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Case report

Multiphasic disseminated encephalomyelitis associated with herpes virus infection in a patient with TLR3 deficiency

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ABSTRACT

We report a case of a 14-year-old girl that presented headache, amaurosis, drowsiness, fever, vomiting and diffuse reduction of muscle strength. She had been diagnosed with ADEM one year before and had a previous diagnosis of Toll-Like 3 receptor deficiency. Cerebrospinal fluid analysis revealed pleocytosis (28/mm^3, 12/mm^3 red blood cells, 70% lymphocytes cells, 2% monocytes cells, 28% neutrophils), normal total protein (38 pg/mL) and normal glucose level (53/mm^3). Studies for CSF oligoclonal bands and serum anti-MOG were negative but polymerase chain reaction (PCR) testing was positive for herpes virus 1. In the first ADEM episode, PCR for herpes virus was also positive. Magnetic resonance imaging (MRI) of the brain revealed disseminated hyperintense lesions on T2-weighted and FLAIR images in the white matter of frontal, parietal and temporal lobes, corresponding to extensive asymmetric areas of demyelination that produced mass effect and gadolinium enhancement. Electroencephalography demonstrated irregular diffuse and generalized slow-wave activity with predominance in frontal region. The diagnosis of multiphasic disseminated encephalomyelitis (MDEM) triggered by herpes simplex virus was made.

Herpes virus is a neurotropic virus that can cause a wide variety of neurological infection-triggered autoimmune disorders and that is particularly damaging to the central nervous system in situations of impaired immune system. TLR3 is expressed in astrocytes and dendritic cells of the central nervous system and is essential for natural immunity to herpes simplex. TLR3-deficient patients have already been described with herpes simplex encephalitis. TLR3 deficiency may predispose and explain autoimmune and demyelinating manifestations induced by herpes virus. The association of multiphasic disseminated encephalomyelitis triggered by herpes virus in a patient with TLR3 deficiency has not been previously reported in the literature.

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating disorder usually encountered in children or adolescents and characterized by multifocal neurologic deficits of rapid onset. A small but important subset of patients with ADEM can have a relapse, being diagnosed with multiphasic disseminated encephalomyelitis (MDEM). ADEM/MDEM is often preceded by various infectious diseases or vaccination (Dale et al., 2000; Pohl et al., 2016). To our knowledge, this is the first case of MDEM associated with herpes simplex virus in a patient with deficiency of Toll Like 3 receptor in the literature.

2. Case report

The patient was a 14-year-old girl who was admitted to our hospital because of a sudden onset of severe headache, vision loss, drowsiness, fever and vomiting. There was no history of recent infection or vaccination. Neurological examination revealed lethargy, decreased level of consciousness, bilateral amaurosis, exacerbated reflexes and diffuse reduction of muscle strength. There were no cerebellar, extrapyramidal and meningeal signs. General physical examination was normal and the patient was afebrile. On laboratory examination, complete metabolic panel were within normal limits, toxicological screening was negative, and complete blood counts were normal except for a mild leukocytosis

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(12.500/mm^3) and elevated C-reactive protein (4.3 mg/L). Examination of the cerebrospinal fluid (CSF) showed pleocytosis (28/mm^3, 12/mm^3 red blood cells, 70% lymphocytes cells, 2% monocytes cells, 28% neutrophils), normal total protein (38 pg/mL) and normal glucose (53/mm^3). Studies for CSF oligoclonal bands were negative. Anti-aquaporin-4 antibody was negative in both CSF and serum and the IgG index was in the normal range. Polymerase chain reaction (PCR) testing was positive for HSV-1 and negative for Epstein-Barr virus, cytomegalovirus, enterovirus, *Toxoplasma gondii, Escherichia coli, Haemophilus influenzae, Neisseria meningitidis* and *Streptococcus pneumoniae*. Peripheral blood viral load for HSV was $2.9 \times {}^{103}$ copies/mL. CSF fungal smear and culture were also negative. The copy number of CSF sample in which HSV-1 DNA was positive by the real-time PCR assay were 4.2×10^4 genome equivalents per ml. Herpes virus DNA was detected in peripheral blood as well. The serum anti-MOG was negative, using the cell-based assay method.

