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Case Report

A Case of Recurrent EBV Meningoencephalitis in a 56-Year-Old Man

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Abstract

Epstain-Barr virus (EBV) is a probably the most ubiquitous human virus, infecting 90-95% of the population worldwide. Primary EBV infection is usually asymptomatic and self-resolved when occurring in childhood. Yet neurological involvement of this virus is reported, usually in immunocompromised patients. We describe a case of immunocompetent 56-year-old male with relapsing EBV meningoencephalitis. He presented to the hospital with a 5-days history of flu-like symptoms. Neurological examination revealed obnubilation, bradypsychia and signs of meningeal irritation. Blood analysis showed mild inflammatory changes. Cerebro-spinal fluid (CSF) changes were consistent with those of aseptic meningoencephalitis – lymphocytic pleocytosis and hyperproteinorachia. PCR CSF viral and bacterial panel failed to provide a conclusive diagnosis. The patient was treated empirically with antibiotics, pathogenetically and symptomatically as well. He was discharged after a 15-days hospital stay in an improved condition. Two days later he was re-hospitalized with worsening of previous symptoms and development of new neurological disorders – unsteady gait and right hemiparesis. An acute cerebral-vascular incident was ruled out. The diagnosis of EBV meningoencephalitis was confirmed with evidence of EBV DNA in CSF by PCR. Serological blood tests with ELISA were positive for VCA IgG and negative for VCA IgM. This result is consistent with a reactivation of latent EBV infection. The patient was tested for immunodeficiency with negative results. He was treated with intravenous Aciclovir with good result.

Keywords: Recurrent EBV Meningoencephalitis; Immunocompetent Man

Introduction

Epstein-Barr virus (EBV) - a member of the gamma-herpes virus subgroup of the Herpesviridae family – is a probably the most ubiquitous human virus, infecting 90-95% of the population worldwide [1]. Primary EBV infection is usually asymptomatic when occurring in childhood, but it induces infectious mononucleosis in adolescence or adulthood [2]. Identified in 1964 in Burkitt lymphoma tissue, EBV is the first infectious agent linked to cancer [3]. EBV occurs in humans only. The transmission occurs predominantly through exposure to infect saliva as a result of kissing, stem cell transplantation, solid organ transplant and less

commonly through sexual contact [4]. After recovery from an acute infection the virus establishes a long-term latent infection in B-cell lymphocytes with possible recurrent reactivations [5]. The key to the establishment of latency in B-cells is the virus ability to induce continuous growth and cell transformation. This property also implies that this pathogen is a potent oncogenic virus [6]. EBV can be associated with B-cell lymphomas such as Hodgkin's and Burkit's lymphoma as well as lymphoproliferative disorders observed in the context of immunodeficiency and particularly in the context of transplantation [7]. Depending on age and immune status EBV neurologic manifestations may occur in up to 18% of patients [8]. EBV neurological manifestations include encephalitis, meningitis, cerebellitis, Guillain-Barre syndrome, transverse myelitis, cranial and peripheral nerve palsy, acute disseminated encephalomyelitis [9]. Encephalitis (E) and meningoencephalitis (ME) are the most common presentations both in children and adults. They can lead to significant, long-term neurological consequences in about 29% even death in about 15,5% of patients. Despite its scarcity EBV encephalitis is described as the third etiology of herpes virus encephalitis and the seventh etiology of infectious encephalitis [6].

EBV DNA is often found in central nervous system (CNS) of immunocompromised patients. Their serology is consistent with reactivation of latent EBV infection [10]. In rare cases reactivation may occur in immunocompetent people and cause neurological diseases [11].

The molecular mechanisms involved in EBV-associated CNS infection (EBV CNS infection) have not been clarified and contrary to other herpes viruses such as Herpes simplex and Varicella-Zoster, there is no evidence that EBV establishes latency in neurons. But EBV infected cells, free virus and gene products can be found in the CNS [12]. Studies have shown that EBV can infect neurons directly (hematogenous or retrograde invasion via nerves) or indirectly via infected B-lymphocytes, induce neuroinflammation and demyelination, promote proliferation, degeneration and necrosis of glial cells, promote proliferative disorders of B and T-lymphocytes and contribute to the occurrence and development of nervous system diseases. The EBV infection may activate T-cells that are cross-reactive with CNS antigens, subsequently inducing an autoimmune response. Anti-neuronal antibodies to myeline oligodendrocyte glycoprotein are identified [11].

