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Acute disseminated encephalomyelitis associated with hepatitis B virus reinfection – Consequence or coincidence?

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\textbf{A B S T R A C T}

Acute disseminated encephalomyelitis (ADEM) is an idiopathic inflammatory demyelinating disease of the CNS that is particularly difficult to differentiate from the first episode of multiple sclerosis. ADEM typically occurs as a post-infectious phenomenon, and usually presents as a monophasic episode, but also includes recurrent and multiphasic forms. We report a case of ADEM associated with hepatitis B virus (HBV) reinfection. After steroid and IV immunoglobulin treatment, neurologic symptoms were improved. We suppose that the HBV reinfection was the cause of ADEM, but possible pathogenetic mechanism is still obscure.

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1. Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory demyelinating disease of the CNS which typically follows acute viral or bacterial infection or vaccination. Numerous infectious agents, have been linked to ADEM. Viruses that have been implicated include coronavirus, coxsackie virus, cytomegalovirus, Epstein–Barr virus, herpes simplex virus, hepatitis A virus, human immunodeficiency virus, influenza virus, measles virus, rubella virus, varicella zoster virus, and West Nile virus [1–3]. Other organisms associated include \textit{Borrelia burgdorferi}, \textit{Chlamydia}, \textit{Leptospira}, \textit{Mycoplasma pneumoniae}, \textit{Rickettsia}, and \textit{beta-hemolytic Streptococcus}. Less than 5\% of all ADEM cases follow immunization. Postvaccinal ADEM has been associated with immunization for rabies, hepatitis B, influenza, Japanese B encephalitis, diphtheria/pertussis/tetanus, measles, mumps, rubella, pneumococcus, polio, smallpox, and varicella [4].

ADEM is usually considered a monophasic disease, but spectrum of postinfectious encephalomyelitis also includes recurrent and multiphasic forms of disseminated encephalomyelitis (DEM) [5]. When the same functional neurological systems are involved, characterizing a stereotypic recurrent neurological deficit identical of the first demyelinating event, it is denominated recurrent encephalomyelitis (RDEM) [6,7]. Multiphasic DEM (MDEM) describes recurrent disease that fulfills criteria for ADEM but involves new anatomic areas of the CNS upon recurrence. Symptoms and signs are different from those in the initial event. The MRI must show new lesions not present during the first attack and demonstrate complete or partial resolution of the lesions associated with the first ADEM episode.

Post-infectious ADEM compose one of the several categories of inflammatory demyelinating disorders (IDD) of the CNS. Recurrent DEM (RDEM) refers to the recurrence, 3 or more months after the first ADEM event, of the same symptoms that occurred at the time of the initial presentation. The MRI findings are similar to those seen at the initial event and are without new lesions, although there may be enlargement of the original lesions.

The diagnosis of ADEM is based on clinical and radiological features [1]. There is no specific biological marker or confirmatory test. ADEM is characterized by multifocal neurologic abnormalities with encephalopathy (e.g., confusion, excessive irritability, or an altered level of consciousness). Widespread deep and subcortical white-matter lesions and gray-matter lesions such as thalami and basal ganglia on magnetic resonance imaging (MRI) are associated with ADEM.

Hepatitis virus is a rare cause of ADEM. Two case of hepatitis C virus (HCV) and two cases of hepatitis A virus with ADEM have been reported [8–11].

We report the case of a 52-year-old woman who developed ADEM during hepatitis B virus (HBV) reinfection. Her previous history of subclinical hepatitis B dated back several years ago.

This is the first case of ADEM with HBV infection.