Magnetic resonance imaging (MRI) of the brain revealed disseminated hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in the white matter of frontal, parietal and temporal lobes, corresponding to extensive areas of demyelination that produced mass effect and gadolinium enhancement (Fig. 1). Lesions also involved the right basal ganglia, centrum semiovale, thalamus and corpus callosum in an asymmetrical manner. Electroencephalography demonstrated irregular, diffuse and generalized slow-wave activity with predominance in the frontal region.

The patient had the previous diagnosis of Toll-Like 3 receptor deficiency that was made due to the investigation of recurrent infections during childhood. Her past medical history was also significant for another demyelinating event characterized by confusion, depressed level of consciousness, tetraparesis and seizures that occurred 1-year before. There were large, bilateral and asymmetric lesions in the frontal and temporal lobes, involving the deep and subcortical white matter. At that moment, the hypothesis of ADEM was suggested and the patient underwent a brain biopsy that confirmed the clinical suspicion. Histology showed perivenular demyelination, gliosis and a striking inflammatory infiltrate of B and T lymphocytes, plasma cells, foamy macrophages, including thick inflammatory cell cuffs around small blood vessels, without fibrinoid necrosis or petechial hemorrhages. On that occasion, CSF PCR and serology were also positive for herpes virus (CSF viral load was 3.9×10^3 genome equivalent per ml). A follow-up brain MRI revealed complete resolution of the lesions six months after the initial ADEM episode. Clinically, the patient recovered from most of the symptoms but remained epileptic, and therefore, was required to take carbamazepine continuously.

The diagnosis of MDEM triggered by herpes simplex virus was made. The patient was initially treated with acyclovir and intravenous steroids and she was referred to the Neurological Intensive Care Unit, where she remained hospitalized for 28 days. Her consciousness level gradually improved and at discharge, most of the neurological symptoms were resolved except for a bilateral amaurosis. During the remission phase, another lumbar puncture was performed and real-time HSV PCR was negative.

After 1 year, the patient remained seizure-free and didn't present any new neurological complaints. She still had low visual acuity (20/60) in both eyes and on neurological examination she had muscle strength grade 4 in right upper and lower limbs, hyperreflexia in all

