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Case report

Epstein-Barr virus meningoencephalitis in a young immunocompetent child: A case report

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HIGHLIGHTS

- EBV meningoencephalitis is relatively rare in immunocompetent children.
- EBV should be considered as a causative agent for children with acute meningoencephalitis, regardless of classical IM symptoms.
- Diagnosis of EBV-related CNS infections relies on serology, molecular testing and neuroimaging studies.
- Treatment of EBV meningoencephalitis with antiviral agents or corticosteroid is controversial.

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ABSTRACT

Epstein-Barr virus (EBV) usually causes mild, asymptomatic, and self-recovered infections in young children. Yet, neurological involvement of this virus has been reported. EBV meningoencephalitis is relatively rare in immunocompetent children. Herein, we describe a case of 2-year-old previously healthy girl presented with high-grade fever and exudative tonsillitis. Her neurological examination showed alteration of consciousness and neck stiffness. A history of generalized tonic-clonic seizures was noted. A diagnosis of EBV meningoencephalitis was definitely confirmed by a positive result for serum viral capsid antigen IgM, and a detection of EBV DNA in cerebrospinal fluid. Her neuroimaging studies demonstrated evidence of leptomeningeal enhancements along bilateral parietal cortical sulci and around the brainstem with a hypodense lesion in the left parietal area – the typical findings of EBV meningoencephalitis. This patient was treated with intravenous corticosteroid without antiviral agents. Her clinical symptoms gradually improved. She was discharged from the hospital on the 19th day of hospitalization without neurological sequelae. Although EBV is not a primary causative agent of meningoencephalitis in immunocompetent children, it should always be considered regardless of the presence or absence of classical infectious mononucleosis symptoms. Early recognition and properly treatment are important for a good prognosis.

1. Introduction

Primary Epstein-Barr virus (EBV) infections usually spontaneously recover with mild or no symptoms in young children. Neurologic manifestations of this virus are relatively rare, and frequently seen in immunocompromised patients [1, 2]. Encephalitis and meningoencephalitis are the main clinical diagnosis which usually occurs in thalamus, basal ganglia, optic nerve, brain stem, cerebellum, and spinal cord. Clinical manifestations vary according to the site and severity of infection, but the common features include alteration of consciousness, vasculitis, and hemorrhage [3]. The disease prognosis is good, in which majority of cases completely recover with no neurological consequences [1]. Since clinical manifestations of EBV encephalitis and meningoencephalitis are non-specific and may overlap considerably with other etiologies of central nervous system (CNS) infections, the diagnosis can be challenging, and usually relies on a combination of serological, molecular, and neuroradiological studies [1, 4].

Herein, we described the case of EBV meningoencephalitis in a young immunocompetent child who presented with high-grade fever and

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exudative tonsillitis, and had a complete recovery without neurological sequelae.

2. Case presentation

A 2-year-old girl was admitted to our hospital with 2-day history of fever, severe sore throat, neck pain, vomiting and poor intake. On admission, she looked fatigue with moderate dehydration. Physical examination revealed high-grade fever (body temperature 39.9°C), pharyngeal erythema, and enlarged tonsils with whitish tonsillar exudates. The patient had neither lymphadenopathy nor hepatosplenomegaly by palpation. An initial neurological examination demonstrated a stiff neck on all directions, but kernig's and brudzinski's signs were both negative. Other neurological evaluations were unremarkable. The differential diagnosis included acute bacterial meningitis and deep neck infection. Initial laboratory analysis results showed hemoglobin 12.9 (11.5–13.5) g/dL, leukocyte count 10,170 (5000–10,000) cells/mm^3 (lymphocyte 51%, neutrophil 41%, and monocyte 8%), platelet count 239,000 (140,000–450,000) cells/mm^3, erythrocyte sedimentation rate 6 (0–10) mm/hr, and procalcitonin 0.20 (>2.0) ng/mL. Blood chemistry revealed glucose 112 (74–109) mg/dL, sodium 128 (136–145) mEq/dL, potassium 3.7 (3.4–4.5) mEq/dL, total calcium 8.9 (8.6–10.2) mg/dL. Liver transaminases were within normal ranges. Lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis revealed leukocyte 250 (0–7) cells/mm^3 (neutrophil 20%, lymphocyte 80%), no erythrocytes, glucose 58 (40–80) mg/dL (CSF/blood glucose ratio: 0.45), and protein 35 (5–40) mg/dL. CSF latex agglutination test for *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Streptococcus agalactiae*, and *Haemophilus influenzae* type b were all negative. Since, from CSF profile, acute bacterial meningitis could not be ruled out, empirical intravenous cefotaxime (300 mg/kg/day) was administered.

