Epstein-Barr virus encephalitis: findings of MRI, MRS, diffusion and perfusion

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Epstein-Barr virus is an infection that is known as infectious mononucleosis. Even though the central nervous system is not a primary region of involvement of this disease, neurological complications are reported rarely. In this case report, we evaluated a 15-month-old male who presented to the pediatric neurology clinic due to high fever and a neurologic attack. His serological tests and radiological examinations (magnetic resonance imaging (MRI), MR spectroscopy (MRS), diffusion-weighted imaging (DWI) and MR perfusion) were consistent with Epstein-Barr virus encephalitis, which is a very rare complication of infectious mononucleosis. Additionally, we discuss the MRI, MRS, DWI and MR perfusion findings of our case, which were different from other cases reported in the literature.

Key words: encephalitis, Epstein-Barr virus, magnetic resonance spectroscopy.

Epstein-Barr virus (EBV) is a double-stranded DNA virus from the herpes virus family that is known as a pathogen of infectious mononucleosis (IM). IM is a benign self-limited disease that has a clinical course with fever, pharyngitis, lymphadenopathy, and hepatomegaly. Guillain-Barré syndrome, transverse myelitis, meningitis/encephalitis, and cranial nerve paralyses are some of the rarely reported neurological complications, with an incidence of 0.4% to 7.3%[1]. Central nervous system (CNS) involvement may be the only sign of IM in some cases. In this case report, we evaluated a 15-month-old male who presented to the pediatric neurology clinic due to high fever and a neurologic attack. His serological tests and radiological examinations [magnetic resonance imaging (MRI), MR spectroscopy (MRS), MR diffusion-weighted imaging (DWI) and MR perfusion] were consistent with EBV encephalitis, which is a very rare complication of IM.

Case Report

A 15-month-old male patient was hospitalized in the pediatric neurology clinic with the complaints of high fever and seizure attack. In the physical examination, a single-sided continuous focal seizure attack and findings of left hemiparesis were seen. Serological investigation of the patient revealed positive EBV IgG and EBV IgM antibodies. The laboratory findings were otherwise normal, and electroencephalographic studies were unremarkable. Polymerase chain reaction (PCR) examination was not performed. No underlying disease or immunodeficiency was detected. Due to the suspicion of focal encephalitis, a brain MRI with 1.5 T MR scanner and MRS, DWI and perfusion were obtained. T2-weighted imaging demonstrated diffuse hyperintensity that was occupying the whole right cerebral hemisphere, affecting the right caudate nucleus, basal ganglia and a part of the thalamus, mesencephalon, and left occipital lobe. In T1-weighted images, except for the indistinct sulcus of the right cerebral hemisphere, no pathological finding was present. In the DWI, the previously noted areas, especially the cortical gray matter and basal ganglia, demonstrated restricted diffusion (Fig. 1). DWI technique is sensitive to diffusion of water in the tissue and is assumed to allow discrimination of intracellular and extracellular water. Restriction of diffusion may represent cytotoxic edema with bound water within the

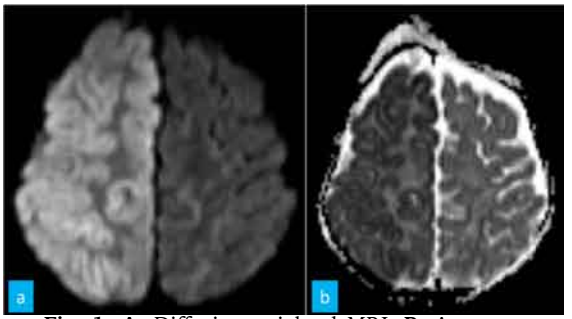

Fig. 1. A. Diffusion-weighted MRI. **B.** Apparent diffusion coefficient (ADC) map shows restricted diffusion in the right cortical gray matter.

cell and reduction of extracellular fluid as a result of cellular swelling.

Except for mild vascular congestion on the right side, no feature was observed in contrast-enhanced T1-weighted images (Fig. 2a, b, c). Significant choline increase in the right cerebral hemisphere in MRS and myo-inositol (MI) peak in short echo spectroscopy were present (MI/creatine (Cr) ratio: 0.46). Decrease in N-acetyl aspartate (NAA) and Cr values (NAA/Cr: 0.49) and lactate peak were observed (Figs. 3, 4). In perfusion examinations, significant decrease in cerebral blood volume (CBV) (Fig. 5) and cerebral blood flow (CBF) were observed in the areas with edema. Time to peak (TTP) was prolonged. Mean transit time (MTT) was decreased. These findings pointed to ischemia; however, the lesions were not matched to a specific vascular territory.

Discussion

Neurological complications of IM were first described in 1931. EBV may clinically exist as meningitis, encephalitis, acute disseminated encephalomyelitis, cranial nerve deficit, cerebellitis, myelitis, peripheral neuritis, or attacks[1]. In our case, single-sided continual focal attack and left hemiparesis findings were present. Although not specific to EBV encephalitis, these findings were thought to be consistent with encephalitis.