Case Presentation

MDM was a 56-year-old male who presented to the Clinic of Infectious diseases of University multiprofile hospital for active treatment with a 5 days history of flu-like illness – fever 38 C, headache, vomiting. He was treated as an outpatient symptomatically. On admission he complained of a progressively worsening headache, photophobia, dizziness and drowsiness. His past medical history included hypertension, class II obesity. The patient was admitted in a general bad condition and subfebrile. Lethargy, obnubilation, bradypsychia and bradylalia were demonstrated. Pulmonary and cardiovascular exams were as follows: respiratory rate – 18/min; oxygen saturation 96% on room air; heart rate 88/min; blood pressure 150/90 mm Hg. The neurological examination revealed signs of meningeal irritation – neck stiffness, bilateral positive Kernig's sign and positive Brudzinski's neck sign, brisk tendon and periosteal reflexes. Chest X-ray and ECG revealed no abnormalities. Abdominal ultrasound revealed hepatic steatosis. Blood tests showed leucocyte count up to $15{,}6.10^9$/L, with left shift – up to 80,9% neutrophils and elevated CRP – 69,6 mg/L. There were no hemostatic disorders and anemia. Renal and liver function tests were unremarkable. Cerebro spinal fluid (CSF) changes were consistent with those of aseptic meningoencephalitis – lymphocytic pleocytosis and hyperproteinorachia. Based on clinical presentation and laboratory findings a provisional diagnosis of aseptic ME was considered.

Three lumbar punctures (LPs) were performed and the results were shown in the table 1.

Indicator Date/	Leuc .106/L	Ly%	Alb g/L	Gluc mmol/L	Chl mmol/L	Pandy	K mE/L	Na mE/L
I-st admission 15.11.25	780	91	0,96	3,36	107	+	2,5	133
19.11.25	800	99	0,76	3,85	117	-	2,6	145
28.11.25	92	90	0,68	4,73	116	-/+	3,1	138

Re-admission 02.12.25	303	100	0,78	2,65	115	+/--	2,7	140
09.12.25	115	/	0,57	5,04	123	+/--	3,1	138
13.12.25	53	68	0,5	4,19	117	-	3,2	144

Table 1: Laboratory changes in cerebrospinal fluid.

RevoDx Meningitis/Encephalitis Pathogen Plus Detection Kit – a real time PCR test intended for the qualitative detection and identification of the specific bacterial, viral and fungal pathogens from CSF was performed. The panel included 17 most common infectious agents. The results were negative for all the three samples (Table 2). The patient's clinical symptoms gradually improved. Meningeal signs were reduced on the 4-th day, the headache and fever – on the 6-th day. CSF lymphocytic pleocytosis tended to reduce notably, hyperproteinorachia relatively slow. Magnetic resonance imaging (MRI) showed evidence of moderate cerebral edema and inflammatory changes characteristic of meningoencephalitis (Figure 1,2). The patient's diagnostic work-up failed to identify the causative agent. He was treated as follows: antibacterials - Ceftriaxone for 9 days; corticoids - Dexamethasone with reducing doses for all hospital stay; diuretics – Mannitol and Furosemide for 5 days; bioproducts - Humman albumin for 3 days; symptomatic remedies.

Etiologic agents	**Results I admission**	**Results re-admission**
Herpes simplex virus type 2	Negative /-/	Negative /-/
Human herpes virus 6	Negative /-/	Negative /-/
Human herpes virus 7	Negative /-/	Negative /-/
Ebstein-Barr virus	Negative /-/	Positive /+/
Cytomegalovirus(CMV)	Negative /-/	Negative /-/
Varicella-zoster virus (VZV)	Negative /-/	Negative /-/
Enterovirus	Negative /-/	Negative /-/
Human parechovirus	Negative /-/	Negative /-/
Mumps virus	Negative /-/	Negative /-/
Listeria monocytogenes	Negative /-/	Negative /-/
Neisseria meningitidis	Negative /-/	Negative /-/
Streptococcus pneumoniae	Negative /-/	Negative /-/
Haemophilus influenzae	Negative /-/	Negative /-/
Escherichia coli K1	Negative /-/	Negative /-/
Streptococcus agalactiae	Negative /-/	Negative /-/
Cryptococcus neoformans/ gattii	Negative /-/	Negative /-/
Mycobacterium tuberculosis	Negative /-/	Negative /-/

Table 2: Data from the 17-component CSF examination panel at the patient's first and second hospitalization.