Two days after admission, the high-grade fever persisted. She had altered level of consciousness, and then developed generalized tonic-clonic seizures for about 1 min. During post-ictal period, she was drowsy and unresponsive to verbal commands. Neurological examination was unremarkable, except for a stiff neck on all directions. An emergency computed tomography (CT) of head and neck showed diffuse leptomeningeal enhancement along bilateral parietal cortical sulci and around brainstem (Figure 1A), as well as a small hypodense lesion involving cortical and subcortical regions of left high parietal lobe which might be focal cerebritis (Figure 1B). In addition, bilateral tonsillitis and multiple cervical lymphadenopathies without an evidence of deep neck space extension were demonstrated. Regarding the serological testing, viral capsid antigen (VCA) was positive for IgM, but negative for IgG, and absent of Epstein-Barr nuclear antigen (EBNA), which was compatible with acute EBV infection. Multiplex polymerase chain reaction (PCR) panel for viral meningitis and encephalitis of the CSF sample was also positive for EBV DNA, and negative for other viruses, including adenovirus, herpes simplex virus (HSV) type 1 and 2, varicella zoster virus, cytomegalovirus, human herpesvirus (HHV) type 6 and 7, parvovirus B19, enterovirus, and human parechovirus. Intravenous methylprednisolone (1 mg/kg/day) was administered for 7 days, without any antiviral

