presents as a headache, vomiting, and high fever. Patients may have neurological symptoms like encephalopathy, convulsions, or motor deficit. A stiff neck and the presence of meningeal irritation (Kernig or Brudzinski signs or nuchal rigidity) on physical examination will direct clinicians to assess the patient in terms of meningitis [2].

We present a 14-year-old male with a diagnosis of acute aseptic meningitis and sinus vein thrombosis by reactivated VZV infection. The patient had a severe headache due to increased intracranial pressure, without other complaints, related to meningitis but no physical examination findings; he had previously been healthy and immunocompetent.

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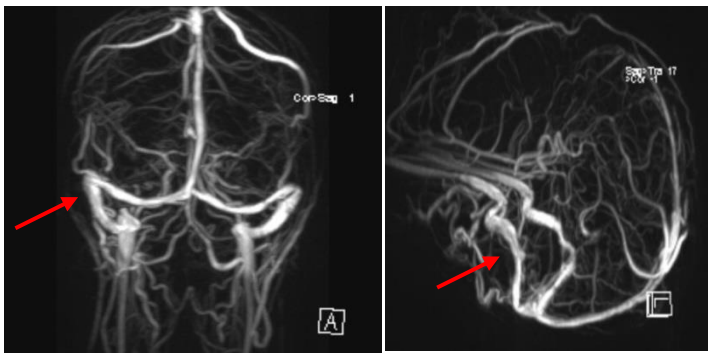
## Case presentation

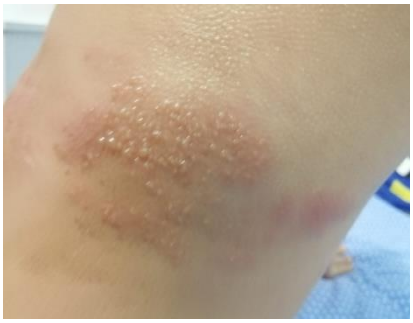
Verbal and written consent was obtained from the patient and family. A 14-year-old male patient attended the pediatric neurology clinic as an outpatient with a severe headache for four days. There were no other complaints such as fever, vomiting, blurred vision, double vision, etc. Headache was severe and continuous, without a special character; however, no factors intensified or lessened the headache. When its severity did not ameliorate after analgesia but continued for four days, an external center performed brain magnetic resonance (MR) imaging for the headache and administered antibiotic treatment with findings consistent with sinusitis. Given that the headache continued with a rash on the body after antibiotics, the patient was referred to our pediatric neurology clinic by the pediatrician at the external center. Physical examination there found a moderate general status, with a pale and anxious appearance. Fever was 37.2°C, respiratory count 17/min, peak heart rate 88/min, arterial pressure 118.75 mmHg, and oxygen saturation 98%. Apart from postnasal purulent discharge and swollen skin with a light pink color and a papule rash in the right lumbar region, there were no pathologic features. A full neurological examination was normal, including the ocular fundus. Due to missing sequences in imaging at the external center, contrast brain MR and MR venography tests were requested. The former identified widespread bifrontal and maxillary sinusitis, while the latter found limited flow, consistent with a thrombus in the right sigmoid sinus (Figure 1). A lumbar puncture was performed with a preliminary diagnosis of increased intracranial pressure (pseudotumor cerebri). Cerebrospinal fluid (CSF) pressure was measured at 27 mmHg. With an intracranial pressure increase, linked to sinus vein thrombosis, the patient consulted with pediatric hematology and was administered two doses per day of low molecular weight heparin. Hypercoagulability studies were normal. CSF glucose was 41 mg/dL (simultaneous blood glucose was 85 mg/dL), and CSF protein was 157 mg/dL. A direct microscopic investigation identified 400 leukocytes/mm3, so ceftriaxone+vancomycin treatment was started with a meningeal diagnosis. CSF included a multiplex polymerase chain reaction (PCR) for meningitis panel and culture.

Figure 1: Magnetic resonance venogram of the brain, showing loss of normal signal intensity in the right sigmoid sinus (red arrows, coronal view, and sagittal view)



On the second day of observation, the vesicular rash in the lumbar region, including dermatomal pain, were consistent with shingles (Figure 2); thus, acyclovir (10 mg/kg/dose, 3 doses) was added to the treatment. With no proliferation of the CSF culture, the multiplex PCR meningitis panel was positive for VZV. Human immunosuppressive virus (HIV) serology was negative. Lymphocyte subgroups, serum immunoglobulin, and complement (C3 and C4) values were normal. The headache gradually diminished and the skin rash ameliorated on the 5$^{th}$ to 6$^{th}$ day of treatment. Acyclovir treatment was administered intravenously for 14 days, but the patient was discharged without complaints by the end of the 14$^{th}$ day. Heparin treatment was continued for three more months. After a four-week follow-up, there were no sequelae and in addition, no comorbidity was identified.

