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LETTER TO THE EDITOR

Acute necrotizing encephalopathy of childhood associated with human herpes virus 6 in Croatia

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Introduction

Acute necrotizing encephalopathy of childhood (ANEC) is a rare syndrome often observed after a viral disease in East Asian children, although it has been sporadically reported worldwide [1]. Hoshino et al. recognized the diagnostic criteria for four syndromes of acute encephalopathy (AE) including acute necrotizing encephalopathy of childhood (ANEC), acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS), and finally hemorrhagic shock and encephalopathy syndrome (HSES) [2]. More than 40% of the patients continue to be unclassified into these specific syndromes [3]. Despite prior viral infections, ANEC is not an inflammatory encephalitis. Cerebrospinal fluid (CSF) pleocytosis is usually absent in patients with ANEC. The hallmark of neuroradiological manifestations of ANEC is multifocal, symmetrical bilateral thalamic lesions [1].

We report a 22-month-old child with ANEC triggered by HHV-6. With this case report, we aim to promote ANEC as a rare, often underdiagnosed syndrome and an important differential diagnosis of AE.

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Case report

A previously healthy 22-month-old boy exhibited a single episode of generalized tonic-clonic seizure preceded by a fever of up to 39.5 °C and coryza one day earlier. On day 4, the fever resolved, but the patient became somnolent. Upon physical examination, he had positive meningeal signs, reduced spontaneous movement, muscle hypertonia, bilateral upward response of the plantar reflex, and gazing with no eye tracking. He developed a blanching macular rash on the trunk and extremities. Family history was unremarkable. His leukocyte count was 4.9×10^9/L with absolute neutrophil count of 0.6×10^9/L and relative lymphocytosis (61%) with 10% of atypical lymphocytes in the differential count. The level of serum C-reactive protein was 0.3 mg/L. Serum electrolytes, transaminases, creatinine, ammonia, lactate, and glucose levels were normal. On day 5, brain magnetic resonance imaging (MRI) revealed bilateral symmetrical thalamic edema with surrounding hemorrhage and decreased apparent diffusion coefficient (ADC) as well as periventricular white matter and cerebellar T2/FLAIR hyperintense lesions (Fig. 1a). There was no post-contrast enhancement. Electroencephalography (EEG) showed diffuse slow waves above the left brain hemisphere.

On day 7, the patient was transferred to the Pediatric Infectious Diseases Department of the University Hospital for Infectious Diseases. CSF examination revealed one white blood cell per cubic millimeter with normal glucose level (3.0 mmol/L) and mildly elevated protein level (0.6 g/L), but with blood-brain barrier dysfunction. CSF polymerase chain reaction (PCR) for HSV and non-polio enteroviruses was negative as well as blood serology for borreliosis and HHV-6. Nasopharyngeal aspirate PCR for influenza A and B was negative. Stool sample analysis for adenovirus and rotavirus was also negative. Upon admission, the treatment included anti-edema therapy, intravenous acyclovir, ganciclovir, and ceftriaxone, but with the exclusion of other microbial causes, only

