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EBV Meningoencephalitis: Two Case Reports

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Abstract

Usual neurological complications of Epstein-Barr virus infection are aseptic meningitis, encephalitis, transverse Usual neurological complications of Epstein-Barr virus infection are aseptic meningitis, encephalitis, transverse myelitis, cerebellitis, Guillain-Barre syndrome, and cranial or peripheral neuritis most commonly in immunocompromised patients. These clinical manifestations may occur alone or accompanied by infectious mononucleosis. Usually, EBV encephalitis occurs infrequently and with non-specific symptoms. Herein, we report two patients: a 24-year-old female with generalized tonic-clonic fever and seizures for ten days. The other was a 28-year-old male with repeated fever, headache, 4-day amnesia, and symptoms of meningeal irritation. Since the physical examination results were not very helpful, the definite diagnosis was achieved by sampling, analysis, and polymerase chain reaction for the cerebrospinal fluid. Our patients had a direct EBV invasion of the CNS and were affected by Epstein-Barr virus encephalitis, confirmed by their clinical test results as a positive polymerase chain reaction of cerebrospinal fluid. The PCR results were negative for a panel of microorganisms that cause bacterial meningitis in the CSF, but positive for EBV. Image findings also did not show any significant results. Patients treated with acyclovir and precision control at the relative center with favorable outcomes. Acyclovir possibly will lessen viral replication. Finally, despite obtaining negative test results of EBV infection, every therapeutic effort should be undertaken and maintained continuous attention.

Keywords: Meningoencephalitis, Meningitis, Epstein-Barr Virus, Meningeal Irritation, Infection, Antiviral Agents

Introduction

Epstein-Barr virus (EBV) infection is often asymptomatic and self-limiting. Additionally, EBV may rarely lead to central nervous system (CNS) complications include Guillain-Barre syndrome, facial nerve palsy, acute encephalitis, demyelinating diseases, meningitis, meningoencephalitis, myelitis, and acute cerebellar ataxia. As well, it may display the symptoms alone or in association with infectious mononucleosis (IM). The most predominance neurologic clinical manifestations are prolonged fever, diarrhea, lymphadenopathy and otitis media.[1] The best management of EBV encephalitis is unclear, because it occurs infrequent and with non-specific symptoms, and its pathophysiology is not fully understood. Since the diagnostic of EBV encephalitis is difficult by the symptoms, then, the definite detection needs to utilize serological and molecular tests in blood or cerebrospinal fluid (CSF), and cranial imaging techniques. Herein, we are presenting two cases with a history of acute meningitis, that the possible presence of EBV should be considered for them.

Case Reports

Case #1 A 24-year-old female patient were admitted with fever and chills and seizures, from 15 days prior to admission, and generalized tonic clonic seizures. The physical examination revealed a fever at 39°C and stiff neck. In the initial evaluation, the patient's laboratory analysis results were as follows:

In CBC test results; Hemoglobin: 11 g/dl, white blood cell count: 9.7 × 10^3/µl (Poly 70% + Lymph 30%), platelet count 369 × 10^3/µl, erythrocyte sedimentation rate: 86 mm/h, and C-reactive protein: 58 mg/L (0-5), MCH: 25.32 Pg. In biochemical results; liver

transaminases, AST and ALT were 86 and 168 U/L respectively, alkaline phosphatase: 383 U/L, creatinine: 1.4 mg/dl, serum sodium (Na): 134 m Eq/L and potassium (K): 5.1 m Eq/L (Table 1). The CSF protein and glucose levels were within normal range and no WBC and RBC were seen in (Table 1). The PCR report was negative for the panel of pathogens causing bacterial meningitis in CSF, while, it was positive for EBV and HSV-1 (Table 1). The brain Magnetic Resonance Imaging (MRI) revealed no significant lesion or abnormality, except a scarce evidence of infection (Figure 1 a & b left).

She was diagnosed with the viral encephalitis and treated with acyclovir empirically, which improved neurological symptoms, until the results of the tests were prepared and a definitive diagnosis was made. Her fever was relieved and the seizure was not repeated and the meningeal symptoms resolved. Subsequent analyses were reported normal.

Case #2 A 28-year-old male patient was referred to the emergency center with headache, feverish symptoms and transient forgetfulness. He had previously been treated with acyclovir at the other Medical Center with the possibility of herpes meningitis. On examination, He had a fever of 38 °C, Rudor and Brudzinski. In the preliminary evaluation, the patient's para-clinical results were as follows:

In CBC test results; Hemoglobin: 17 g/dl, white blood cell count: 13.54 × 10^3/µl (Poly 61% + Lymph 39%), platelet count 247 × 10^3/µl, erythrocyte sedimentation rate: 28 mm/h, and C-reactive protein: 3 mg/L (0-5), MCV: 85 Pg. In biochemical results; liver transaminases, AST, ALT, alkaline phosphatase, serum sodium (Na), and potassium (K) were within normal range (Table 1). As well, in the body fluid analysis, the levels of protein and glucose were within normal range. Total WBC 55 per Cu/mm (Poly 35% + Lymph 65%) and RBC 6000 per Cu/mm were seen in CSF (Table 1). Molecular diagnosis using qPCR on CSF was negative for all pathogens causing Bacterial Meningitis, however, it was positive for EBV (Table 1). In the cranial CT scan and MRI of the brain no abnormality, just a low infection, was detected (Figure 1 a & b right.). Carotid vessels sonography and trans thoracic echocardiography were also normal. He was diagnosed with EBV encephalitis.

