Severe Complications of Varicella Zoster Virus Infection in Two Children

Varicella Zoster Virüsünün İki Çocuktaki Ciddi Komplikasyonları

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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

Öz

Su çiçeği etkenini oluşturan Varisella Zoster virüsü, çocukluk çağında yaygın olarak görülür. Genellikle iyi huylu bir seyr gösterir ve aşılama ile büyük ölçüde önlenebilir. Nadir olarak merkezi sinir sistemi enfeksiyonlarına neden olabilir. Burada hastalardan birinin múlteci olduğu iki suçiçeği kaynaklı merkezi sinir sistemi enfeksiyonu olgusu bildirildik. Her iki hastamızın da suçiçeği aşısı yapılmamışı. Hastaların birincisinde su çiçeğine bağlı meningoensefalit gelişmişti. İkincisinde ise meningoesefalit sonrasında tromboz geliştmişti. Bu yazımızda nadir de olsa, suçiçeği enfeksiyonunun merkezi sinir sistemi enfeksiyonu ve buna bağlı ciddi komplikasyonlara neden olabileceği ve bu yönden çok sayıda mültecinin bulunduğu Türkiye’de suçiçeği aşılamasının önemini vurgulamak istedik.

Anahtar Kelimeler: Merkezi sinir sistemi, suçiçeği, meningoensefalit

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 white blood cell count of 8/mm³ (70% lymphocytes, 30% neutrophils), protein - 117 mmol/L, and glucose - 111 mmol/L (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...
and, therefore, she was put on warfarin sodium. Further investigations were requested for thrombosis and anti-coagulant therapy was initiated. Thrombophilia panel showed that the patient had homozgyous mutation in the MTHFR A1298C and PAI-1 4G>5G 4G/4G genes. Oral warfarin sodium was, then, initiated. The infection was considered to have caused thrombosis by inducing the underlying genetic condition. The PCR analysis of the CSF showed positivity for VZV. On the 14th day, ceftriaxone and acyclovir treatment was discontinued, and the patient was discharged with recommendations of oral warfarin sodium and scheduled follow-up visits. Neurological and other system examination findings were normal at her last follow-up visit.

**Discussion**

Chickenpox is a contagious disease which is frequently seen during childhood. In the U.S., an estimated 10,000 of four million chickenpox cases per year are hospitalized due to complications and almost 100 of these cases die as a direct cause of chickenpox. In addition, several studies including all age groups in many countries have shown a mortality rate of 1/100,000 in Israel, 1/40,000 in the U.S., and 1/30,000 in the United Kingdom, while 1.42 to 2 deaths occur per 100,000 children aged 1 to 14 years.

Following the approval of chickenpox vaccine by the U.S. FDA in 1995, the vaccine was introduced into the national immunization programs in several countries. In Turkey, it was introduced into the national immunization program in 2013. In communities vaccinated for chickenpox, a significant decline in the rates of chickenpox-associated mortality and morbidity due to serious infections, such as pneumonia and CNS infections was reported. Aseptic meningitis due to chickenpox in unvaccinated patients was first reported by Johnson and Milbourn in a four-case study. All four patients had pleocytosis of the CSF, two had elevated levels of proteins in the CSF, and one patient had convulsion. Of our cases, one was not vaccinated, as chickenpox vaccine was not introduced into the national immunization program during his childhood, while the other one was unable to be vaccinated, as she was a Syrian refugee. Both cases had pleocytosis. In addition, the second case had convulsion which did not recur after anti-epileptic treatment. Therefore, both cases were at risk for developing chickenpox and associated complications.

In a study performed by Koskiniemi et al., among 3,231 patients with viral CNS infection, 46% had positive CSF-PCR results and 29% of those were found to be induced by VZV. Our first patient, who was referred with the findings of 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. In a study performed by Pollak et al., 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. 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. 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. In both of our 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**

Surgical and Medical Practices: S.G., Concept: S.K., Design: M.A., Data Collection or Processing: B.Ö., Analysis or Interpretation: S.K., S.G., Literature Search: B.Ö., Writing: M.A.
Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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