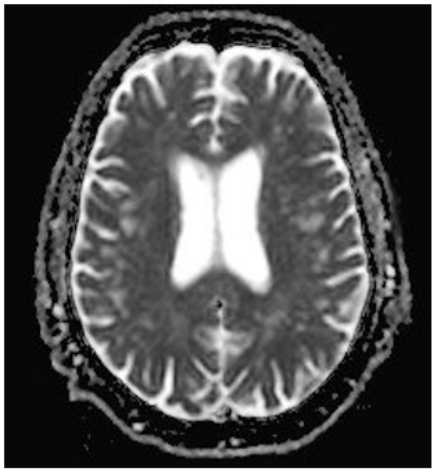

Figure 1: MRI brain axial. Bilateral subcortical white matter hyperintensities.

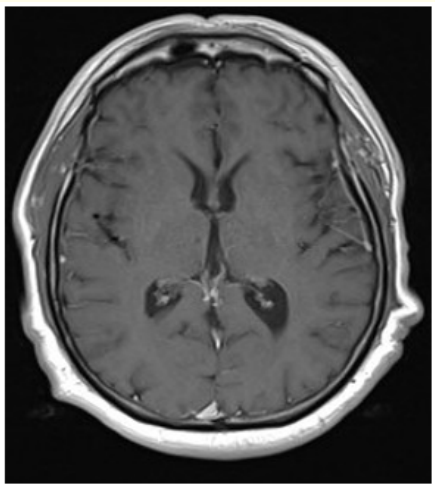

Figure 2: MRI brain axial. A cervical myelon hyperintensity.

MDM was discharged after 15 days hospital stay with a diagnosis of aseptic ME. He was in an improved general condition and declared no complaints. CSF findings were not within normal ranges but also improved.

Two days later MDM presented to the clinic of Infectious diseases again. He complained of an extreme asthenia, headache, fever, weakness in his right limbs and inability to walk. On readmission he was febrile – 38,2℃ and demonstrated right hemiparesis and signs of meningeal irritation – neck stiffness and bilateral positive Kernig's sign. Considering that an acute neurological consultation and brain imaging - CT scan was made. A medical emergency – transient ischemia attack of stroke was ruled out. The patient controlled pelvic tanks.

MRI imaging natively and with contrast - Gadobutrol (Gadovist) revealed a heterogenous topography of brain damage (Figure 3,4 and 5). Repeated blood tests revealed mild leucocytosis – up to 14,9.109/L with a left shift – up to 85,1% neutrophils. Three more LPs were performed and CSF analysis again showed changes consistent with aseptic ME. This time Multiplex PCR panel for viral, bacterial and fungal pathogens was positive for EBV DNA in all three samples. Serological blood testing with ELISA was positive for EBV viral capsid antigen (VCA) IgG and negative for VCA IgM. This result was consisted with reactivated latent EBV infection. No matter that in this medical history there is no data presuming immunodeficiency the patient underwent 2 HIV tests with ELISA and 1 with Western blot following nationally validated testing algorithm. All results were negative. The levels of 4 classes immunoglobulins (G, A, M, E) were within normal ranges.

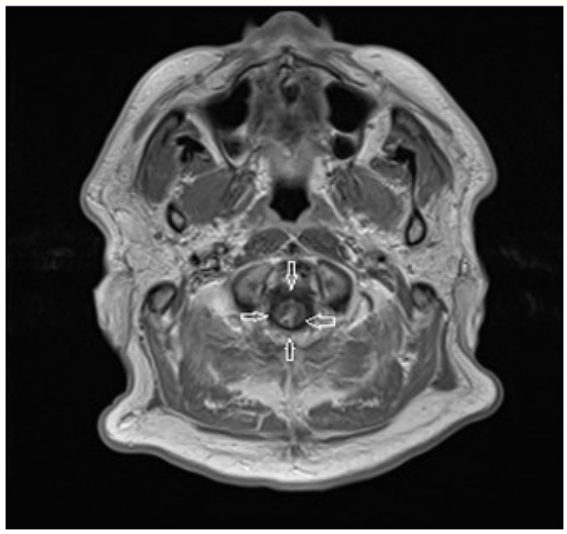

Figure 3: MRI axial. Increased signal intensity temporo-parietally in dura mater area.