Table 1. Laboratory Test

Index		Case #1	Case #2
CBC	Hemoglobin	11 g/dL	17 g/dl
	White blood cell count	9.7 × 10^3/µl	13.54 × 10^3/µl
	Platelet count	369 × 10^3/µl	274 × 10^3/µl
	Erythrocyte sedimentation rate	86 mm/hour	28 mm/h
	C-reactive protein	58 mg/L	3 mg/L (0-5)
	MCH	25.32 Pg	30 Pg
	AST	86 U/L	10 U/L
	ALT	168 U/L	18 U/L
	Alkaline phosphatase	383 U/L	167 U/L
	Creatinine	1.4 mg/dl	1.4 mg/dL
	Na	134 mEq/L	140 mEq/L
	K	5.1 mEq/L	4.4 mEq/L
CSF	Appearance	Semi clear	Semi clear
	Color	Crystal	Crystal
	Supernatant Color	Semi clear	Crystal /Clear
	Volume	2 cc	2.5 cc
	Glucose	49 mg/dl	53 mg/dl
	Protein	17 mg/dl	18.5 mg/dl
	WBC	0 Per Cu/mm	55 Per Cu/mm
	RBC	0 Per Cu/mm	6000 Per Cu/mm
Pathogens causing viral Meningitis	HSV-1 *(Herpes Simplex Virus-1)*	Positive	Negative
	HSV-2 *(Herpes Simplex Virus-2)*	Negative	Negative
	CMV *(Cytomegalovirus)*	Negative	Negative
	EBV *(Epstein Barr Virus)*	Positive	Positive
	VZV *(Varicela-Zoster Virus)*	Negative	Negative
	EV *(Entrovirus)*	Negative	Negative
	HpeV *(Pareachovirus)*	Negative	Negative

