Severe Complications of Varicella Zoster Virus Infection in Two Children

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Abstract

Infection with Varicella Zoster virus, which is the causative agent of chickenpox, is commonly seen during childhood. It has typically a benign course and can be substantially prevented by vaccination. Rarely, it may result in central nervous system infections. Herein, we report two cases of chickenpox-induced central nervous system infection, one in a refugee. Both patients were not previously vaccinated for varicella. Meningoencephalitis developed in one of the patients due to the varicella. In the other patient, thrombosis developed after meningoencephalitis. This article underlines that, although rare, chickenpox can lead to meningoencephalitis and related serious complications, and highlights the importance of chickenpox vaccination in Turkey where there is a high number of refugees.

Keywords: Central nervous system, chickenpox, meningoencephalitis

Introduction

Varicella Zoster virus (VZV), the causative agent of chickenpox, proliferates in the respiratory mucosa and, then, enters into the reticuloendothelial system through blood and the lymphatic system, ultimately resulting in vesicular skin rash. While it often follows a benign course, 5.5% of cases with a healthy immune system may experience related complications. Neurological complications are one of the most frequent reasons of hospitalization, which often develop within two to six days after the appearance of skin rash. Cerebellar ataxia is the most common central nervous system (CNS) complication. Acute meningoencephalitis, on the other hand, is a less frequent complication, although it may cause serious morbidity and mortality.

VZV is a species-specific virus which only affects human and has no other hosts. Varicella vaccine was approved by the United States (U.S.) Food and Drug Administration (FDA) in 1995 and, thereafter, introduced into the national immunization programs in several countries. In Turkey, it was introduced into the immunization program in 2013 to be administered on the 12th month of life. The incidence rates of chickenpox and related complications decreased after the introduction of the vaccine to routine use. Polymerase chain reaction (PCR), which is used to diagnose viral infections, is an effective method for the diagnosis of chickenpox. In particular, identification of VZV in the cerebrospinal fluid (CSF) using PCR is valuable in the diagnosis of varicella meningoencephalitis.

Herein, we report two cases of VZV-induced CNS infection presenting with distinct clinical pictures.
Case Reports

Case 1

Written consent was obtained from the patient’s family. A 7-year-old male patient was referred to our clinic with the complaints of high fever, vomiting, rash, and headache. He had vesicular rashes on the face and the trunk for three days, which then spread to the whole body. He developed these symptoms after the appearance of similar symptoms in his classmates. He was seen by a pediatrician two days ago, and was prescribed desloratadine syrup, a topical antibiotic, and acyclovir oral suspension. However, he was referred to our pediatric emergency unit after his complaints increased, despite medical treatment.

His medical and family history was non-specific, and his developmental stages were age-appropriate. The vaccination card of the patient did not show that he was vaccinated against chickenpox. Sporadically active, scabbed vesicular lesions were seen on the trunk, hairy skin, arms, and the legs. During neurological examination, he was conscious, cooperative, and positive for neck stiffness and Kernig’s and Brudzinski’s signs, suggestive of the main findings of meningeal irritation. He had no pathological reflexes, and cerebellar and other system examinations were normal.

The patient was hospitalized in the pediatric neurology ward. Laboratory findings were as follows: hemoglobin: 12.9 g/dL, white blood cell count: 11.500/mm³, platelet count: 205.000/mm³, and C-reactive protein (CRP): 0.33 mg/dL (0-0.5 mg/dL). Peripheral blood smear test revealed a neutrophil rate of 46%, lymphocyte rate of 46%, and monocyte rate of 8%. Routine biochemistry results were within the normal ranges.

Based on the preliminary diagnosis of meningoencephalitis, lumbar puncture was performed. The CSF was clear in gross examination with a white blood cell count of 30/mm³ (70% in lymphocyte, 30% in neutrophil characteristics), protein - 33.5 mg/dL (15-45 mg/dL), chloride - 122 mmol/L, and glucose - 56 mg/dL (simultaneous blood glucose 90 mg/dL). With a preliminary diagnosis of VZV meningoencephalitis, the patient was put on empiric treatment with intravenous acyclovir and ceftriaxone. Cranial magnetic resonance imaging (MRI) revealed normal findings. PCR analysis of the CSF was positive for VZV. Therefore, due to the confirmed diagnosis of VZV meningoencephalitis, empiric treatment with intravenous acyclovir was continued, while ceftriaxone was discontinued. During clinical follow-up, his headache and vomiting gradually decreased after the third day of the treatment. The patient was discharged following the completion of acyclovir treatment to 14 days. Neurological system examination and other system examination findings were normal at his last scheduled follow-up visit.

