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Case Report

Encephalitis associated with Zika virus infection and reactivation of the varicella-zoster virus in a Brazilian child

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Abstract

We report a case of encephalitis associated with Zika virus infection and reactivation of varicella-zoster virus in the central nervous system of a Brazilian child. This case raises the possibility that reactivation of the latent varicella-zoster virus may be a mechanism of neurological impairment induced by acquired Zika virus infection.

Keywords: Encephalitis. Human herpesvirus 3. Zika virus infection.

INTRODUCTION

Zika virus (ZIKV) is a flavivirus (*Flaviviridae* family) that is mainly transmitted through the bite of the *Aedes aegypti* mosquito. Human infection by ZIKV, when symptomatic, is generally manifested as an acute, benign, and self-limiting disease, characterized by maculopapular exanthema, conjunctival hyperaemia, mild fever (sometimes absent), and polyarthralgia. The recent epidemic in the Americas, specifically occurring in Brazil (2015), was associated with an increased number of microcephaly and Guillain-Barré syndrome cases[1]. In 2016, atypical cases of ZIKV infection associated with other severe neurological impairments were described, including encephalitis, meningitis, transverse myelitis, and encephalomyelitis; in addition, cases of death in individuals with autoimmune diseases were reported[1-3]. Presently, we report a case of encephalitis associated with ZIKV infection and varicella-zoster virus (VZV) reactivation in the central nervous system (CNS) of a Brazilian child.

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CASE REPORT

In January 2016, an eight-year-old male child with progressive myoclonic epilepsy (PME) was admitted to an emergency hospital in Brazil with status epilepticus. The child had cerebellar ataxia, regularly used phenobarbital and carbamazepine, and previously suffered two to five daily myoclonic seizures or tonic spasms in the upper and lower extremities and upwards gaze deviation, which resulted in frequent falls. Three days before hospitalization, the child developed mild fever, drowsiness, and adynamia. On the eve of the day of admission, the child experienced tonic-clonic seizures without recovery of consciousness between episodes. Exanthema, conjunctival hyperaemia, or joint swelling were not observed in the child or in his relatives. Diazepam was administered along with a phenytoin-loading dose and empirical treatment with both intravenous acyclovir and ceftriaxone. During the first days of hospitalization, the patient required additional doses of intravenous diazepam and supplementary doses of phenytoin due to repeated seizures.

Blood cell count, urea, creatinine, sodium, and aminotransferases values were within normal limits. Cranial computed tomography and brain magnetic resonance imaging with gadolinium infusion were normal. In the sample collected five days after fever onset, protein and glucose levels in the cerebrospinal fluid (CSF) and the leukocyte count were within the normal range. The electroencephalogram showed frequent

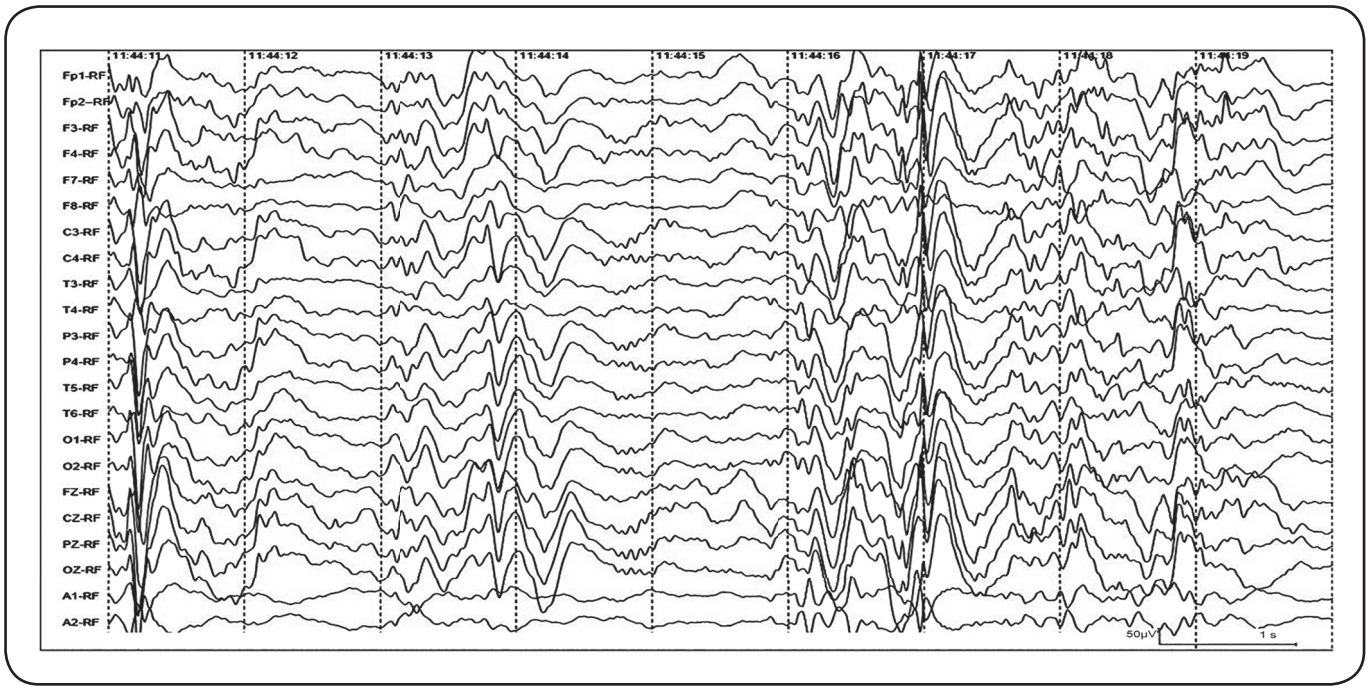

FIGURE 1: Electroencephalogram showing generalized spike-wave and multispike-wave complexes, diffuse disorganization activity, and periods of generalized voltage attenuation.

epileptiform discharges (**Figure 1**) of widespread distribution. After the seventh day of hospitalization, the patient exhibited a return to his previous clinical condition, with some daily episodes of generalized myoclonus and tonic spasms, moderate intellectual deficit, language delay, and ataxic gait.