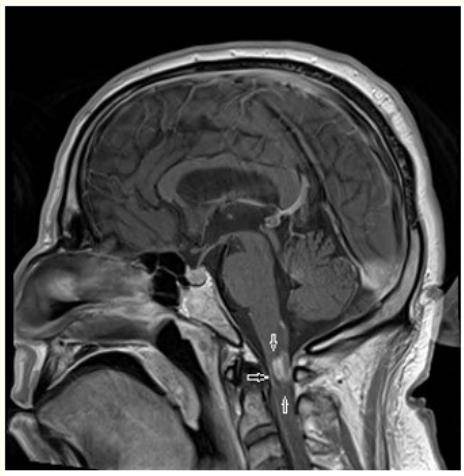

Figure 4: MRI sagittal. Post-contrast images. Heter-intense lesions in the cervical myelon with characteristics of intramedullary abscesses and increased signal intensity of the medulla oblongata.

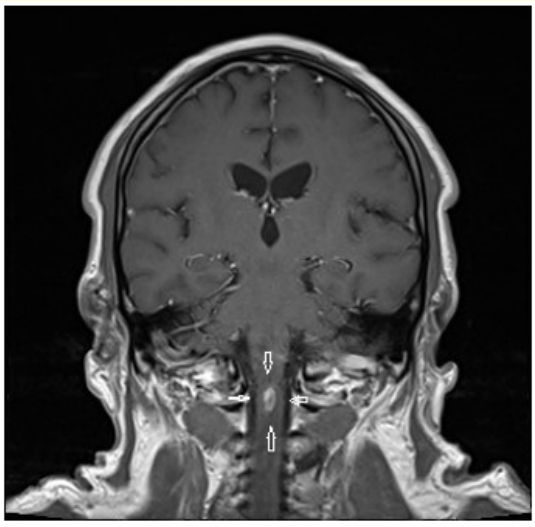

Figure 5: MRI frontal. Heter intense lesions in cervical myelon with characteristics of intramedullary abscesses.

The patient's treatment was started with intravenous (IV) Aciclovir. An antifungal antibiotic was added to the therapy. Anti-edematous, corticosteroid and symptomatic agents were again included. This time meningeal signs persisted for 3 days, fever and intermittent headache – for 10 days. Right hemiparesis regressed to monoparesis on the upper limb and the patient was able to walk. He requested for discharge and left the clinic after a 14 days hospital stay.

At 4 weeks follow-up visit he was in a general good condition, afebrile with steady gait and slight monoparesis on the right upper limb. He had discontinued the treatment against medical advice.

Discussion

The limited number of publications on EBV CNS infections mainly reports isolated clinical cases. A review of case reports made by Peuchmaur M., *et al*. aimed to summarize published data on EBV encephalitis. According to this study the majority of cases with EBV-related neurological disorders involved encephalitis – 64,42%, sometimes associated with meningitis as it was in our patient. There was a mild prevalence of males – 58%. 45% of subjects were between 20 and 60 years of age [6] – which was the same age group of our patient – a 56-year-old male.

The most common general symptoms cited in the literature are non-specific – headache and/or fever in 83% and digestive disorders in 40%. The most frequently observed neurological disorders are confusion in 35%, cerebellar syndrome in 30%, generalized tonic-clonic seizures in 26%, meningeal signs in 16% [6].

In our case the patient presented with fever, headache, vomiting, obnubilation, signs of meningeal irritation. He demonstrated some symptoms cited as less common – notable asthenia in 14% cited, irritability and anhedonia – in 12% cited [6].