Case 2

Written consent was obtained from the patient’s family. A 60-month-old Syrian refugee girl was referred to our clinic with the complaints of fever, rash, headache, convulsion, and impaired consciousness. She had vesicular rashes which started four days ago on the trunk and the back and, then, spread to whole body. She had fever with a body temperature of 39 °C. She was admitted to our pediatric emergency unit, as she developed impaired consciousness, orientation loss, somnolence, and walking impairment.

Her medical and family history was non-specific, and her developmental stages were age-appropriate. The vaccination card of the patient did not show that she was vaccinated against VZV. On admission, the body temperature was 37.2 °C (armpit), blood pressure was 105/75 mmHg, heart rate was 108/bpm, and respiratory rate was 20/min. Sporadically active, scabbed and crusted vesicular lesions were noted on the trunk, arms and legs. Her physical examination showed that her overall status was moderate, although she was confused and poorly cooperative. There were no findings of meningeal irritation. No pathological reflex was noted. Except impaired walking, other system examinations were normal.

Laboratory findings were as follows: hemoglobin: 13.8 g/dL, white blood cell count: 11.200/mm³, platelet count: 199.000/mm³, erythrocyte sedimentation rate: 34 mm/h, and CRP: 27.3 mg/dL (range: 0-0.5 mg/dL). Peripheral blood smear test showed a neutrophil percentage of 88%, lymphocyte percentage of 8%, and monocyte percentage of 4%. Liver enzyme results were as follows: aspartate aminotransferase: 302 U/L (0-40 U/L), and alanine aminotransferase: 191 U/L (0-40 U/L). Other laboratory findings were as follows: creatine kinase: 1912 U/L (0-250 U/L), sodium: 137 mmol/L, potassium: 3.84 mmol/L, prothrombin time: 14.7 sec (9-13.5 sec), international normalized ratio: 1.3, activated partial thromboplastin time: 31.2 sec (28-35), and D-dimer: 8.078 (0-230) ng/mL. Cranial MRI showed normal findings.

Based on the preliminary diagnosis of CNS infection, a lumbar puncture was performed. The CSF was clear in gross examination with a cell count of 8/mm³ cells (7 lymphocytes, 1 neutrophil), protein of 17.5 mg/dL (15-45 mg/dL), chloride of 117 mmol/L, and glucose of 53 mg/dL (simultaneous blood glucose: 80 mg/dL). With a preliminary diagnosis of VZV meningoencephalitis, the patient was put on empirical treatment with ceftriaxone and acyclovir. Since she had convulsion, anti-epileptic treatment was also initiated. No new episode was seen following anti-epileptic treatment. On the third day of follow-up, the patient developed left leg swelling with increased temperature and caliber difference, compared to the right leg. Doppler ultrasonography of the left lower extremity venous system showed a thrombus.
Written consent was obtained from CNS infection, did not suffer from convulsions or impaired consciousness, although he demonstrated signs of meningeal irritation. On the other hand, the second patient had mental fog and convulsions. To find an association between the neurological complications and chickenpox, VZV nucleic acid should be detected in the CSF-PCR results, and VZV-specific intrathecal antibody production should be demonstrated or VZV-IgM antibodies should be identified in the CSF.\(^8\) In a study performed by Pollak et al.,\(^7\) 20 of 44 patients, who were suspected to have viral encephalitis, had VZV in the CSF as confirmed by PCR. Although the CSF cultures of both our cases had no growth, PCR analysis showed positivity for VZV. In addition, individuals with a hereditary risk factor such as MTHFR mutation are at a lifelong risk for developing thrombosis upon an acquired stimulus, such as infection.\(^8\) In the second case presented here, thrombophilia panel was requested after deep vein thrombosis development, indicating a MTHFR gene mutation. Development of thrombosis suggested that the underlying infection induced the hereditary origin.

In their study including 113 patients, Jaeggi et al.\(^9\) reported acute cerebellar ataxia in 16 (14%), meningoencephalitis in 10 (9%), CNS complications in 26 (23%), and febrile convulsions in nine patients (8%). A study from Turkey including 228 patients demonstrated that 22 patients (9.6%) had meningoencephalitis, 15 (6.5%) had acute cerebellar ataxia, and 29 (12.7%) had febrile convulsion.\(^10\) In our both cases, the disease progressed with rash and CNS infections developed as acute complications. Development of meningoencephalitis two to three days after the onset of rash is also consistent with the literature reports.

In conclusion, although chickenpox usually follows a benign course in children, it may also result in severe complications, as in our cases. Currently, immunization provides an effective protection from chickenpox and related complications. However, endemics may occur in areas such as our country, when immigrants are allowed from unvaccinated communities. Therefore, it should be kept in mind that chickenpox, one of the most frequent viral infections of childhood, may follow a serious clinical course along with CNS complications, and the importance of vaccination should never be underestimated.

**Ethics**

*Informed Consent:* Written consent was obtained from both family members.

*Peer-review:* Externally peer-reviewed.

**Authorship Contributions**

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References