Figure 2: Vesicular lesions with an erythematous background in the left lumbar region



## Discussion

Central nervous system (CNS) infections are significant clinical events with potential morbidity and mortality. Meningitis, an infection of the protective membranes of the CNS, plays a critical role in the spectrum of these infections. The use of conjugated vaccinations reduces the incidence of meningitis from bacterial agents, with viral meningitis as one of the most common types. Enteroviruses, herpes simplex virus (HSV), and VZV are the main etiologic agents of viral meningitis, with other viral vectors such as mumps orthorubulavirus, measles morbillivirus, influenza type A and B, arboviruses (e.g., West Nile virus), and lymphocytic choriomeningitis mammarenavirus leading to meningitis [3].

Herpes zoster is a function of the reactivation of VZV in the sensory ganglion cells after chickenpox or vaccination, with peaks in the 6$^{th}$ to 7$^{th}$ decades of life [4]. In children, recent publications find that it generally peaks from 10 to 14 years of age [5]. In the elderly or immunosuppressed, reduction in cell-mediated immunity to VZV is thought to trigger varicella zoster reactivation [6].

Neurological complications may develop following primary infection and reactivation of VZV, such as encephalitis and cerebellitis. Complications observed with lower frequency include 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) [7].

Development of neurological complications like meningitis linked to VZV reactivation is believed to be rare, especially in an immunocompetent child [1]. A study with 92 pediatric patients with herpes zoster reported meningitis in only 5.4% of cases [6]. For this reason, herpes zoster aseptic meningitis is also rare in children with resilient immune systems. Yet, in our patient, there were no results considered to be a specific immune failure in either interrogation about history, family history, or via blood tests.

It is known that neurological complications with VZV infection emerge with immune suppression and vesicular rash [8]. In the literature, pediatric cases are discussed in conjunction with the diagnosis of meningitis with atypical shingles rash in those who are immunocompetent but do not have a skin rash, those with erythema, and papules but no vesicles [4]. Localized pain and paresthesia are common before the occurrence of a rash in herpes zoster. Typical rashes in shingles present in the form of vesicles with dermatomal distribution [9]. In the literature, there are cases with a VZV meningeal diagnosis without a rash and/or irritation findings [8].

A study by Mehta et al. [10] discussed the rare neurological complication of CVT in two cases with chickenpox infection. In the literature, there are adult cases that develop thrombosis of primary infection with VZV [11]. However, a single case associated with acute herpes zoster and cerebral venous sinus thrombosis was found in a 73-year-old male patient [12]. In our literature screening, we did not encounter other pediatric cases associated with aseptic meningitis or cerebral venous sinus thrombosis, nor was they linked to varicella zoster reactivation.

VZV is the only virus replicating in the veins and has been shown to cause vasculopathy in humans. The mechanism for cerebrovascular events following VZV infection may be vasculitis; however, the pathogenesis of a vascular disease is still controversial [10]. A variety of histopathological studies of patients with chickenpox vasculitis show the virus to be in the vein wall causing a non-cytolytic infection in smooth muscle cells, which may cause functional injury to vascular endothelium. These thromboses and smooth muscle cells may lead to subendothelial proliferation of fibroblasts and collagen, causing stenosis [13]. Formation of a thrombus in the venous sinuses is a result of stasis and hypercoagulopathy status due to local trauma in the vein wall, known as the Virchow triplet [14].

VZV meningitis diagnosis is linked to clinical findings with an observation of VZV DNA in CSF with PCR. These patients require antiviral, as well as symptomatic treatment with

IV heparin and oral anticoagulants [11]. Early initiation of antivirals is required, since delayed or inadequate treatment may cause serious neurological complications or even death. As such, IV acyclovir of 10 mg/kg is recommended three times a day for 10-14 days for VZV meningitis [15]. Our patient was discharged in good health after 14 days of IV acyclovir treatment.

**Conclusion**

Children with acute severe headache require a CSF investigation, including CSF pressure measurements even without meningeal findings, although vascular complications must be considered, while venographic and arteriographic assessments should also be planned.

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