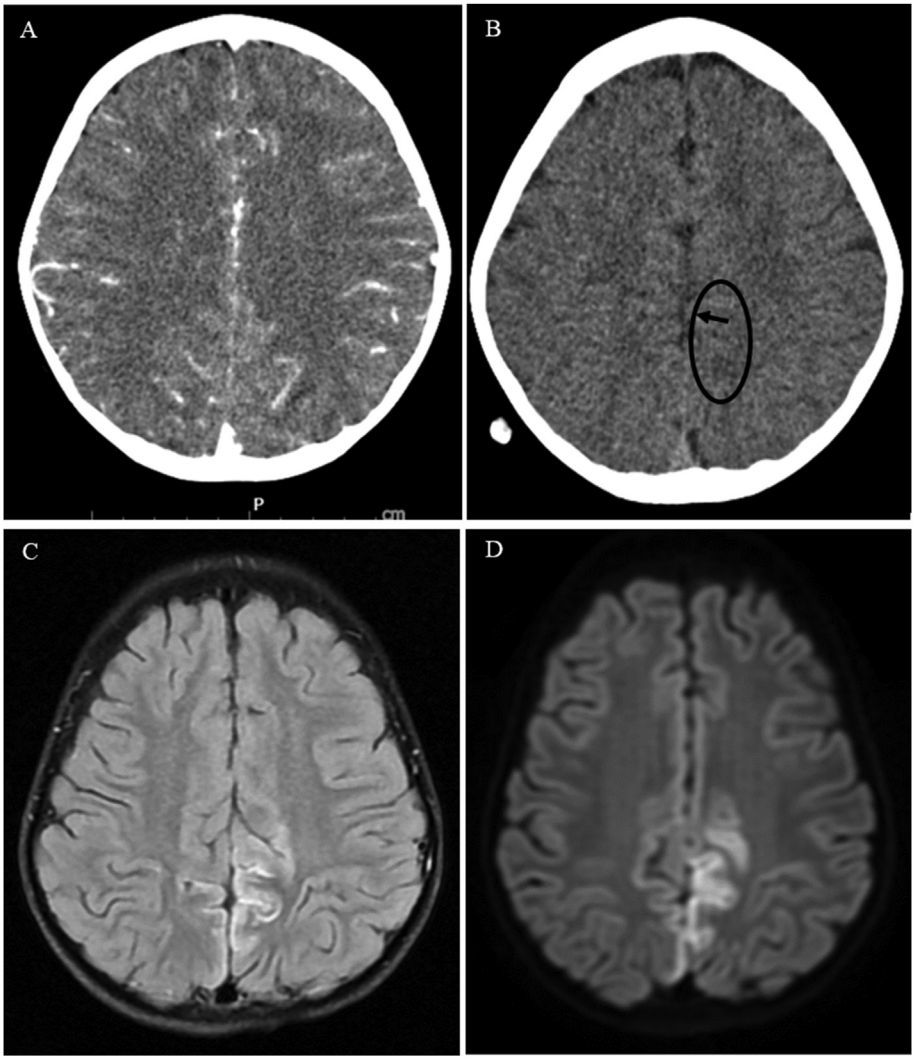

Figure 1. Neuroimaging studies of the patient. (A) Brain computed tomography with contrast media showed diffuse leptomeningeal enhancement along bilateral parietal cortical sulci and around brainstem; (B) Brain computed tomography without contrast media showed a small hypodense lesion involving cortical/subcortical region of left high parietal lobe which might be focal cerebritis (arrow); (C) T2-weighted FLAIR sequence of the brain magnetic resonance imaging showed a significant regression of leptomeningeal enhancement along surface of brainstem, and a circumferential hyperintense rim at midbrain and pons; (D) Multishot diffusion-weighted magnetic resonance imaging of the brain with multiplexed sensitivity encoding (MUSE) technique showed new subacute stage of cortical infarctions at parasagittal bilateral parietal lobes.

agents. Empirical intravenous cefotaxime was discontinued once the final negative blood and CSF results for bacteria were reported. On the fifth day of admission, her level of consciousness significantly improved. A brain magnetic resonance imaging (MRI) on the 10th day following seizure episode revealed a significant regression of leptomeningeal enhancement along surface of brainstem, and a circumferential T2/FLAIR hyperintense rim at midbrain and pons (Figure 1C). Additionally, a subacute stage of cortical infarction at parasagittal bilateral parietal lobes (Figure 1D), and very thin subdural hemorrhage along left temporooccipital convexities were noted, which were likely to be sequelae from EBV infection. She gradually recovered and was discharged from the hospital after 19 days of admission without any neurological sequelae. At 4-week follow-up visit, she could talk and walk well, and her neurological examination were unremarkable.

3. Discussion

EBV meningoencephalitis is a relatively rare and severe complication of EBV infections which mainly observed in immunocompromised hosts. In this paper, we report a case of EBV meningoencephalitis in a young immunocompetent child, presenting with high-grade fever, acute exudative tonsillitis, multiple cervical lymphadenopathies (CT neck findings), neck stiffness, generalized seizures, and altered state of consciousness, who had a confirmed diagnosis by serology, molecular testing, and neuroradiological findings. The patient had a complete recovery without neurologic sequelae after a course of corticosteroid treatment.

EBV infection of the CNS can be classified into two categories which include CNS diseases associated with primary or reactivated EBV infections, and CNS syndromes related to chronic EBV infections. It can manifest concurrently with infectious mononucleosis (IM) during an acute phase of disease, or present lately during a convalescent phase of illness [5]. In our patient, her clinical features of high-grade fever and exudative tonsillitis, together with a positive VCA IgM, a negative VCA IgG and an absent of EBNA in serum, as well as a detectable EBV DNA in CSF suggested that the meningoencephalitis was caused by primary EBV infection. The pathogenesis of neurological manifestations associated with EBV infections remains unclear. Three possible mechanisms are a direct invasion of EBV to nervous system, a reactivation of latent virus infections, and an immune-mediated infection in which the host immune system produces autoimmune T-lymphocytes and anti-neuronal antibodies to myelin oligodendrocyte glycoprotein [1, 6, 7, 8].

The prevalence of EBV encephalitis/meningoencephalitis varied across studies, ranged from 2 to 31% [9, 10, 11, 12, 13]. The highest incidence was noted among young children aged 0–4 years which was the same age group of our patient [1]. The clinical presentations were nonspecific with or without symptoms of IM. In the Encephalitis Registry of the Hospital for Sick Children (Toronto, Canada) which collected data of children with acute encephalitis from EBV infection during 1994–2003 found that 81% had fever, 66% had headache, and 48% had seizures which included generalized and focal seizures. Only one child in this case series had EBV encephalitis coincidentally with symptoms of classic IM [13]. In another retrospective study, which reviewed data of children with EBV-related neurological infections at the children's hospital of Chongqing Medical University (Chongqing, China) during 2008–2019, demonstrated that fever was the main clinical presentation (83%), followed by signs of intracranial hypertension (58%), and meningeal irritation (38%) [1]. Similar to the Canadian study, all children with EBV-related encephalitis/meningoencephalitis in this study had no symptoms of IM [1, 13]. Since the pathogenesis of EBV-related CNS diseases might be attributed to a latent viral reactivation or an antibody-mediated post-infection inflammatory response, the typical clinical pictures of IM might not be necessarily exhibited in all cases of EBV encephalitis/meningoencephalitis. Therefore, EBV should be considered as one of the causative agents of acute encephalitis and meningoencephalitis in young children, regardless of the presence or absence of classical IM symptoms as well as the host immune status.