2. Case report

A 52-year-old woman experienced the first attack of CNS demyelinating disease in May 2011. Her presenting symptoms were loss of sensation of left-sided facial, slurred speech and
memory problems particularly poor concentration; all of which dated back 7 days before hospitalization. On neurologic examination she had a left-sided facial supranuclear paresis with hypoaesthesia in distribution of II and III trigeminal branches and dysarthria. Brain MRI showed three enhancing right-sided lesions size of 14, 18 and 21 mm – one lesion was located in frontal subcortical region and two lesions were located in periventricular occipital region. All lesions showed strong contrast enhancement. MRI of the C spinal cord was normal. The CSF analysis showed elevated total protein (66 mg/dL) without pleocytosis, and more oligoclonal bands, some of which were present in serum. Serologic analysis for HBV showed negative HBs-Ag with increased HBs-Ab and HBc-Ab titers. Other laboratory testing for specific and non-inflammatory demyelinating diseases were normal or negative. After extensive workup, she was diagnosed with probable ADEM. Treatment with high-dose methylprednisolone over 5 days resulted in a marked improvement with regression of symptoms.

After 3 months, in August 2011 she was hospitalized again because of the second clinical presentation in terms weakness of the right arm. On neurologic examination she had a mild paresis in the right arm.

Repeated MRI showed a new enhancing lesion in the left frontoparietal region diameter of 15 mm. MRI of the C spinal cord remained normal. This time, her serum showed high transaminase levels and positive HBs-Ag. PCR DNA analysis has not confirmed viremia, but the result of liver biopsy was active chronic hepatitis. After the second clinical presentation and repeated workup, she was diagnosed with relapsing ADEM and received a 5-day course of IV immunoglobulin after which she stabilized and made substantial recovery.

After following 8 months of clinical and imaging follow-up (without further treatment), she has been stable clinically and radiologically, no additional relapses occurred (Figs. 1–3).

3. Discussion

The pathogenetic mechanism of ADEM is still obscure. Possibly, a T cell mediated autoimmune response to myelin basic protein, triggered by an infection or vaccination, underlies its pathogenesis [12,13]. A number of infectious agents, mainly viruses, have been shown to be associated with ADEM, including coronavirus, coxsackie virus B, Epstein–Barr virus, herpes simplex virus,
human herpes virus 6, measles, mumps, rubella, Borrelia burgdorferi, chlamydia, legionella, and Mycoplasma pneumoniae [14]. ADEM associated with HCV has been reported before [9], and recently Sim et al. report a case of ADEM associated with hepatitis C virus (HCV) infection with positive serum and cerebrospinal fluid (CSF) anti-HCV antibody [15]. In a case of acute transverse myelitis associated with chronic HCV infection, anti-HCV antibody was present in the CSF [16]. It is hypothesized that the virus might have penetrated blood brain barrier and involved the CNS directly. Likewise, patients with HBV infection should be examined carefully for CNS symptoms during follow up.

In our case, after the second clinical presentation that followed three months of the initial event with new symptoms and new active demyelinating lesion, this patient was diagnosed as “recurr-ent ADEM” whose probable causative trigger is hepatitis B virus re-инфекция. Although the PCR DNA analysis has not confirmed viremia, liver biopsy showed the active chronic hepatitis, which indicates the possibility of inoculation of the virus in hepatocytes and probable reinfection. This case shows that HBV infection can be associated with ADEM, so the possibility of HBV infection should be investigated in cases of ADEM. We suppose that virus-triggered autoimmunity or direct viral invasion played a role in the genesis of ADEM. Molecular mimicry between HB antigen(s) and one or more myelin proteins, or a non-specific activation of autoactive lymphocytes, could constitute possible pathogenetic mechanisms for these adverse neurological events [17].

Distinguishing ADEM from the first attack of MS represents a common diagnostic challenge and has prognostic and therapeutic implications [1,18,19]. Reliable clinical diagnostic criteria for ADEM in adults are still not established. When compared to MS lesions, those of ADEM tend to be larger and more edematous. Contrast enhancement is typical in ADEM and most lesions often enhance simultaneously, underscoring their synchronous course.

Is this case a monophasic or multiphasic form of ADEM – it is questionable?

If it is a multiphasic ADEM, the prognosis is uncertain about the possible future relapses, and therefore differentiation from MS. Some of patients with ADEM may finally develop MS, but it is difficult to accurately predict in which patients this will occur. Therefore, prolonged follow-up is required to establish a diagnosis.

Author’s contribution

Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content and administrative, technical and material support was performed by Lazibat and Brinar.

Conflict of interest statement

There is no conflict of interest.

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