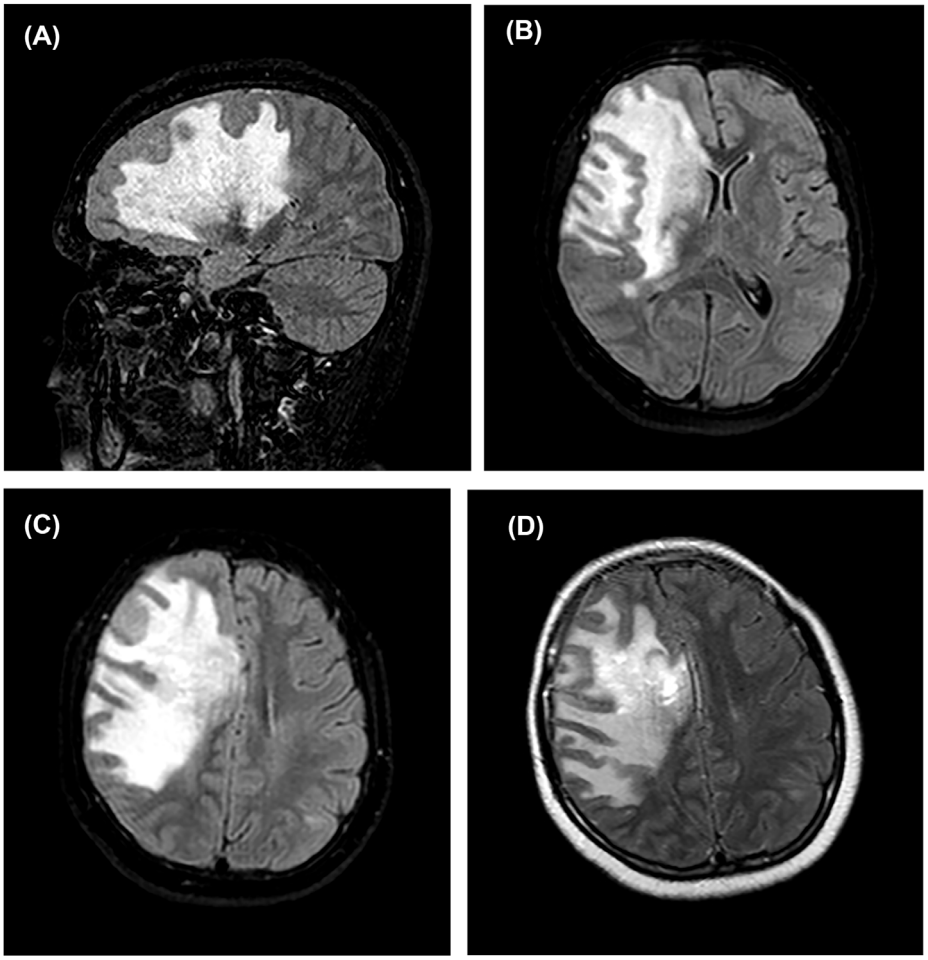

Fig. 1. Non-contrast sagital (A) and axial (B, C) FLAIR MRI showing a diffuse, asymmetric hyperintensity involving supratentorial white matter, thalamus and basal ganglia and producing mass effect. Contrast axial T1-weigthed image (D) showing significant gadolinium enhancement.

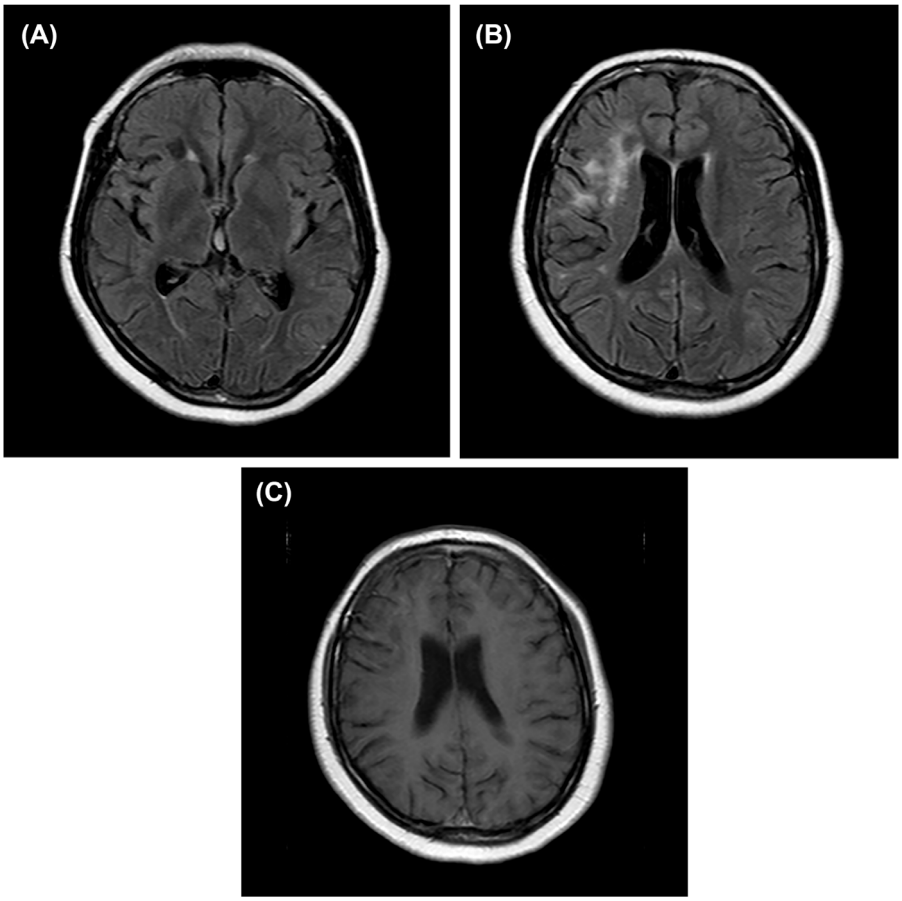

Fig. 2. Non-contrast axial FLAIR (A and B) MRI showing partial resolution of demyelinating lesions, with remaining white matter hyperintensities in frontal and parietal lobes. Axial T1-weighted image showing no gadolinium enhancement (C).