In the general practice, establishing the diagnosis of EBV meningoencephalitis is challenging since the majority of cases do not present with clinical syndromes of IM. CSF profiles of aseptic meningitis with evidence of EBV DNA by PCR can help confirming a diagnosis [4]. Although our patient presented with high-grade fever and exudative tonsillitis, it was initially difficult to link EBV as the cause of acute meningoencephalitis until we noted multiple cervical lymphadenopathies from the CT neck, and obtained positive results in the serological and molecular testing. Neuroimaging study can be performed as an adjunctive diagnostic modality in the diagnosis of EBV encephalitis and meningoencephalitis. The neuroimaging findings in our patient are similar to previous reports that illustrated the typical findings of brain MRI including symmetric T2-weighted hyperintensities in the cortical and subcortical areas, brainstem, and corpus callosum along with meningeal enhancement [4, 14]. In the Canadian case series, 80% of children with EBV encephalitis and underwent a brain MRI had abnormal studies, in which the main findings were increased T2-weighted signals in the basal ganglia, thalamus, subcortical white matter, and temporal lobes [13].

Tuberculous meningitis was unlikely in this case because of the lack of typical clinical manifestations (e.g., prolonged fever, headache, irritability, malaise, poor weight gain/weight loss), history of TB contact, and other laboratory clues (e.g., raised intracranial pressure, elevated protein level in CSF) [15]. Additionally, an autoimmune encephalitis, one of the important differential diagnoses of EBV encephalitis, was less likely due to the uncommon age of onset, absence of complex neuropsychiatric symptoms (e.g., behavior changes, repetitive movements, orofacial dyskinesia, autonomic instability), and inconsistency of neuroimaging findings [16, 17]. Thus, we did not further workup for *Mycobacterium tuberculosis* and autoantibodies, in particular anti-N-methyl-D-aspartate receptor (anti-NMDAR) or anti-myelin oligodendrocyte glycoprotein (anti-MOG), in this patient.

Currently, there are no standard guidelines for the treatment of EBV encephalitis and meningoencephalitis. The mainstay of therapy is supportive care. The role of antiviral agents and corticosteroid is controversial. Previous studies suggested that ganciclovir and acyclovir have good *in vitro* activity against the lytic phase of EBV infections, but the clinical therapeutic effects are limited. Nevertheless, these antiviral agents can be reasonably considered as a treatment regimen in selected cases, particularly those with evidence of direct EBV invasion of the brain [18, 19]. In 2017, a randomized, double-blind, placebo-controlled trial showed promising results of oral once-daily valganciclovir which significantly suppressed EBV viral replication and substantially decreased oral shedding of the virus [20]. Corticosteroids may be beneficial in the cases with immune-mediated EBV-associated neurologic disease, and fulminant IM [19]. In addition, rituximab, an anti-CD20 monoclonal antibody targeting B cells, might be a treatment option for such patients who failed first-line immunotherapy [21]. The role of intravenous immunoglobulin in treatment of viral encephalitis is currently unclear due to the limited scientific evidence regarding its clinical efficacy and benefit [22]. In our patient, corticosteroid therapy was administered without any antiviral agents. She appeared to respond favorably, and gradually recovered without residual neurological complications.

In conclusion, EBV meningoencephalitis is mainly seen in immunocompromised cases, but should be considered in young children presenting with CNS disease with full or partial clinical pictures of IM. The diagnosis is challenging, and usually relies on a combination of serologic tests, molecular techniques, and neuroimaging studies. Early recognition and properly treatment are crucial for a good prognosis.

