Case Report

Limbic encephalitis with antibodies to glutamic acid decarboxylase presenting with brainstem symptoms

Faruk Incecik, Ozlem M. Hergüner, Dincer Yıldızdaş[1], Ozden Horoz[1], Seyda Besen

Departments of Pediatric Neurology, and [1]Pediatric Intensive Care Unit, Cukurova University Faculty of Medicine, Adana, Turkey

Abstract

Limbic encephalitis (LE) is a neurological syndrome that may present in association with cancer, infection, or as an isolate clinical condition often accompanying autoimmune disorders. LE associated with glutamic acid decarboxylase antibodies (anti-GAD) is rare in children. Here, we characterized the clinical and laboratory features of a patient presenting with brainstem involvement with non-paraneoplastic LE associated with anti-GAD antibodies. In our patient, after plasma exchange, we determined a dramatic improvement of the neurological deficits.

Key Words

Brainstem symptoms, glutamic acid decarboxylase antibodies, limbic encephalitis

For correspondence:
Dr. Faruk Incecik, Toros mah. 78186 sok. Yeşilpark Evleri, Kat: 7, no: 13, Adana, Turkey.
E-mail: fincecik@yahoo.com

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Introduction

Limbic encephalitis (LE) is a neurological syndrome that may present in association with paraneoplastic and non-paraneoplastic causes. Non-paraneoplastic LE may be associated with systemic autoimmune disorders, autoantibodies to cell membrane antigens such as voltage-gated potassium channels (VGKCs), and, less frequently, autoantibodiesto intracellular antigens such as glutamic acid decarboxylase (GAD).[1-3]

GAD has been recently identified as a target of humoral autoimmunity in a small subgroup of patients with non-paraneoplastic LE. Anti-GAD antibody-associated LE is a rare inflammatory brain disease characterized by subacute memory loss, psychiatric symptoms, seizures, and sometimes signal abnormalities involving the mesial temporal lobes and other areas of the limbic system. Besides that, the neurologic spectrum of anti-GAD autoimmunity also includes brainstem, extrapyramidal, and spinal cord syndromes.[4-6]

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To our knowledge, there have been a few previously reported children with anti-GAD-associated LE. In LE associated with anti-GAD, brainstem involvement is rare. Here, we present a 15-year-old boy with brainstem symptoms associated with anti-GAD antibodies.

Case Report

A 7-year-old boy was admitted to our hospital because of behavioral changes, dysphagia, ptosis, diplopia, and drowsiness for 2 days after a history of upper respiratory infection a week before his admission. Five days before admission, he had headache, fever, and vomiting 4–5 times a day. Because of those symptoms, he was seen by a doctor on fifth day of the illness and was prescribed oral amoxicillin. His other past medical history was unremarkable; he had no family history of seizures or neurological and immune disorders.

On neurological examination in our clinic, he had drowsiness, oropharyngeal weakness, slurred speech, left abducens nerve palsy, horizontal nystagmus, and bilateral ptosis. His deep tendon reflexes were present but reduced, and was negative Babinski sign. On the fourth day following his admittance, he developed respiratory difficulty and mild quadriparesis, and he was intubated.

On laboratory examination, routine hematological and biochemical analyzes were normal. Initial and repeat magnetic resonance imaging (MRI) of brain was normal. Interictal electroencephalography (EEG) showed epileptiform

abnormalities both temporal regions. Cerebrospinal fluid sample (CSF) showed normal protein and cellular content. Serological and CSF assays for infectious agents, including viral etiologies, *Mycoplasma pneumoniae, Chlamydiapneumoniae,* and Lyme, were negative. A serological panel for autoimmune disorders was negative, including erythrocyte sedimentationrate, C-reactive protein, anti-nuclearantibodies, double-stranded deoxyribonucleic acid (DNA) antibody, romatoid factor, and complement levels.The nerve conduction studies and spinal MRI were also normal.

All evaluation of him did not suggest the possibility of infections, neoplasms, or toxic or metabolic etiology. We suspected limbic encephalitis but searching for anti-neuronal antibodies (anti-Hu, Yo, Ri, LGI1, CASPR2, Ma2/Ta, CRMP5/CV2, amphiphysin, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPAR], and N-methyl-D-aspartate receptor [NMDAR]), could not performed in our hospital. However, only anti-GAD antibodies could be performed with highly positive titers.

