



Varicella-zoster Virus Encephalitis in an Immunocompetent Child Without Vaccination

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ABSTRACT

Chickenpox, the primary infection of the Varicella-zoster virus (VZV), is usually a benign, self-limiting disease and it rarely causes severe complications. Encephalitis is a rare neurological complication of VZV in previously healthy children. We report on an immunocompetent child without vaccination diagnosed with VZV encephalitis who was treated with acyclovir and methylprednisolone and recovered completely.

Keywords: Varicella-zoster virus, encephalitis, vaccination, immunocompetent, children

Introduction

The Varicella-zoster virus (VZV) is an enveloped double-stranded DNA alphaherpesvirus which primarily causes chickenpox, a highly contagious airborne disease. Chickenpox is an acute infectious disease which usually affects children without vaccination and has a self-limiting course in younger children (1,2). However, on rare occasions, it can cause severe complications such as neurological complications (3). VZV can affect the central and peripheral nervous system and cause meningitis, encephalitis, cerebellitis, acute myelitis, stroke, optic neuritis, vasculopathy, or myelopathy. These central nervous systems (CNS) complications can follow

both primary infections and the reactivation of VZV (1-4). Encephalitis is another neurological complication of primary VZV infection, and in previous reports, the incidence of encephalitis associated with VZV ranged from 0.5 to 2.4% in children (4,5). VZV encephalitis typically occurs in immunocompromised patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome, transplantation, or autoimmune disease. However, VZV encephalitis can occur in immunocompetent children in rare cases (2,3). Herein, we report on an 11-year-old immunocompetent child with VZV encephalitis who was treated with acyclovir and methylprednisolone and completely recovered without any neurological sequelae.

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Case Report

A previously healthy 11-year-old male was admitted to the emergency department with a 4-day history of vomiting and a 2-day history of fever, headache, dizziness, and weakness with inability to walk. The patient had been seen at a different hospital two days prior due to vomiting and was discharged to home after symptomatic treatment. He had a history of chickenpox 15 days prior. He had no vaccination history for VZV. On examination, he had multiple small scars, some with scabs and a few vesicular eruptions across his whole body as a manifestation of the recent varicella infection (Figure 1). The general examination, including his vitals, was found to be within normal limits. His neurological examination revealed lethargy, slow speech, and cerebellar ataxia. Motor examination revealed normal tone and nearly normal power (4/5) in both his upper and lower limbs. Deep tendon jerks were increased in both his lower limbs, and his plantar reflex was flexor bilaterally. Sensory examination was normal. No signs of meningeal irritation and no other cranial nerve abnormality were detected. Cefotaxime and acyclovir were administered for suspected CNS infection. Laboratory tests revealed a leukocyte count: $12.800/\text{mm}^3$, a neutrophil count: $10.860/\text{mm}^3$, a lymphocyte count: $1.110/\text{mm}^3$, a platelet count: $326.000/\text{mm}^3$, C-reactive protein: 0.7 mg/dL , and his biochemical parameters were normal except for high creatinine (serum creatinine 1.19 mg/dL). Abdominal ultrasonography revealed nephropathy, and acyclovir was administered according to renal dosage. Coronavirus disease-2019 (COVID-19) polymerase chain reaction (PCR) was negative. Cranial computed tomography and arterial-venous cranial angiography were normal. Contrast-enhanced craniospinal magnetic resonance imaging (MRI) showed non-specific