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References

[1] H. Cheng, D. Chen, X. Peng, P. Wu, L. Jiang, Y. Hu, Clinical characteristics of Epstein-Barr virus infection in the pediatric nervous system, BMC Infect. Dis. 20 (1) (2020) 886.
[2] T. Martelius, M. Lappalainen, M. Palomäki, V.J. Anttila, Clinical characteristics of patients with Epstein Barr virus in cerebrospinal fluid, BMC Infect. Dis. 11 (2011) 281.
[3] L. Huang, X. Zhang, X. Fang, Case report: Epstein-Barr virus encephalitis complicated with brain stem hemorrhage in an immune-competent adult, Front. Immunol. 12 (2021), 618830.
[4] K.J. Baldwin, C.L. Cummings, Herpesvirus infections of the nervous system, Continuum (Minneap Minn). 24 (5, Neuroinfectious Disease) (2018) 1349–1369.
[5] H. Fujimoto, K. Asaoka, T. Imaizumi, M. Ayabe, H. Shoji, M. Kaji, Epstein-Barr virus infections of the central nervous system, Intern. Med. 42 (1) (2003) 33–40.
[6] H. Wang, K.L. Munger, M. Reindl, E.J. O'Reilly, L.I. Levin, T. Berger, et al., Myelin oligodendrocyte glycoprotein antibodies and multiple sclerosis in healthy young adults, Neurology 71 (2008) 1142–1146.
[7] Y. Nakamura, H. Nakajima, H. Tani, T. Hosokawa, S. Ishida, F. Kimura, et al., Anti-MOG antibody-positive ADEM following infectious mononucleosis due to a primary EBV infection: a case report, BMC Neurol. 17 (1) (2017) 76.
[8] N. Obel, M. Høier-Madsen, H. Kangro, Serological and clinical findings in patients with serological evidence of reactivated Epstein-Barr virus infection, APMIS 104 (6) (1996) 424–428.
[9] F. Ben Abid, M. Abukhattab, H. Ghazouani, O. Khalil, A. Gohar, H. Al Soub, et al., Epidemiology and clinical outcomes of viral central nervous system infections, Int. J. Infect. Dis. 73 (2018) 85–90.
[10] J. Ai, Z. Xie, G. Liu, Z. Chen, Y. Yang, Y. Li, et al., Etiology and prognosis of acute viral encephalitis and meningitis in Chinese children: a multicentre prospective study, BMC Infect. Dis. 17 (1) (2017) 494.
[11] Y.F. Fu, C.B. Huang, Z.F. Huang, Clinical analysis and pathogenic study on 126 cases of viral encephalitis, Chin. J. Aesthet. Med. 21 (10) (2012) 71–73.
[12] A. Mailles, J.P. Stahl, Infectious encephalitis in France in 2007: a national prospective study, Clin. Infect. Dis. 49 (12) (2009) 1838–1847.
[13] A. Doja, A. Bitnun, E.L.F. Jones, S. Richardson, R. Tellier, M. Petric, et al., Pediatric Epstein-Barr virus-associated encephalitis: 10-year review, J. Child Neurol. 21 (5) (2006) 384–391.
[14] S. Vyas, R. Suthar, V. Bhatia, N. Bhardwaj, R. Aggarwal, P. Singhi, et al., Brain MRI in Epstein-Barr virus meningoencephalitis in children, Ann. Indian Acad. Neurol. 23 (5) (2020) 621–624.
[15] R. Aulakh, S. Chopra, Pediatric tubercular meningitis: a review, J. Pediatr. Neurosci. 13 (4) (2018) 373–382.
[16] C.G. Bien, C.I. Bien, Autoimmune encephalitis in children and adolescents, Neurol. Res. Pract. 2 (2020) 4.
[17] T. Cellucci, H.V. Mater, F. Graus, E. Muscal, W. Gallentine, M.S. Klein-Gitelman, et al., Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient, Neurol. Neuroimmunol. Neuroinflamm. 7 (2) (2020) e663.
[18] N. Bhatti, E. Larson, M. Hickey, D. Seal, Encephalitis due to Epstein-Barr virus, J. Infect. 20 (1990) 69–72.
[19] J. Andersson, I. Ernberg, Management of Epstein-Barr virus infections, Am. J. Med. 85 (1988) 107–115.
[20] J.E. Yager, A.S. Magaret, S.R. Kuntz, S. Selke, M.L. Huang, L. Corey, et al., Valganciclovir for the suppression of Epstein-Barr virus replication, J. Infect. Dis. 216 (2) (2017) 198–202.
[21] S. Kim, S.J. Ahn, K. Chu, Epstein-Barr virus-associated acute disseminated encephalomyelitis successfully treated with rituximab: a case report, Encephalitis 1 (3) (2021) 85–88.
[22] J.N. Wagner, A. Leibetseder, A. Troescher, J. Panholzer, T.J. von Oertzen, Efficacy and safety of intravenous immunoglobulins for the treatment of viral encephalitis: a systematic literature review, J. Neurol. 269 (2) (2022) 712–724.