Viral genome assessments of the CSF (Day 5) by polymerase chain reaction (PCR) and reverse transcription PCR were negative for herpes simplex type I, herpes simplex type II, enterovirus, dengue virus, St. Louis encephalitis virus, West Nile virus, and chikungunya virus but were positive for ZIKV and VZV. Two sets of primers and probes were used to test for ZIKV: the first was specific for virus envelope gene targets, and the second was specific for non-structural protein 5 (NS5) gene targets[4]. For VZV, VP22 and VM20 primers were used[5]. Acute-phase serum (Day 5) PCR tests were negative for all tested flaviviruses. To minimize the potential of a false-positive result and contamination carry-over, all precautionary measures were followed as recommended by standard protocols[4,5].

Virus isolation attempts in C3/36 cells were negative. Immunoglobulin M (IgM)-capture enzyme-linked immunosorbent assay (ELISA) did not detect antibodies against ZIKV or VZV in the acute-phase serum or CSF. A urine sample was not obtained for analysis. Unfortunately, convalescent serum was not obtained. Serum VZV ELISA-immunoglobulin G (IgG) was positive. In addition, the child had suffered chickenpox when he was two years old.

DISCUSSION

According to the Brighton Collaboration case definitions for encephalitis, the presence of fever, hyporesponsiveness, and convulsive epileptic status categorized the case at level 3 of diagnostic certainty, which was supported by the detection of ZIKV ribonucleic acid (RNA) and VZV deoxyribonucleic acid (DNA) in the patient's CSF. Normal brain MRI and the absence of CSF pleocytosis in ZIKV-related encephalitis has previously been reported[2].

This patient had PME that began in early childhood. PME may be caused by rare gene defects, immune diseases, or degenerative disorders. Despite the advances in molecular medicine, PME etiology remains undetermined in a large proportion of patients[6].

After primary infection (chicken pox), VZV remains latent in the dorsal roots, cranial nerves, and autonomic nerve ganglia. The primary cause of CNS impairment may be an immunomodulated reaction to viral replication at low levels rather than viral cytopathology itself. The clinical findings of zoster encephalitis may be similar to other viral encephalitides[7-8]. One of the forms of VZV encephalitis presentation is a convulsive status epilepticus, including patients with a history of epilepsy[9]. Moreover, VZV encephalitis without rash, fever, imaging abnormalities, and/or CSF pleocytosis is also possible[8].

Some flaviviruses encode inhibitors of the type I interferon (IFN-I) system. Viral antagonists typically dampen but do not completely shut down the host response and block IFN-I induction or repress their receptor signaling[10]. A recent study found that the ZIKV NS5 protein inhibits the IFN-I system at both of these levels[11]. Other research suggests that ZIKV RNA-encoded sequences can inhibit the production of IFN-I and, to a lesser extent, the response mediated by melanoma differentiation-associated protein 5 (MDA-5) RNA sensors[12].

IFN-I is considered the most potent autocrine and paracrine secreted virus-induced cytokine and is critical in establishing an efficient adaptive and acquired immune response[10]. Because VZV establishes latency in sensory ganglia, the adaptive T cell response is necessary to prevent symptomatic reactivations of endogenous VZV. The common age-related decrease in VZV-specific T cells or a decrease resulting from immunosuppressive diseases or therapies is associated with an increased risk of VZV reactivation[8]. A proposed mechanism for VZV CNS impairment involves virus reactivation from cranial nerve ganglia followed by transaxonal spreading of the virus to the meninges, brain parenchyma, and adventitial layer of cerebral arteries, whereupon productive virus infection induces tissue damage through a direct effect or an indirect effect of virus-induced inflammation[7-8].

Our findings suggest that reactivation of the latent endogenous VZV infection within the sensory ganglia to the CNS may be one of the mechanisms of neurological damage induced by the acquired ZIKV infection. However, the finding of zoster skin lesions has no diagnostic specificity for zoster encephalitis and may be merely a marker of critical illness. Similarly, the VZV, which spread to the CSF in this case, could also be devoid of etiological significance regarding ongoing CNS impairment by ZIKV infection. We should also consider the possibility that VZV reactivation in the CNS may have been the true etiology of the neurological symptoms. Additionally, it is possible that neither ZIKV nor VZV caused the clinical findings, but, rather, another viral process may have contributed to fever, drowsiness, and the lowering of the patient's seizure threshold, which led to status epilepticus. Without convalescent serum sample analysis, it is difficult to determine the main or initial cause of the patient's acute illness. Some cases of encephalitis with clinical and laboratory evidence of ZIKV infection have recently been reported[2,3]. However, to date, this is the first case in which encephalitis associated with ZIKV infection was observed with VZV reactivation in the CNS.

This case suggests that ZIKV screening should be performed on encephalitic patients who are living in or returning from endemic areas, even in the absence of rash, conjunctival hyperaemia, or arthralgia. Finally, the detection of VZV DNA in the CSF may denote transient CNS immunologic compromise during ZIKV infection.

Ethical considerations

Informed consent was obtained from the patient's guardians, and this study was approved by Piauí State University Ethics Committee (CAAE: 65885516.4.0000.5209).

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Conflicts of interest

The authors declare that there is no conflict of interest.

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