Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis following herpes simplex virus encephalitis

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Introduction

Autoimmune encephalitis (AE) in children is not attributable to a specific aetiology in the majority[1]. Adults and children taken together, tumours (21%) and infections (58%) are reported as being the most common triggers[2]. Herpes simplex virus encephalitis (HSE) is one of the established infective aetiologies shown to trigger immune activation leading to N-methyl-D-aspartate receptor (NMDAR)-antibody encephalitis. The median interval to its development varies from 24 to 40 days[3,4]. Other infections thought to trigger AE include mycoplasma, human herpes virus 6 and 7, influenza H1N1 and Epstein-Barr virus[4]. Vaccination and other autoimmune diseases are also reported as antecedents[5]. Evidence suggests that these external factors may act as an adjuvant to patients' underlying genetic propensity to autoimmunity[6].

Post-herpes simplex virus (HSV) AE, often misinterpreted as inadequately treated or relapsing HSV encephalitis, is mostly reported in relation to detection of NMDAR antibodies[8]. However, HSE has been shown to trigger other cell-surface or synaptic autoimmune responses as well[9]. This includes detection of anti-dopamine receptor 2, anti γ-aminobutyric acid (GABA) A receptor antibodies and other antibodies against unknown neuronal cell surface proteins[4,10]. We report on an infant who developed a classical syndrome of AE following HSE. To our knowledge, this is the first such report from Sri Lanka.

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Case report

An eleven-month-old previously healthy infant presented to a regional hospital following several episodes of right-sided clonic seizures associated with fever. He remained drowsy, had right-sided focal weakness and was treated as infectious meningoencephalitis. He had a white blood count of 9500/µl (N -70%, L-25%), haemoglobin of 10.4g/dl and C-reactive protein of 0.2mg/dL. The cerebrospinal fluid (CSF) analysis revealed 36 white blood cells/µl (L-90%, N-10%), 3200 red blood cell/µl, protein of 118 mg/l and glucose of 49 mg/dl (random plasma glucose 69 mg/dl) from an atraumatic tap. CSF culture was sterile; however, infant's CSF and the mother's buccal swabs tested positive for HSV-I on polymerase chain reaction (PCR) testing. Computed tomography (CT) scan revealed an infarction in the left pericentral frontal cortex attributable to on-going HSV meningoencephalitis. He made a full recovery following a course of intravenous acyclovir at a dose of 250mg/m^2 every eight hours for 21 days.

However, two days after discharge he developed recurrence of seizures, manifesting as right upper limb tonic-clonic movements with eye deviation to the right side. He was unusually drowsy and intermittently irritable. There was progressive loss of babble and motor skills resulting in eventual loss of head and trunk control. He developed marked movement disorder manifesting as perioral and facial dyskinesia, abnormal twisting movement of trunk, choreoathetosis and dystonic movements of upper limbs. Self-biting was frequent. He had sleep disturbance. Dysautonomia was not noted during assessments.

Repeat CSF examination showed cell count of 9 lymphocytes, protein 16 mg/dl and CSF sugar 3.5mmol/l. The PCR testing for HSV 1 remained positive, but with a higher cycle threshold value. Magnetic resonance imaging showed areas of encephalomalacia with gliosis in right temporal and left parietal lobes with evidence of bleeding within, bilateral asymmetrical white matter changes and atrophic right hippocampus and mild cerebral atrophy, more extensive than findings in the initial CT scan. Electroencephalography showed evidence of slower background bilaterally with delta and theta waveforms with greater effect over the right

temporal chain of electrodes. Even by 10th day of intravenous acyclovir (250mg/m^2) for the second time, his condition did not show any improvement.

Given the progressive cognitive decline despite adequate treatment for HSV and the new symptomatology consistent with NMDAR-antibody encephalitis, he was treated with combined pulsed intravenous methyl prednisolone (30mg/kg/ day for 5 days) and immunoglobulins (2g/kg over two days) while continuing on intravenous acyclovir. Since the response was poor, he was commenced on plasma exchange performed as five cycles every other day which resulted in a subtle improvement in alertness and vocalization. After a second dose of intravenous immunoglobulins, a significant improvement in alertness and speech occurred. Rituximab given weekly for four weeks, coupled with intensive rehabilitation resulted in significant clinical improvement. His movement disorder was controlled using a combination of medications including haloperidol (0.375mg twice daily), sodium valproate 100mg twice daily, benzhexol 1mg three times a day and clonidine 12.5µg twice daily. He remained seizure free on two anti-seizure medications (levetiracetam 125mg twice daily and clobazam 5mg twice daily). NMDAR-antibodies tested using cell-based assay in the third CSF sample was negative and due to limited resources, we were not able to investigate for any other causative antibodies. CSF was analysed for the third time, 14 days after second CSF examination, while he was still symptomatic with pronounced features of NMDAR encephalitis. This time he was negative for HSV 1.

At six months post-discharge from the hospital, he demonstrated only a mild right hemiparesis. Currently he is 36 months old, off all immune therapies and anti-seizure medications and remains well except for a subtle left-hand dominance.

Discussion

Since its first description in 2007, there has been an exponential number of reports and research related to AE. NMDAR-antibody encephalitis is the commonest, accounting for 4% of patients presenting with encephalitis in the UK[2]. A study from Sri Lanka of 99 adults and children presenting with encephalitis, detected NMDAR antibodies in 2%[11]. Infections are among the list of known triggers of these antibodies[12].

HSE is characterized by an unfavourable neurological outcome in 20% and death in 15% affected adult patients[13]. It presents as a monophasic illness; however, in some cases it causes recurrence of symptoms due to relapse, reported in 5% or incomplete inactivation after antiviral therapy[4,14]. HSV infection induced immune-mediated recurrence of symptoms is a more frequent possibility, reported to affect up to 20% of cases of HSE[15]. Lower frequency of seizures, presence of movement disorder and failure to respond to a second course of acyclovir should alert the clinician to this possibility[4]. It is recommended that AE be considered in all cases of recurrence of symptoms in treated HSE.

Role of HSE in AE, has been postulated to be related to a secondary autoimmune response in the central nervous system (CNS) resulting in production of anti-NMDAR antibodies. It has been hypothesized that there is a virus induced neuronal destruction exposing neuronal antigens to systemic immunity, initiating a primary autoimmune response resulting in synthesis of anti-NMDAR antibodies. Another theory describes nonspecific B cell activation and/or molecular mimicry due to shared epitopes between HSV and NMDAR. NMDAR antibodies are reported to occur in 9-27% of post HSE patients[4]. They are also reported in the CSF of HSE patients[16]. It is more frequent among the younger age group where it follows a shorter time interval between the HSE and AE presentation[4]. Children, particularly those less than 4 years, experience a more aggressive disease with predominance of a movement disorder[4].

It has been shown that even though the prototype clinical semiology suggests diagnosis of anti-NMDAR encephalitis, about 26% may be negative for NMDAR antibodies[17]. Our patient may belong to this category. Children with classic phenotype of AE but negative testing for neural antibodies, may be diagnosed as probable antibody-negative paediatric AE based on defined criteria[18].

This case highlights the importance of consideration of AE in those who relapse after treatment of HSV encephalitis. Prompt analysis for HSV PCR and NMDAR antibodies and early commencement of immunotherapy results in better outcome. Early escalation to second-line immunotherapy with monoclonal antibody rituximab or intravenous cyclophosphamide should be considered in poor responders.

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