millimetric hyperintensity in the right frontal region. A lumbar puncture was performed, cerebral spinal fluid (CSF) was clear in appearance, and its pressure was normal. Laboratory examination of CSF revealed no cells, a normal protein level of 14.6 mg/dL , and a normal glucose level of 94 mg/dL . A multiplex PCR test for CSF was positive for the VZV. Blood serology tests were positive for VZV immunoglobulin (Ig) M and IgG. Bacteriologic culture of CSF and blood were negative. A sleep electroencephalogram (EEG) was performed on day 2 of admission. It showed a moderate amplitude of theta delta waves, evaluated as minimal cerebral dysfunction. According to the clinical and laboratory findings, this clinical course was diagnosed as encephalitis associated with the VZV. On the 3rd day of admission, he had hypertension, bradycardia, and worsening consciousness. On eye examination, he had no papilledema. A second craniospinal MRI was performed which only showed mucosal thickening in the right maxillary ethmoid and sphenoid sinuses. Due to his rapid clinical worsening, autoimmune encephalitis triggered by a viral infection could not be excluded. For these reasons, 2 g/kg intravenous immunoglobulin (IVIG) and 2 mg/kg/g methylprednisolone were administered, and the acyclovir dosage was increased to normal. His consciousness improved within one day, and his neurological examination was completely normal after seven days. After his bacterial cultures were negative, cefotaxime was discontinued on the 7th day. His anti-N-methyl-D-aspartate receptor (NMDA) receptor panel was negative for a blood sample. His immunoglobulins and lymphocyte panel were checked and found to be normal. In addition, the patient's HIV serology was negative. On the 14th day of admission, a second lumbar puncture was performed, CSF was clear in appearance, and its pressure was normal. Laboratory examination of CSF revealed no cells, a normal protein level of 17.5 mg/dL , and a normal glucose level of 61 mg/dL . The multiplex PCR test of CSF was negative for VZV, and acyclovir was discontinued after 14 days. After six days, methylprednisolone was tapered down and discontinued after 30 days. The patient completely recovered and had no neurological complications in the follow-up.

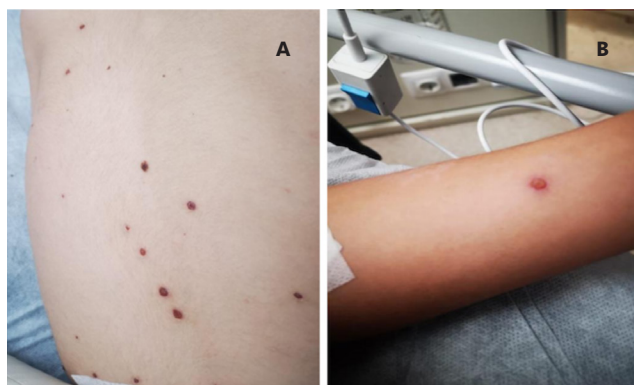


Figure 1. On admission, the patient had multiple small scars, some with scabs (A), and a few vesicular eruptions (B) on his whole body as a manifestation of a recent varicella infection

Discussion

Chickenpox, the primary infection of VZV, is a usually benign and self-limiting childhood disease. However, it rarely causes life-threatening complications affecting hematological, neurological, respiratory, cutaneous, and/or gastrointestinal systems. These complications are more common in patients with immunosuppression,

T-cell defects, genetic mutations such as ribonucleic acid polymerase (POL) III mutations, underlying diseases, such as chronic cutaneous or pulmonary diseases, and in adults (2,3). Neurological involvement in healthy children following VZV is rare (4). We report on an immunocompetent child without vaccination diagnosed with VZV encephalitis who was treated with acyclovir and methylprednisolone, and recovered completely.

VZV is a human neurotrophic virus which remains latent in the nervous tissue (1). The neurological complications of VZV can be caused by the primary infection or virus reactivation (6). The pathogenesis of neurological complications was reported as direct VZV infection of affected tissue, persistent inflammation, and virus-induced hypercoagulability. However, the pathogenesis of VZV encephalitis is still unclear, and the possible mechanism of VZV encephalitis has been associated with vasculopathy and/or radiculitis (1,7).

VZV encephalitis can be diagnosed with clinical, laboratory, or radiologic findings. VZV encephalitis usually presents with symptoms of headache, altered mental status, and the characteristic rash of varicella. However, VZV infections can cause CNS complications with or without rash (1). The laboratory findings of CSF can be normal or include pleocytosis (7). PCR analysis of CSF for diagnosis has high sensitivity and specificity. However, a negative test result does not exclude the diagnosis of VZV encephalitis (7,8). In patients with negative cerebrospinal fluid PCR results, detecting CSF VZV IgM antibodies can be helpful in diagnosing encephalitis (8). Cranial MRI can show encephalitic changes; however, there is no typical presentation, and MRIs are often normal (6). The electroencephalogram may be normal or show nonspecific abnormalities such as slowing basal activity (2,7). In our case, VZV PCR was positive in the CSF. Cranial MRI revealed nonspecific millimetric hyperintensity in the right frontal region, and his EEG showed minimal cerebral dysfunction. All these findings were compatible with VZV encephalitis.

