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Neurological Complications Diseases of Epstein-Barr virus

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Abstract

Epstein-Barr virus infection results in a spectrum of diseases, with the host immune response playing a key role in shaping the clinical manifestations. Infectious mononucleosis is the prototype EBV infection and is characterized by fever, sore throat, cervical and generalized lymphadenopathy, hepatosplenomegaly, and somatic complaints of fatigue and malaise. This condition generally is a benign, self-limited illness in healthy persons. In this article, the term "infectious mononucleosis" refers to the disease caused by primary EBV infection, although other agents can cause "infectious mononucleosis-like" disorders that are clinically similar to the EBV-associated disease.

Keywords: Meningoencephalitis; Alzheimer's disease; Parkinson's disease

Implications for Practice

Epstein-Barr virus (EBV) infection is common in children and usually resolves spontaneously. The most common clinical manifestations of EBV infection include infectious mononucleosis, prolonged fever, lymphadenopathy, exudative tonsillopharyngitis, otitis media, and diarrhoea. Although extremely rare, EBV may also cause central nervous system (CNS) involvement such as demyelinating disease, acute encephalitis, meningitis, meningoencephalitis, myelitis, polyradiculitis, polyradiculomyelitis, cranial or peripheral nerve palsies, and acute cerebellar ataxia. In addition, EBV-related severe organ damages are usually seen in immune compromised patients. Epstein-Barr virus (EBV) was found as a causative agent in 2 to 5% of viral encephalitis and meningitis cases. In EBV encephalitis, patients may present with fever, headache, stiff neck, altered mental status, irritability, lethargy, and, rarely, a comatose state. Epstein-Barr virus should be considered as a possible causative agent for any child with acute encephalitis, as clinical findings of EBV encephalitis are usually nonspecific. In the diagnosis of EBV encephalitis, EBV antibodies and nucleic acid amplification tests in blood or cerebrospinal fluid and cranial imaging studies can be useful [1].

EBV And Alzheimer's disease

Alzheimer's disease (AD) is a multifactorial, common, complex, and severe neurodegenerative disorder that primarily affects older adults and is characterized by progressive cognitive decline accompanied by a decline in motor function [2]. The main pathological hallmarks are the aggregation of amyloid-beta peptides forming extracellular plaques and aggregation of hyper phosphorylated forming intracellular neurofibrillary tangles with neuroinflammation, gliosis, and neurodegeneration Researchers have found that different viruses may involve different pathways and have varying distributions in different brain regions, and infection-related

EBV and Brain Tumors

EBV is an oncogenic virus that is closely associated with the development of various malignancies, including various brain tumors, such as primary CNS lymphoma (PCNSL) and glioma. EBV-encoded viral proteins and non-coding RNAs can promote tumor cell proliferation, differentiation, invasion, metastasis, immune escape, and anti-apoptosis [3].

EBV In Encephalitis and Meningitis

Encephalitis includes viral encephalitis and viral meningitis. Viral encephalitis is primary encephalitis caused by direct viral invasion of the brain parenchyma. The main clinical manifestations are brain parenchymal damage and intracranial hypertension. Viral meningitis is a diffuse inflammatory syndrome of the pia mater and arachnoid caused by various viral infections. Acute onset is more common, with clinical manifestations including fever, headache, vomiting, and signs of meningeal irritation. Aseptic meningitis is known to be closely associated with encephalitis, but its exact pathogenesis is unclear [4]. The diagnosis is based on EBV heterologous IgM antibody tests, seropositivity of IgM for viral capsid antigens, and/or positive CSF PCR and imaging studies.

EBV And Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease that can involve white matter and, in rare cases, gray matter lesions in acute or sub-acute states. It is common in children and is characterized by demyelinated lesions throughout the brain and spinal cord, and can even involve the basal ganglia, thalamus, and brainstem. The clinical features include acute onset, multifocal neurological deficits with a monophasic course, and a typical clinical course of rapid neurological deterioration over several days [5]. Most patients have viral prodromal symptoms followed by the development of focal neurological deficits and a good prognosis after symptomatic treatment, although some cases experience severe complications and mortality

EBV and Parkinson's disease

Parkinson's disease (PD) is another common neurodegenerative disorder of aging caused by a combination of genetic and underlying environmental factors. The main pathological features of PD are degeneration of nigrostriatal dopaminergic neurons, reduction of striatal dopamine, and the formation of abnormal protein aggregates in neurons, such as Lewy vesicles. The aging nervous system is

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susceptible to the direct and indirect effects of infection, and bacterial or viral infections are considered a potential risk factor. Predominantly lymphocytic leukocytosis, mildly increased protein levels, and EBV antibodies in the CSF and serum of patients with PD suggest the involvement of EBV infection in the development of PD [6].