Imaging findings of EBV encephalitis range in a wide spectrum from normal findings to diffuse signal changes affecting either the white or grey matter[2]. In the literature, there are only a few articles about the evaluation of CNS infection of EBV with DWI. Restricted diffusion is a sign that the water is limited in cells due to cytotoxic edema. However, reversible diffusion restriction was also reported in conditions such as temporary ischemia, after attacks and hypoglycemia[3]. Another important point is the presence of reversible restriction of diffusions related to many CNS lesions due to inflammation or other causes. It is thought to arise because of the tendency to cytotoxic edema in these areas as a result of mechanisms that could not be explained clearly.

Magnetic resonance spectroscopy (MRS), which enables measurement of some in vivo biochemical markers in the MR examination, increases the specificity of MRI. Spectroscopic assessment is helpful in the differential

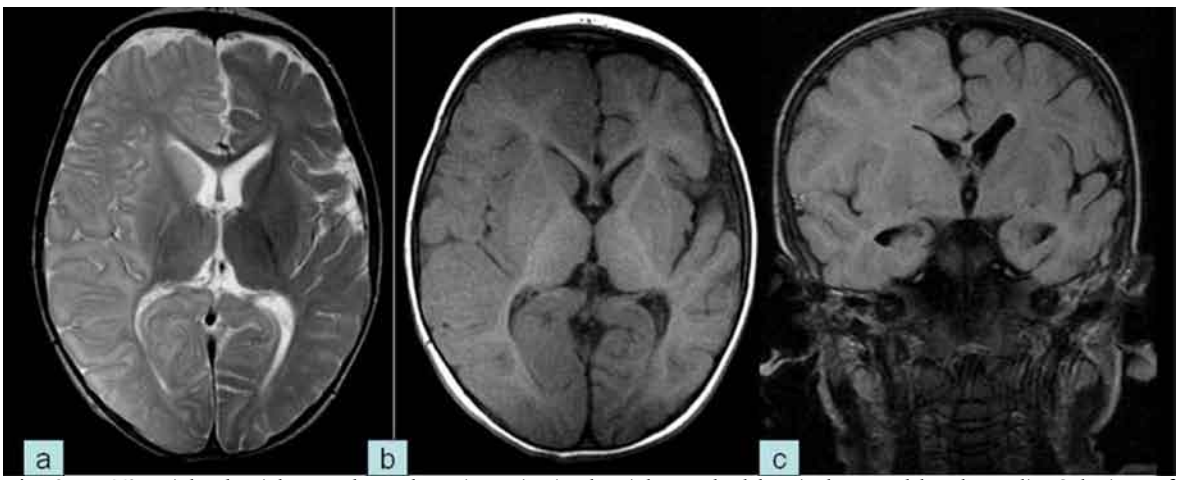

Fig. 2. A. T2-weighted axial MRI shows hyperintensity in the right cerebral hemisphere and basal ganglia. Splenium of the corpus callosum and left occipital lobe were also affected. **B.** T1-weighted axial MRI shows sulcal effacement of the right cerebral hemisphere. **C.** Coronal FLAIR image shows diffuse hyperintensity of the right cerebral hemisphere.

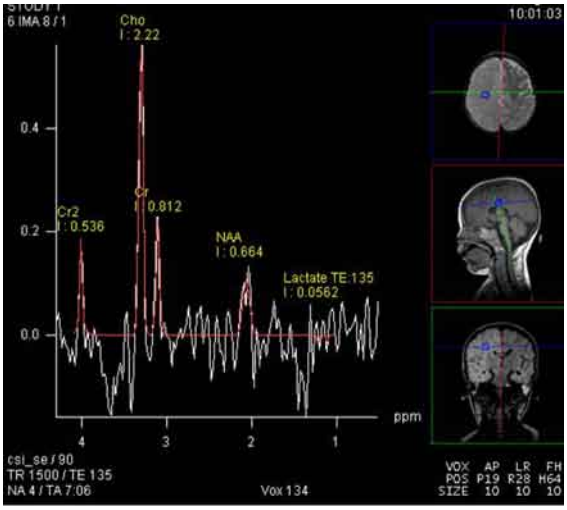

Fig. 3. Mild echo MRS reveals increasing choline, lactate and decreasing N-acetylaspartate (NAA) and creatine (Cr).