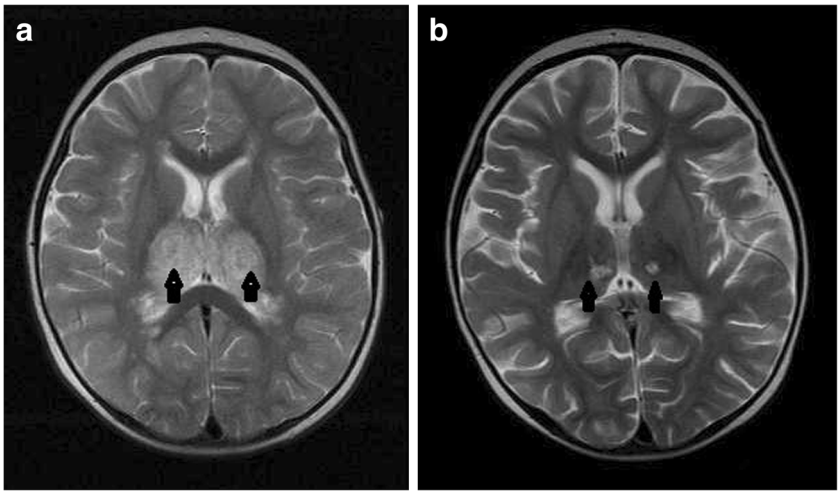

Fig. 1 MRI of the brain (T2-weighted image-WI). **a** Bilateral symmetrical thalamic edema with surrounding hemorrhage (black arrows). **b** Complete regression of bilateral thalamic edema with residual hemosiderin deposits (black arrows)

ganciclovir (10 mg/kg) was continued for 21 days. During admission, he received high-dose corticosteroids and six cycles of plasmapheresis. Given the radiological suspicion of Leigh syndrome (LS), he received thiamine for 21 days as well. On day 18, brain MRI revealed complete regression of all lesions with residual hemosiderin deposition (Fig. 1b). Clinical improvement consisted of normal spontaneous movement, reduced muscle hypertonia, and normal eye tracking. On day 21, HHV-6 seroconversion was observed. Four weeks later, a repeated serology for HHV-6 showed a continuing rise in the IgG antibody titer. Our patient slowly recovered. The residing neurological sequelae consisted of hypertonia, slightly weaker right arm, impaired speech, and incomplete contact acquisition. Upon follow-up, a month and a half later, further neurological improvement was recorded with residual hypertonia of the legs and diffusely irregular, but improved, EEG report.

Discussion

We describe a rare case of ANEC associated with HHV-6 from Croatia with complete regression of brain lesions within 18 days from the onset of fever and 11 days after the initiation of corticosteroid therapy with plasmapheresis. ANEC is often associated with influenza virus infection, but parainfluenza, varicella, HHV-6, herpesvirus 7, enterovirus, rotavirus, herpes simplex virus, rubella, measles, and bocavirus infections may also precede it. Initially, our patient had negative serology for HHV-6. However, the second and third serology showed seroconversion thus proving the association between HHV-6 and ANEC.

The differential diagnosis of ANEC is complex and includes acute infectious encephalopathy syndromes (AESD, MERS, HSES), bacterial, viral, and autoimmune inflammatory disorders as well as vascular diseases. Although some features, such as the absence of systemic organ involvement and abnormal ADC in our patient, were more typical for AESD than for ANEC, the lack of biphasic seizures ruled out AESD. The diagnosis of MERS or HSES would have been inconsistent with the clinical and neuroradiological criteria [2]. Based on the laboratory and imaging findings, we excluded meningitis and viral encephalitis, as well as vascular causes of AE syndromes in children. ADEM typically shows asymmetrical involvement of the centrum semiovale, basal ganglia, and thalamus while ANEC does not. An important differential diagnosis is the LS. Similar to LS, T2-weighted brain MRI in ANEC shows multiple symmetric lesions in the brainstem, pons, and thalami [4].

Patients with ANEC often have an exaggerated immune response to prodromal viral infections by producing elevated pro-inflammatory cytokines [1]. The immunomodulatory therapy that suppresses cytokine production has the potential to improve the outcome of ANEC. Methylprednisolone pulses, intravenous immunoglobulin, and plasmapheresis should be effective [1, 3].

The prognosis of ANEC varies from complete recovery to death. The mortality rate is about 30% and less than 10% of patients recover completely while the neurological sequelae are frequent in survivors [1]. Our patient recovered gradually, with residual impaired speech. Although we used ganciclovir more as a salvage therapy for HHV-6 central nervous system infection, to the best of our knowledge, it has not been previously used in the treatment of ANEC associated with HHV-6 [1, 3, 5]. In comparison to scarce similar reports, our case differs also in a relatively good disease outcome despite the severity of presentation, late administration of steroids, not using intravenous immunoglobulin nor inducing the recommended therapeutic hypothermia [1, 3]. We believe that all patients suspected of having ANEC should receive a trial of steroids with

plasmapheresis. If there is no improvement, other cytokine modulators should be considered.

Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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