Seizures were not observed. On readmission our patient manifested unsteady gait and inability to walk. Neurological examination revealed right hemiparesis. It was a diagnostic dilemma as cerebellar syndrome is one of the most observed neurological disorders – in 30%, leading to unsteady gait. In the same time right hemiparesis is most common a result of an acute neurovascular disease. Neurological consultation and neuroimaging – CT scan – ruled out such medical emergency.

Blood analysis most frequently reveals normal or low leucocyte count. CRP is within normal range or with mild elevation. Mild leucocytosis is observed in 37% [6].

Blood tests of our patient showed mild leucocytosis with left shift and a mild elevation of CRP. CSF changes cited in literature demonstrates lymphocytic pleocytosis with a median value 47/ mm^3in 83% of cases and a moderate hyperproteinorachia with a median value 0,87g/L in 82% [13]. In our case, these changes were more demonstrative, especially with regard to pleocytosis, and tended to decrease slowly with fluctuations. They were improved but not within normal ranges even on discharge.

MRI imaging is preferred for evaluating the extend of involvement and monitoring therapy response. When MRI is performed encephalitis related abnormalities are found in 69% of patients. In 41% the abnormalities affect multiple anatomical regions. Some of them are mentioned more frequently such as the cerebellum, basal ganglia, frontal lobe. No localization is specific for EBV encephalitis [6]. There are discrepancies between the CT scans and MRI scans in more than half of cases. This highlights the necessity of performing a brain MRI scan for patients presenting with EBV ME [6].

The diagnosis EBV CNS infection is confirmed with evidence of EBV DNA in CSF by PCR [14].

The EBV PCR tests are positive in 87% of the CSF samples with wide ranging viral loads. When encephalitis occurs in the context of past EBV infection all the EBV PCR tests on CSF samples are positive [6]. On the contrary negative EBV PCR tests on CSF samples occur only in the context of primary infections.

Our patient did not benefit from EBV PCR tests on CSF samples during the first hospitalization. Blood serological test for EBV VCA was not made. During the second hospitalization his CSF samples were positive for EBV DNA. Blood serological test with ELISA was positive for VCA IgG and negative for IgM. This results consistent with reactivated past EBV infection. We discussed the hypothesis that an unidentified agent causing aseptic ME triggered reactivation of latent EBV infection. If reactivation occurs in the circulation the disrupted blood CSF barrier may allow free virus into the CSF [15].

Considering clinical course, we presume that our patient developed a relapse of the disease. After an initial improvement in clinical signs and laboratory CSF changes, he demonstrated a worsening of previous symptoms and developing new neurological disorders. Stone JA., *et al*. describe a similar case of relapsing EBV ME in a renal transplant recipient [16].

Patients living with HIV/AIDS are at a great risk of developing CNS infections. Saikawa H., *et al*. find out that among the 20% of immunocompromised cases, six are HIV positive [17].

MDM underwent a series of tests to establish his immune status. He was immunocompetent. 29% of cases with benefit from medium or long-term follow-up experience different types of disabilities. Among those presenting with sequelae their type and intensity vary.

Most frequently it is cognitive, sensory, diplopia or psychomotor retardation. The causes of death are generally linked to complications occurring in the context of coma, tetraplegia, multisystem organ failure, edema and brain hemorrhage. Mortality is observed in 15,5% of all cases [6]. Our patient was discharged in an improved condition, not fully recovered but without complications.

There are no clear guidelines for treatment of EBV ME. The mainstay of therapy is supportive care. The role of antivirals and corticosteroids is controversial. There are growing reports that patients receiving Acyclovir presented a positive evolution [18].

Corticosteroids are commonly administered to reduce inflammation. Our patient was treated with intravenous Acyclovir when the diagnosis of EBV ME was confirmed with a good result.

Conclusion

EBV ME is a relatively rare severe neurological complication of EBV infection. It is mainly seen in immunocompromised cases but should be considered in immunocompetent as well. At present the detection of EBV DNA in CSF and serum treatment is a common standard for confirming the diagnosis.

Clinical manifestations are not specific and the diagnosis can be challenging. Neuroimaging studies – CT scan and MRI as a diagnostic modality contribute to the exact diagnose. The early recognition and properly treatment are crucial for a good prognosis. The patient receiving Aciclovir present a positive evolution.

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