limbs, Hoffman's sign was positive in the right limb and inexhaustible clonus was present in the lower left limb. A follow-up brain MRI revealed partial lesion resolution without evidence of new active lesions (Fig. 2).

3. Discussion

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating central nervous system disorders that is among the most frequent demyelinating syndromes in childhood. Population-based studies show the incidence of ADEM to be 0.3–0.6 per 100,000 per year. ADEM is generally considered a monophasic disease. However, recurrent ADEM has been described and defined as multiphasic disseminated encephalomyelitis (MDEM). Accordingly, a second event is defined as the development of new symptoms more than 3 months after the start of the incident illness (Pohl et al., 2016). MDEM is rarely described in the literature and evidence is extremely poor with respect to the factors associated with the recurrence of ADEM (Bohlega et al., 2008; Honigman et al., 2003).

Features of ADEM/MDEM are quite well delineated. ADEM is clinically characterized by an acute onset of encephalopathy in association with multifocal neurologic deficits that are commonly preceded by prodromal symptoms such as fever, malaise, irritability, somnolence, headache, nausea, and vomiting. Encephalopathic signs include restlessness, lethargy, hallucination, confusion and altered sensorium. Common focal or multifocal neurological signs are hemiparesis, pyramidal signs, optic neuritis, seizures, ataxia and cranial nerve palsies. A severe presentation resulting in admission to an intensive care unit, as in our case, has been reported in 15%–25% of patients with ADEM (Dale et al., 2000). The hallmark of ADEM pathology consists of perivenular sleeves of demyelination associated with inflammatory infiltrates of myelin-laden macrophages, T and B lymphocytes, occasional plasma cells, and granulocytes (Pohl et al., 2016). In patients with ADEM, the CSF is nonspecific, showing most commonly a moderate pleocytosis with a high percentage of lymphocytes and monocytes and increased or normal total protein. Oligoclonal bands are rare and when present, the diagnosis of multiple sclerosis is strengthened. CSF examination can also be useful to exclude viral encephalitis (Pohl et al., 2016). Neuroimaging is extremely important in establishing the diagnosis of ADEM/MDEM. Lesions are extensive, typically multiple, poorly marginated, asymmetric and are predominant in the white matter. They often follow the outline of the cortical ribbon, or may consist, as in our case, of very large, globular areas of increased signal intensity that produce a mass effect. The involvement of the deep gray substance (thalamus, basal ganglia) is noted in 15–60% of cases. The large lobar high intensity lesions, which may be seen in ADEM/MDEM, are rarely seen in multiple sclerosis. Follow-up imaging commonly shows complete or partial resolution of MRI abnormalities in the majority of patients with ADEM/MDEM (Dale et al., 2000; Pohl et al., 2016; Sejvar, 2008). In our case, the association of clinical, radiological and histological findings established the diagnosis of MDEM.

The pathogenesis of ADEM and, especially of MDEM, are unclear (Azumagawa et al., 2016). Viral epitopes resembling myelin antigens have the capacity to activate myelin-reactive T cell clones through molecular mimicry, and can thereby elicit a CNS specific autoimmune response (Olival et al., 2013). Alternatively, ADEM may be caused by the activation of existing myelin-reactive T cell clones through a non-specific inflammatory process. Experimental models suggests that a phenomenon of epitope spreading secondary to a destructive CNS viral infection results in a secondary autoimmune response and chronic