Discussion

Encephalitis, which is a histopathological definition of inflammation of the brain parenchyma, is a severe and fatal disease of the central nervous system. However, EBV rarely causes encephalitis in immune compromised patients, in particular. In this paper, we describe a case of EBV encephalitis in an immunocompetent child, presenting with typical symptoms of viral encephalitis, such as fever, headache, and altered mental status. The pathogenesis of EBV encephalitis is still unclear. Neurological complications usually occur concurrently with typical manifestations of infectious mononucleosis; however, they may also present during the resolution phase of infection. The possible mechanisms are described as direct viral invasion to brain parenchyma, the infiltration of cytotoxic T-lymphocytes into the neural tissue, and antibody-antigen complex deposition in neural structures. In addition, EBV may induce CNS involvement, such as demyelinating disease, acute encephalitis, meningitis, myelitis, polyradiculitis, polyradiculomyelitis, and cranial nerve palsies. Sumaya demonstrated that EBV was a causative agent in 3.6% of cases of 2357 patients living in New York who were diagnosed with meningitis or encephalitis [7].

Although the definite treatment of EBV encephalitis is controversial, previous reports suggested that acyclovir and corticosteroids therapies might be reasonable. Although several reports have demonstrated that antiviral agents including acyclovir, valganciclovir, ganciclovir, and cidofovir have in vitro activity against the lytic phase of EBV infections, no antiviral agents are approved for the treatment of EBV infections. Acyclovir may reduce viral replication and nasopharyngeal virus shedding; however, its clinical benefits still remain to be elucidated. In this case, acyclovir therapy was given for 14 days. Although the prognosis of EBV encephalitis is usually good in the majority of cases (85%), it can be fatal in some patients.

In our patient, acyclovir therapy was initiated empirically and it was then continued to manage severe neurological symptoms, even after EBV diagnosis was made. Some reports suggested the use of antivirals for severe EBV infection, which might be beneficial. In a study including 45 patients who had severe manifestations of EBV infection including CNS and peripheral nervous system involvement, thrombocytopenia, aplastic anemia, acute renal failure, and myocarditis, the patients received antiviral therapy; 39 of them had a favorable outcome, while six patients died. In this study, acyclovir was the most commonly given antiviral regimen, as monotherapy in 35 patients.

Conclusion

Unfortunately, the pathogenesis of EBV in CNS disease is not fully understood, and there are few effective treatments. Some studies have reported that cimetidine can treat patients with chronic EBV reactivation, but its efficacy has not been confirmed in neurological disorders (Kerr, 2019). In addition, antiretroviral drugs have been reported to induce long-term remission in MS, but the exact mechanism is not known. Further, valpromide, an amide derivative of valproic acid, inhibits the expression of BRLF1 and BZLF1 and, therefore, can inhibit some of the viral and cellular genes involved in EBV lysis infection, but there are few related studies and further validation is needed. For cases of direct viral attack with or without a secondary immune response, antiviral therapy has the potential to delay disease progression and its combination with intravenous immunoglobulin therapy may enhance the treatment efficacy. Notably, exosomes are small extracellular vesicles with a diameter of 30–100 nm and include carrying proteins, nucleic acids, and lipids that mediate cell-to-cell signaling to regulate various functions of the host cell. Exosomes can serve as ideal carriers for the delivery of protein- or RNA-based therapeutic drugs to the brain and are potentially valuable biomarkers for the clinical diagnosis and treatment of diseases. EBV can use exosomes containing viral proteins and various RNAs to cross the BBB, enter target cells through the exosome surface membrane proteins, bind to target cell surface proteins, transfer its cargo to the target cells, affect the signalling pathways of the target cells, trigger various responses in the target cells, and participate in the development of the CNS. However, studies on this topic are limited.

In general, EBV can enter the body via direct infection or indirectly via B-cell invasion, enter the CNS by regulating the function of B- or T-lymphocytes, and cause neuro inflammation and immune disorders, finally leading to the development of nervous system diseases. However, the molecular and pathogenic mechanisms underlying EBV infection need to be further investigated, and research in this area will be beneficial in providing better strategies for the diagnosis and treatment of EBV-related neurological diseases.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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