On the basis of the clinical and laboratory findings, the patient was diagnosed as non-paraneoplastic LE with anti-GAD antibodies. Levetiracetam therapy was started for EEG findings. Intravenous immunoglobulins (IVIG) 0.4 g/kg/day was administered for 5 days for the presumed diagnosis of non-paraneoplastic LE. After IVIG treatment, neurological condition did not improve. Then, we used plasmapheresis (PE) for 5 daily, followed by 3 exchanges consecutive days. After PE, IVIG 0.4 g/kg for another 5 days were administered again. After that combined treatment, we determined a dramatic improvement of his neurological symptoms.

Discussion

LE is a neurological syndrome that may present in association with cancer, infection, or as an isolate clinical conditionoften accompanying autoimmune disorders. Non-paraneoplastic LE have been described in association with autoimmune disorders. The list of autoantibodies identified in patients with non-paraneoplastic LE has been expanding. These are the antibodies targeted against cell-membrane antigens such as VGKC, novel cell-membrane antigens, the NMDAR, and GAD.[1-3]

GAD autoantibodies are associated with various neurologic conditions, such as stiff person syndrome, cerebellar ataxia, LE, myasthenia gravis, and epilepsy described mainly in adults.[7,8] Anti-GAD-associated neurological diseases are rare in children.[4-6]

The pathogenic properties of GAD antibodies have not been completely elucidated. GAD is an intracytoplasmic, rate-limiting enzyme that converts the excitatory neurotransmitter glutamate into the inhibitory gamma-aminobutyric acid (GABA).[7] Two GAD isoforms (65 and 67 kDa) are found in GABAergic neurons and pancreatic b-cells.[9] GAD 65 is highlyexpressed in CA1 and the hippocampal dentate gyrus. GAD 65 is an intracellular protein, but it has been suggested that it could be exposed on the cell surface during exocytosis from GABAergic neurons, allowing a pathogenic antibody-antigen interaction to occur. It has been postulated in other anti-GAD neurologic disorders like stiff-man syndrome and cerebellar ataxia that GAD 65 antibodies impair GABAergic synaptic transmission by reducing GABA synthesis and/or interfering with exocytosis of GABA.[10,11]

There have been a report on few cases of LE with anti-GAD antibody in recent literature.[4-6,12-14] Mishra *et al*.[12] reported a 15-year-old boy with non-paraneoplastic, anti-GAD-associated LE presenting with subacute headache, memory disturbance, psychiatric symptoms, and seizures. The other one, Korff *et al*.[13] described the case of a 6-year-old patient who had developed refractory epilepsy, developmental regression, and type 1 diabetes mellitus, in association with elevated plasma and cerebrospinal fluid GAD antibody. In another case, Akman *et al*.[14] reported a 16-year-old female with immune deficiency who was diagnosed with acute-onset non-neoplastic LE. Brainstem involvement had not reported in these previous studies. However, our patient presented with brainstem symptoms. To our knowledge, this is the first report of brainstem involvement of LE associated with anti-GAD in the children.

The treatment of anti-GAD-related neurological conditions relies either on enhancement of GABA activity or on immunosuppression. The treatment for associated with anti-GAD has included corticosteroids, immunosuppressants, PE, IVIG, and GABAergic drugs.[9] A large study of anti-GAD-related LE demonstrated poor response to steroid pulses.[15] Another study suggests that with the LE subtype, PE is more effective than steroids and IVIG.[5,13] In our patient, we used combination of PE and IVIG. After treatment, we determined a dramatic improvement of the neurological findings. Korff *et al*.[13] found that plasmapheresis was the most effective treatment in decreasing anti-GAD levels in their patient with LE, whereas intravenous immunoglobulin and intravenous and oral corticosteroids had no effect on GABA levels or seizure frequency. As same, Mazzi *et al*.[5] reported that plasma exchange has effected in LE. In our patient, the use of plasma exchange had resulted in an improvement on symptoms.

In conclusion, this report underlines the importance of early diagnosis ofimmune-mediated encephalopathy and screening for specific autoantibodies. The recognition of encephalitis associated with anti-GAD is important because of the potential response to the treatment.

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