There are no specific guidelines for the treatment options for VZV encephalitis in immunocompetent children. Based on case reports and small series, acyclovir (10-15 mg/kg intravenously every 8 hours) is the treatment of choice and its recommended duration is 10-14 days. In immunocompromised patients, the treatment is recommended to be prolonged to 21 days (8). In addition to acyclovir, some experts recommend corticosteroids for their anti-inflammatory effects (1,2,8). Early diagnosis and intravenous acyclovir treatment may result in clinical

benefits and prevent neurological complications and sequelae (2). Our case received acyclovir for 14 days and methylprednisolone for 30 days and completely recovered.

Several primary immunodeficiencies have been reported to predispose patients to severe varicella infections. Secondary immunodeficiencies, such as HIV infection, immunosuppressive medication, etc., can also predispose individuals to severe VZV infection in addition to primary immunodeficiencies (3). For these reasons, evaluating the immune status of patients with a severe varicella infection is essential. In addition to the standard immunodeficiency tests, detailed genetic tests for primary immunodeficiency can be planned for these patients. Our patient's immunoglobulin levels and lymphocyte panel were normal, and he had no known secondary immunodeficiencies.

VZV encephalitis can cause irreversible brain damage, resulting in mental retardation, stroke, giant cell arteritis, and granulomatous aortitis (6). In very rare cases, it has been reported that VZV encephalitis can trigger autoimmune anti-NMDA receptor immunoreaction and cause the occurrence of NMDAR antibodies leading to encephalopathy (9). Anti-NMDAR encephalitis following the Herpes simplex virus is a more frequently described condition. However, in the literature, only four adult patients with VZV-associated anti-NMDAR encephalitis have been reported to date (9-12). This disease is characterized by encephalopathy, behavioral changes, psychosis, memory deficits, seizures, abnormal movements, autonomic dysfunction, and coma. It is more common in young women, and after a prodromal period, it often begins with sudden behavioral and personality changes. These symptoms are followed by seizures, decreased levels of consciousness, abnormal movements, autonomic instability, and hypoventilation (11). The diagnosis can be made by CSF anti-NMDA antibody positivity (9). Acyclovir and immunomodulatory treatments such as corticosteroids, IVIG, and plasma exchange can be used in its treatment (9-12). Our case had a rapid clinical worsening, and autoimmune encephalitis triggered by a viral infection could not be excluded, and for these reasons, IVIG and methylprednisolone were administered. Due to a limited CSF sample, we could not perform a cerebrospinal fluid NMDAR analysis to exclude this diagnosis. We could only perform the test of the NMDAR panel on a blood sample, and this was negative.

Chickenpox is a vaccine-preventable disease. Worldwide, there are several formulations of varicella vaccines, and all contain live attenuated VZV. Streng et al. (13) evaluated 1.263 varicella-associated pediatric hospitalizations after a VZV

vaccination program had begun in Germany. They reported that the incidence of varicella-associated neurologic complications in children decreased by approximately 60% during the first seven years following the recommendation for universal VZV vaccination. Our case had no vaccination history for VZV, and the development of severe complications in our patient may be due to his lack of vaccination.

In conclusion, although VZV infections are generally mild and self-limiting in children, life-threatening complications and even death can occur. VZV encephalitis is a rare neurological complication of VZV infection in previously healthy children, and vaccination can prevent these severe complications. We reported on a rare pediatric case of VZV encephalitis who completely recovered with acyclovir and methylprednisolone treatment. During the COVID-19 pandemic, other viral infections and their rare complications should be kept in mind, and we should start early treatment in order to prevent possible complications and squeals.

Ethics

Informed Consent: Written informed consent for presenting clinical data and using photographs in this manuscript was obtained from the patient's parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.G.Ö., A.A.K., F.Y.A., Ü.Y., Design: G.G.Ö., A.A.K., F.Y.A., Ü.Y., Data Collection or Processing: G.G.Ö., A.Ö., M.Y.Ç., M.G., F.Y.A., Ü.Y., Literature Search: G.G.Ö., A.Ö., M.Y.Ç., F.Y.A., Ü.Y., Writing: G.G.Ö.

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