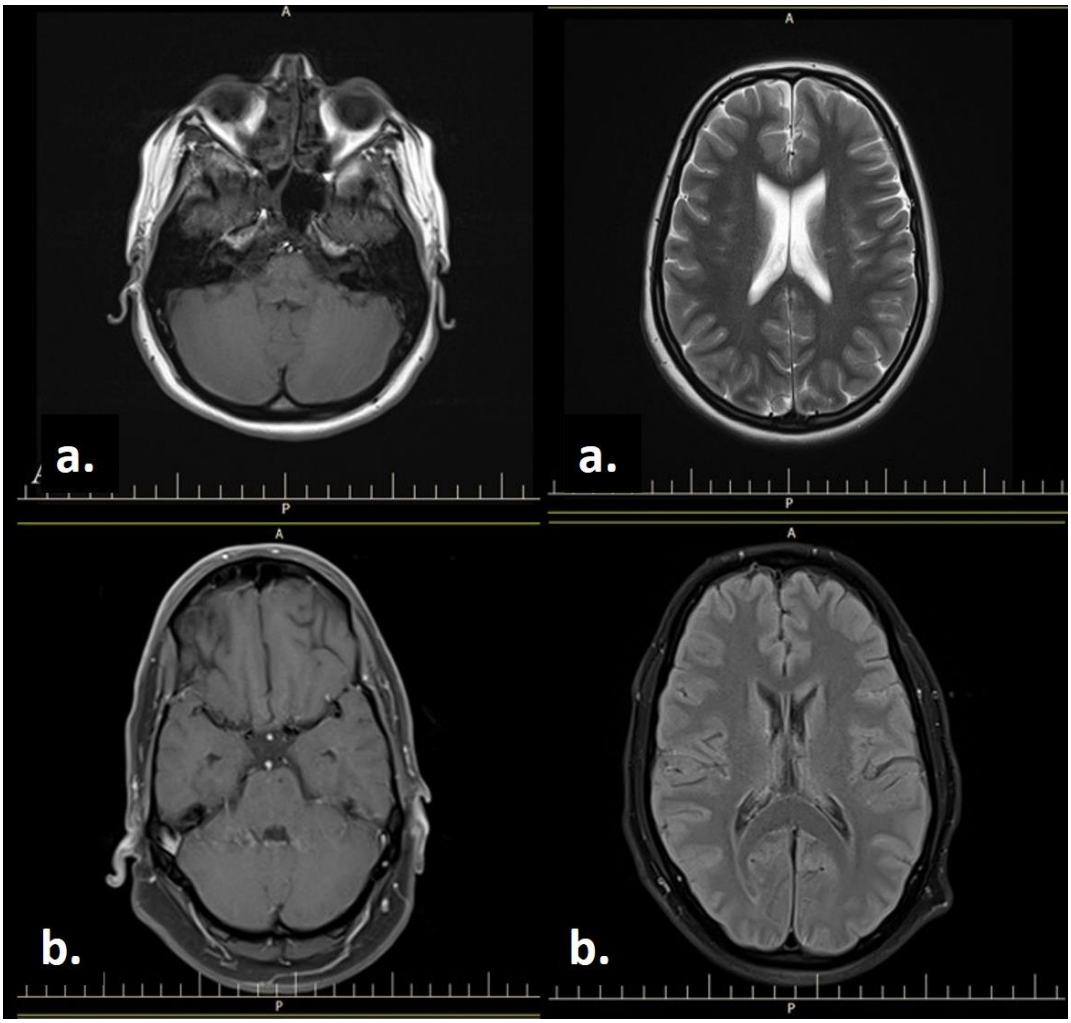

Figure 1. Brain MRI Image Showing no Restricted. Left **(a, b)** for Case 1. Right **(a, b)** for Case 1.

Based on the preliminary diagnosis of meningo-encephalitis, acyclovir therapy was initiated empirically, which improved neurological symptoms. His fever was cut off and the meningeal symptoms disappeared. Following treatment, tests were reported as normal.

Discussion

In a study, EBV has introduced as a contributing factor in 3.6% of the 2357 cases of meningitis or encephalitis residing in New York.[2] Another study in 2011 revealed that encephalitis associated with EBV infection was shown in 2-9.7% of children hospitalized with encephalitis.[3] As well, EBV was found as a causative agent in 2 to 5% of all viral encephalitis and meningitis cases.[1] Accordingly, the incidence of EBV encephalitis is less than 0.5%, but it may be increased to 7.3% among whose are hospitalized with IM.[4] There are other several case reports of EBV encephalitis, as reported a 6-year-old girl with a 5-day decrease in consciousness and activity, and no significant physical examination, but there was a neurological examination of decreased verbal and stimulatory responses, and in PCR analysis of the CSF, the presence of EBV, Herpes Simplex 1 was reported.[5]

The pathogenesis of EBV encephalitis is not fully understood and is consistent with direct infectious mechanisms, besides indirect immune-mediated reactions.[6-8] By the way, our patients presented a direct invasion of EBV to the CNS as well-defined by a positive PCR in the CSF.

For diagnosis of any acute illness of uncertain etiology, EBV should be considered.[9] As, MRI results is normal in up to 40% of cases,[8] about the other brain dysfunctions, MRI in our case study showed no abnormality. Relatively normal MRIs from these two reports suggested that the disease has been in the early stages of its progress or related to a probable lack of sensitivity of standard MRI imaging. Perhaps the MR

lesions may vanish in a short interval of the disease period. Our brain MRI and scan findings did not reveal any evidence of brain damage. Nonetheless, these findings are contradictory to Ono et al.[9] and Hashemian et al.[5] PCR analysis of CSF for EBV encephalitis possess a very high diagnostic sensitivity (approximating 80-100%). It also provides to screen the effectiveness of antiviral therapy in these patients. Our positive CSF PCR results presented EBV infection of the CNS.

Conclusion

The definite treatment of EBV encephalitis is debatable, because the existing evidences are relay on present case reports. The role and effectiveness of antiviral therapy is vague, and EBV infection is self-limiting. Prior reports suggest that antiviral agents such as acyclovir, ganciclovir, and some others have *in vitro* activity against the lytic phase of EBV infection. There are not any completely approved antiviral drugs for the absolute treatment of EBV. Acyclovir possibly will lessen viral replication; however, its clinical profits have not been well established.

Considering the clinical symptoms and according to a great number of past clinical experiences, both of our cases got under antiviral therapy with acyclovir from the beginning, until the results of the tests were prepared and diagnosis became evident. Consequent acyclovir therapy, neurological symptoms improved and the patients' fever was resolved to normal.[7] In the context of an infectious encephalitis, at least 21 days' treatment with intravenous appropriate dose of acyclovir is necessary for the PCR-confirmed cases of viral meningoencephalitis. The first case was started on antiviral therapy acyclovir 10 mg/kg intravenously (IV) every 8 hours for 21 days and her symptoms started resolving day-by-day. Since, our second case had kidney stones, he was treated with oral acyclovir (800 mg, 5 times per day). In conclusion, every therapeutic effort should be made and keep on attentive to EBV infection even after encountered with any negative test results.

Conflict of Interest

The authors declare no conflicts of interest.

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