inflammation (Pohl et al., 2016; Pohl and Tenembaum, 2012). Overwhelming evidence has shown that ADEM is not due to direct viral infection of the CNS, but that it is a secondary immune-mediated phenomenon. In fact, patients commonly present with ADEM/MDEM following an infection or post vaccination, although in many cases no clear antecedent history of either is present. Reported predisposing factors include influenza virus, cytomegalovirus, Epstein Barr virus, rubella, enterovirus, *Mycoplasma, Chlamydia, Campylobacter* and *Streptococcus* (Dale et al., 2000). Herpes simplex virus (HSV) is a rare etiological factor and probably a poor prognostic factor for acute disseminated encephalomyelitis (Sánchez-Menoyo et al., 2018). HSV is a neurotropic virus that can cause a wide variety of CNS infection-triggered autoimmune disorders. Several studies implicate members of the Herpesviridae family in the pathogenesis of multiple sclerosis, for example (Olival et al., 2013). Relapsing episodes of CNS demyelination seen in HSV latently infected animals are caused either by reactivation of HSV residing in the CNS itself or virus transported to the CNS after reactivation of a latent infection in peripheral sensory or autonomic ganglia (Sánchez-Menoyo et al., 2018; Sarioglu et al., 2014). HSV is particularly damaging to the CNS in situations of an impaired immune system, like in our case(Kondo et al., 2005). We believe that viral replication may have worked as a trigger to MDEM. A genetic predisposition could have explained why our patient developed ADEM-like encephalopathy rather than an acute viral encephalitis. Moreover, perhaps ADEM/MDEM and viral encephalitis may be considered part of a spectrum of diseases rather than complete distinct entities, depending on if HSV works as a trigger or as a direct etiology. In any case, further studies are encouraged to elucidate all possible clinical manifestations of HSV in the CNS.

There are 11 Toll Like Receptors (TLRs) described in humans. Ligands for such receptors are molecular structures found in most pathogens. Stimulation leads to activation of NF-κβ, which promotes the expression of genes encoding antiviral, antibacterial and inflammatory related products. TLR3 is expressed in astrocytes and dendritic cells of the central nervous system (CNS) and it recognizes processed microorganisms through a double strand of viral RNA (Zhang et al., 2007). TLR3-mediated immunity is essential for natural immunity to herpes simplex in the CNS during primary infection in childhood. Experimental data demonstrated a causal relationship between TLR3 deficiency, impaired TLR3 signaling, abnormally weak IFN-α production, enhanced viral replication, and higher levels of cell death upon viral infection (Guo et al., 2011; Zhang et al., 2007). TLR3-deficient patients have already been described with herpes simplex encephalitis. Some studies suggest that the CNS-restricted impairment of TLR3 responses underlies the pathophysiology of herpetic encephalitis (Lim et al., 2014; Zhang et al., 2007). In our patient, TLR3 deficiency probably contributed to make her more susceptible to replication and manifestation of herpes virus in CNS. Therefore, it is reasonable to imagine whether the patient would have had a relapse of ADEM if she did not have TLR3 deficiency. Another question is whether the primary immunodeficiency itself could have favored the abnormal demyelinating immune reaction. Patients with other types of immunodeficiency have already been associated with ADEM. There is likely an association between TLR3 deficiency and autoimmunity or demyelination. Some studies have shown that TLR3 also have a regulatory role in the experimental autoimmune encephalomyelitis process (Mills et al., 2011). Also, it have been reported that parenteral injection of a TLR3 ligand, suppressed relapsing–remitting EAE (Touil et al., 2014). In addition, a study reported that oligodendrocytes (involved in myelination and axonal support) express TLR3 (Bsibsi et al., 2002). These findings allow us to imagine that TLR3 deficiency could have been implicated in the pathogenesis of demyelination in this patient.

4. Conclusion

We report a case of unusual recurrence of inflammatory demyelinating encephalopathy in a patient with toll-like 3 receptor deficiency. Our case illustrates the complex interaction between viruses, the immune system and the CNS. There is a clear need to conduct further studies related to MDEM and the role of herpes viruses in demyelinating disorders. TLR3 deficiency may predispose to and explain autoimmune and demyelinating manifestations induced by HSV, including ADEM/MDEM.

Declaration of Competing Interest

None.

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