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CASE REPORT

Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis

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Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a treatment-responsive encephalitis associated with anti-NMDA receptor antibodies, which bind to the NR1/NR2 heteromers of the NMDA receptors. It is a highly characteristic syndrome evolving in five stages: the prodromal phase (viral infection-like symptoms), psychotic phase, unresponsive phase, hyperkinetic phase, and gradual recovery phase. It has been considered as a paraneoplastic syndrome usually affecting childbearing-age female with ovarian tumors; however, recent reports suggest a much higher incidence of nonparaneoplastic cases in children. We report a 14-year-old girl with anti-NMDA receptor encephalitis without a detectable tumor who showed a nearly complete recovery after intensive immunotherapy.

1. Introduction

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a new category of treatable encephalitis associated with "anti-NMDA receptor antibodies." In 2005, Dalmau et al[1] first described antibodies to neuronal cell membrane antigens in four women with ovarian teratoma-associated limbic encephalitis in a culture of hippocampal neurons.[2] Two years later, they identified the antibodies, which are antibodies to the NR1/NR2B heteromers of the NMDA receptors and expressed in the hippocampus/forebrain.[2,3] The antibodies disappear with clinical improvement, suggesting their pathogenic role.

This clinical course progresses through five phases: the prodromal phase, psychotic phase, unresponsive phase, hyperkinetic phase, and gradual recovery phase.[2,4] Patients typically develop schizophrenia-like psychiatric symptoms, usually preceded by nonspecific viral-like symptoms (fever, headache, or fatigue). Consequently, most patients have been initially diagnosed with a psychiatric disorder. After reaching the peak of psychosis, they developed seizures followed by an unresponsive state, decreased level of consciousness, central hypoventilation frequently requiring

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mechanical ventilation, orofacial-limb dyskinesias, and autonomic symptoms.[2,5] The disorder is usually severe and can be fatal but it is potentially reversible. Once patients overcome the hyperkinetic phase, spontaneous progressive improvement is expected within months and full recovery can also be expected over 3 or more years.[2,4]

All indicated tests for infections, autoimmunity, and classic paraneoplastic antibodies were negative.[2,4] Brain images, brain magnetic resonance imaging (MRI), and single-photon emission computed tomography are usually unremarkable, but focal enhancement in the medial temporal lobes may be observed. The cerebrospinal fluid (CSF) reveals nonspecific finding. Eelectroencephalogram (EEG) monitoring during the unresponsive and hyperkinetic phases showed diffuse delta activity without paroxysmal discharges, despite frequent seizure attack.[2,4] The antibodies to NR1/NR2B heteromers of the NMDA receptors were found in the serum and CSF of all patients.[3,4]

The pathogenesis remains unknown. However, this disorder is considered to be an antibody-mediated encephalitis. The hypothesis of schizophrenia is based on the low activity of NMDA receptors.[5–7] Therefore, it is postulated that NMDA receptor antibodies may cause inhibition rather than stimulation of the NMDA receptor, contributing to the development of schizophrenia-like symptoms. The antibodies have been attributed to the functional blocking of NMDA receptor in presynaptic γ-aminobutyric acid-mediated interneurons of the thalamus and frontal cortex, causing a decrease of release of γ-aminobutyric acid. This results in disinhibition of postsynaptic glutamatergic transmission, excessive release of glutamate in the prefrontal cortex, and glutamate and dopamine dysregulation that might contribute to development of schizophrenia-like psychosis and bizarre dyskinesias.[8]

2. Case Report

A previously healthy 14-year-old female complained of headache and dizziness for 2 days. The following 2 days, she was found restless and with emotional lability (bizarre inappropriate smiling). The next day, she was admitted to the pediatric ward because of extreme irritability and insomnia. The following days, she was mute and had auditory hallucination, claiming that she heard music so she sang and clapped. Declined memory and obsessive-compulsive disorder (always asking for washing her hair) developed. She received H1N1 vaccine 1 month before onset of the first neurological symptoms. During the first admission, CSF study, serology survey for viral infection, EEG, brain MRI, and single-photon emission computed tomography were carried out, and all showed negative findings. So, she was transferred to psychiatric department for suspicion of bipolar or schizophrenia. Treatments of clonazepam or risperidone were tried, but the patient began to have orofacial dyskinesia. Thus, her family asked for discharge against medical advice. In the afternoon of the same day, fever and feeding difficulty with a resultant choking event developed. The patient was admitted again, and aspiration pneumonia was diagnosed. Because of massive orofacial dyskinesia, violent stereotyped movements of the mouth, jaw and tongue, and progression of conscious disturbance, she was transferred to our hospital at her parents' request. On admission, the patient presented with decreased consciousness (E2V2M4: open eyes in response to painful stimulation, incomprehensible sounds, and withdrawal in response to painful stimulation) and orofacial dyskinesia. Initially, orofacial dyskinesia could be controlled with lorazepam; but about half a day later, this symptom became more frequent and poorly responsive to lorazepam, and seizure (general tonic-clonic posture) attacks were also noted. She received antiepileptic drugs, starting with valproic acid, and then continuous intravenous infusion of midazolam (up to 20 μg/kg/min), at the same time 3-day pulse therapy of solumedrol (30 mg/kg for 3 days) was prescribed. Neither treatment was effective. She was stuporose, violent orolingual dyskinesia persisted, and autonomic dysfunction (periodic hypotension and excessive sweating) developed. Thus, midazolam was tapered off and thiopentol (5 mg/kg intravenous bolus following by continuous infusion: 1 mg/kg/h) was added. EEG done during stuporose state showed diffuse general slow waves, indicative of diffuse cerebral dysfunction. The repeated CSF study showed unremarkable results (white blood cells: 2/mm^3, red blood cells: 13/mm^3, glucose: 103 mg/dL, and protein: 35.6 mg/dL). Brain MRI also showed unremarkable result (Figure 1). Because of the negative finding of the studies regarding common autoimmune disorders (systemic lupus erythematosus, hyperthyroidism) and viral infections (herpes simplex virus, Epstein-Barr virus, cytomegalovirus), the data of EEG and brain MRI and clinical features, anti-NMDA receptor encephalitis was highly suspected. So intravenous immunoglobulin (IVIG) 1 g/kg body weight day was given for 2 days. Over the following weeks, the patient's consciousness and orofacial dyskinesia improved gradually. The following brain MRI and abdominal computed tomography (CT) were unremarkable too. Later, serum antibodies to NR1/NR2 heteromers were identified (performed by Dr Josep Dalmau at the Philadelphia University in the USA). About 2 months after admission, she became oriented but still had weakness of bilateral lower limbs, insomnia, slight impairment in recent memory, and slow speech velocity. Over the following months, expression and comprehension and muscle power recovered fully.

3. Discussion

This is a report of characteristic clinical course of anti-NMDA receptor encephalitis, showing its five distinct phases: a preceding viral-infection like illness; psychiatric symptoms; unresponsiveness; and developed orofacial dyskinesia, seizure, and autonomic instability (episodes of hypotension and sweating). After aggressive immunotherapy, the patient eventually recovered. The massive orofacial dyskinesia were poorly responsive to valproic acid and high dose midazolam (up to 20 μg/kg/min) but ameliorated gradually after thiopental use. Because successful treatment with immunotherapy had been reported,[3,9,10] pulse therapy with methylprednisolone and IVIG (1 g/kg/d for 2 days) were also administered for the patient. Orofacial dyskinesia and unconsciousness showed substantial improvement after IVIG use.