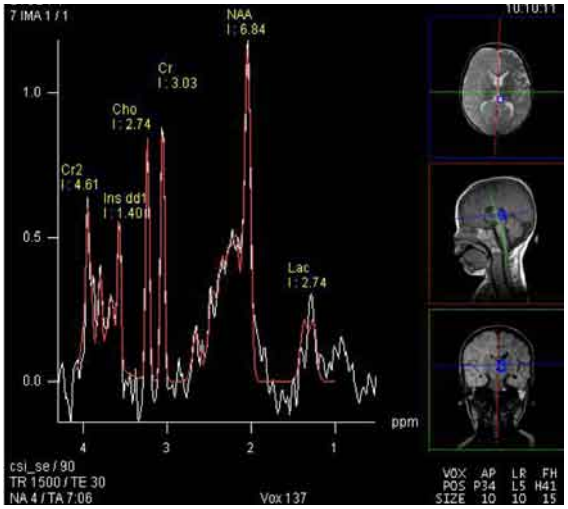

Fig. 4. Short echo MRS shows increasing myo-inositol and lactate and decreasing NAA-Cr.

diagnosis of findings of the CNS, such as ischemia, demyelization, inflammation, and direct toxic or metabolic injuries, which are nonspecific clinically and in imaging techniques. If a lesion develops due to an ischemic cause based on cellular hypoxia due to hypoperfusion, hypoxemia or mitochondrial disease, in contrast to increased lactate levels, a decrease in NAA levels is observed[4]. Even though elevation in lactate levels occurs due to anaerobic glycolysis as a result of decreased oxygen levels, decrease in NAA displays neuronal loss developing due to cell death. Increased lactate in serum and MRS was reported in metabolic brain diseases and especially in mitochondrial encephalopathies[5].

Detection of high levels of amino acids (AA) - macromolecules (MM) in MRS and MI in combination can be the evidence of inflammation or infection. Additionally, AA-MM peaks were observed before NAA peaks in short echo spectroscopic evaluation in the presented case. Increasing signal in AA-MM localizations shows the activation of immune system cells, as happens in human immunodeficiency virus (HIV)[6].

Presence of an increase in MI together with choline values is an important finding for inflammation or infection. In MRS examination for a normal adult brain MI, MI resonance is composed of a mixture of MI (70%), MI–monophosphate (15%) and glycine (15%[7]. MI resonance was described as glial specific marker, and the cause of this description was its absence in neuronal cell cultures of MI, but presence in glial cells. While the functions of MI in the CNS are not known exactly, among its known functions are to serve as a precursor of inositol phosphates, to act as a pioneer for some second messengers in the brain and to contribute to brain osmoregulation. Change in MI levels, especially an increase, in hypoxia/ischemia or metabolic diseases has not been reported.

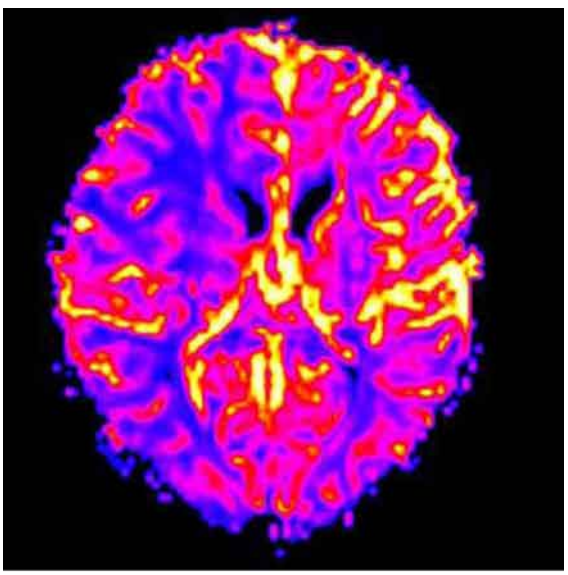

Fig. 5. MR perfusion shows decreased relative cerebral blood volume in the affected area.

Epstein-Barr virus (EBV) encephalitis is more common than often appreciated, and in the National Institute of Allergy and Infectious Disease (NIAID) Collaborative Antiviral Study Group series, it was the most common agent to mimic herpes simplex encephalitis (HSE). Although patients with HSE occasionally have normal MRI scans, the majority have imaging findings in the inferomedial temporal lobes[8]. Indeed, because PCR is not 100% sensitive, MRI can sometimes identify patients with HSE in whom the PCR is initially negative. Weil et al.[9] documented three patients in whom initial PCR was negative, but because of high clinical suspicion and compelling MRI findings, the patients were presumptively treated for HSE. All three patients had MRI abnormalities in the temporal lobes and later had positive PCR results. The spectrum of imaging abnormalities in HSE reflects the edema, hemorrhage and necrosis seen pathologically.

The right cerebral hemisphere was completely involved in our case. These findings are different from the current literature, as focal lesions were commonly reported. Despite the absence of lactate peak, increase of choline level together with MI made us consider an inflammatory event more than an ischemia. However, in our case, choline increase and MI peak were present together with lactate peak in the right hemisphere in MRS. NAA and Cr were significantly reduced. Furthermore, with the help of MRS, DWI and perfusion findings of EBV encephalitis, a differential diagnosis of encephalitis and ischemic events was attempted. However, IgM positivity was the finding that ascertained the diagnosis in our case.

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