Anti-NMDAR Encephalitis in Association with Herpes Simplex Virus and Viral and Bacterial Zoonoses

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Abstract

Multiple co-infections can predispose a patient to autoimmune encephalitis. Out of thirty cases of N-methyl-D-aspartate receptor (NMDAR) encephalitis seen at a single tertiary referral center, only two cases of co-infection with NMDAR encephalitis were identified. One of these cases was highly interesting due to the presence of more than one co-infections along with the presence of cortical dysfunction, seizures, and orofacial dyskinesias at the onset in a male in the absence of tumors, which was refractory to initial treatment.

Keywords: Anti-N-methyl-D-aspartate receptor encephalitis, *Bartonella henselae*, *Borrelia burgdorferi,* herpes simplex virus, Japanese encephalitis virus

Introduction

Infective pathogens have been implicated as triggering factors for half of the nontumor-related anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. Out of thirty cases of anti-NMDAR encephalitis seen at our institution, we identified two cases with significant recent infections related to the clinical manifestations of typical autoimmune encephalitis. One of these cases was of clinical importance due to the presence of more than one identified infections in the absence of tumor.

Case Report

A 44-year-old gentleman presented with progressive language difficulty and intermittent right facial and upper limb twitching for 2 weeks, followed by aggressive behavior. There was no preceding illnesses or recent traveling. He was a lorry driver across Sarawak state of east Malaysia. Upon admission, he was confused, disoriented, and agitated. Neurological assessment revealed receptive dysphasia, fluctuating conscious level, and psychosis. There was marked orofacial dyskinesias and faciobrachial dystonia. A series of right head jerky versive seizures was observed, with progression to involve ipsilateral limb and subsequently prolonged generalized seizures requiring invasive mechanical ventilation. Electroencephalography showed ictal focal discharges from the left frontocentral region with contralateral spread and after-going theta slowing. Brain magnetic resonance imaging was unremarkable. Lumbar puncture demonstrated elevated cerebrospinal fluid (CSF) proteins at 4.6 g/dl with no white cells and a normal glucose ratio.

He was confirmed herpes simplex virus encephalitis (HSVE) following positive pretreatment CSF HSV polymerase chain reaction (PCR) and serum ELISA. Intravenous (IV) acyclovir was initiated. Despite that, his mental status continued to deteriorate, and seizure control remained challenging with four anti-epileptic drugs (phenytoin, levetiracetam, carbamazepine, and diazepam). Paired CSF and serum anti-NMDAR antibodies were positive on week 2. He was immediately started on high-dose IV methylprednisolone for 5 days, followed by high-dose oral prednisolone. Antibodies associated with other limbic encephalitis were negative. Despite clinical and electrographic seizure control, he had persistent mental and cognitive deficits. A course of IV immunoglobulin (Ig) was added on day 14, followed by maintenance oral prednisolone and azathioprine. IV cyclophosphamide 500 mg/m^2 was commenced shortly after with remarkable response. His behavior and psychotic symptoms improved slowly over the next several weeks. At the last follow-up 2 months later, he had residual mild receptive dysphasia and cognitive deficits (Mini-Mental State Examination 24/30). Further investigations revealed positive CSF PCR for Japanese encephalitis (JE) virus, serum *Bartonella henselae* serology (IgM <1:1, IgG 1:128), and serum *Borrelia burgdorferi* serology (IgM and IgG, 1:1024), which was confirmed with Western blot. Extensive investigative workup for the underlying malignancy and auto-immune diseases including whole-body computed tomography scan, connective tissue screenings, anti-neuronal antibodies, and upper and lower gastrointestinal endoscopy was negative.

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Discussion

Herein, we detail the first case of typical anti-NMDAR encephalitis following multiple co-infections with HSV, JE virus, *B. burgdorferi,* and *B. henselae*. We postulate that these co-infections could have collectively triggered the underlying immunopathogenesis of autoimmune encephalitis, more than just immune epiphenomenon. The patient's previous work exposure in an epidemiologically JE-endemic Sarawak state, Malaysia, with a propensity for multiple zoonoses predisposed him to contacting these pathogens.[1] Positive IgM with high-titer IgG antibodies against both *B. henselae* and *B. burgdorferi* implicated recent infective process, rather than cross-reactivity as antibody screening for other auto-immune markers was negative.

HSVE can induce autoimmune encephalitis mediated by autoantibodies against the NR1 subunit of NMDAR, resulting in a pathogenic reduction in synapsin expression, a synaptic marker in hippocampal neuronal cultures.[2] This postinfectious immune-mediated process more often manifests as a distinct "relapse" encephalitis or clinically worsening HSVE following treatment, with movement and psychiatric symptoms predominant.[3] One study found no difference in clinical presentation of patients with or without detected NMDAR antibodies.[4]

The link between isolated JE and anti-NMDAR encephalitis is less well described, but appeared similar to HSVE, presenting with relapse movement disorder and/or behavioral symptoms following partial recovery of initial monophasic acute infection.[5]

From our understanding, there have been no reported cases of anti-NMDAR encephalitis following *B. henselae or B. burgdorferi* infections. While the available high-titer serology results in this gentleman suggest recent infections by both pathogens, questions persist regarding its pathogenic role in inducing NMDAR antibody. However, both lyme neuroborreliosis and bartonellosis are known to cause a spectrum of CNS manifestations including headache and seizures to neuropsychiatric and cognitive impairments in both immunocompetent and immunocompromised hosts.[6,7] The present findings require further evaluation in patients with anti-NMDAR encephalitis.

Conclusion

There is increasing evidence supporting the role of CNS infections in triggering a secondary autoimmune response, resulting in the production of anti-NMDAR antibodies. Identification of associated multiple infective pathogen requires high clinical suspicion with extensive investigations toward potential etiologies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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