Anti–Glutamic Acid Decarboxylase Limbic Encephalitis Without Epilepsy Evolving Into Dementia With Cerebellar Ataxia

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Objectives: To expand the spectrum of the clinical presentation of anti–glutamic acid decarboxylase antibodies–related limbic encephalitis and to improve the recognition of this entity.

Design: Case study.

Setting: University hospital.

Patient: An 11-year-old-girl with progressive mood and behavioral disorder, speech impairment, and short-term memory impairment who manifested cerebellar ataxia with nystagmus during the disease course.

Interventions: Blood and cerebrospinal fluid analysis including autoantibodies, electroencephalography, brain and spinal magnetic resonance imaging, and cognitive and neuropsychological assessment were performed. High-dose methylprednisolone sodium succinate pulses, cycles of intravenous immunoglobins, mycophenolate mofetil, and rituximab as well as antipsychotics and benzodiazepine were administered.

Results: Diagnosis of anti–glutamic acid decarboxylase antibodies–related limbic encephalitis was made. The clinical features during the first months of disease included only mood, behavioral, and memory impairment. After 5 months, despite immunotherapies, cerebellar ataxia with nystagmus appeared with brain magnetic resonance imaging evidence of cerebral atrophy. No clinical or infracclinical seizures were recorded during follow-up.

Conclusions: Anti–glutamic acid decarboxylase antibodies–related limbic encephalitis can present with only behavioral or neuropsychological symptoms without any epileptic disorder. Moreover, cerebellar ataxia related to anti–glutamic acid decarboxylase antibodies can be observed in patients with limbic encephalitis during the disease course.


Limbic encephalitis (LE) is a clinicopathological entity characterized by inflammation of limbic structures causing mediotemporal lobe symptoms. Although it mainly affects adults with tumors, nonparaneoplastic cases and a few pediatric patients have recently been described. It is suspected in individuals presenting with limbic signs and symptoms (temporal seizures, impairment in recent memory, affective disorder) and displaying fluid-attenuated inversion recovery and T2 magnetic resonance imaging (MRI) hyperintensity involving the medial temporal regions. The diagnosis is confirmed by detection of the following: (1) specific LE-related autoantibodies (Abs), including Abs directed against membrane antigens (voltage-gated potassium channel, N-methyl-D-aspartate receptor, γ-aminobutyric acid B receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) and onconeural Abs, (2) an associated neoplasm, or (3) inflammation at histopathological analysis. Recently, LE related to anti–glutamic acid decarboxylase (GAD) Abs has been reported in patients presenting with epileptic seizures as the predominant clinical feature. Herein, we describe a pediatric case of LE associated with anti-GAD Abs displaying a severe and progressive disease course in the absence of any epileptic disorder.

REPORT OF A CASE

An 11-year-old-girl, with no previous medical history, had a progressive mood and behavioral disorder for 1 month with impaired performance at school, slow speech, short-term memory impairment,
sudden and frequent bursts of crying, anxiety, and hyperphagia. Electroencephalography showed low-amplitude theta-delta rhythms on the left temporoparietal regions, without paroxysmal abnormalities. Brain MRI showed T2 and fluid-attenuated inversion recovery hyperintensity in the cortical-subcortical mesial temporal region bilaterally, more extensive on the left (Figure, A). Spinal MRI findings were unremarkable. Unmatched oligoclonal IgG bands were detected in the cerebrospinal fluid (CSF). Findings on extensive serum and CSF tests for viral, bacterial, and fungal infections were negative. Serum N-methyl-D-aspartate Abs were not detected. There were anti-GAD Abs in the serum (641 U/mL; reference range, <1.0 U/mL) and CSF (6 U/mL; reference range, <0.2 U/mL). Anti–voltage-gated potassium channel complex Abs were found in the serum (154 pmol/L; reference range, 0-100 pmol/L) but not in the CSF. Onconeural Abs (anti-Yo, anti-Hu, anti-Ri, anti-Ma1, anti-Ma2, anti-CV2/CRMP5, anti-amphiphysin) were absent. The patient developed autoimmune thyroiditis with Abs against thyroglobulin and thyroperoxidase, requiring L-thyroxin therapy. Findings were negative for transglutaminase IgA and antiendoxyme IgA. No alteration of glucose levels was detected at any time. The patient was treated with repeated pulses of high-dose methylprednisolone sodium succinate and 4 cycles of intravenous immunoglobulins with no significant improvement.

Serial electroencephalography performed during follow-up showed disappearance of slow rhythms; no clinical or infracerebral seizures were recorded during monitoring.

Five months after onset, the level of serum anti-GAD Abs was lower at 69 U/mL (CSF anti-GAD Abs 4 U/mL; oligoclonal bands still positive), but the patient developed nystagmus and severe ataxia with progressive gait disturbance. There was no improvement with mycophenolate mofetil or further high-dose methylprednisolone pulse followed by rituximab (375 mg/m² of body surface area in 4 days). Symptomatic treatment with antipsychotics and benzodiazepine produced only minimal improvement on behavior. No seizures occurred at any time during the follow-up. Longitudinal brain MRI demonstrated prominent bilateral temporal lobe atrophy with involvement of the frontobasal and insular regions at 1 month from the onset, with mild progression at months 2, 4 (Figure, B), and 6. Total-body MRI results and a search for paraneoplastic markers were negative.

Figure. Brain magnetic resonance imaging. A, Coronal fluid-attenuated inversion recovery imaging performed at admission shows hyperintensity (arrows) involving the cortical-subcortical mesial temporal region bilaterally, more extensive on the left, where the signal abnormalities also affect the subinsular region. B, Coronal T2-weighted imaging performed 4 months later demonstrates severe atrophic changes of the affected regions with ex vacuo dilatation of the ventricular system and adjacent subarachnoid spaces.

The few reported cases of LE associated with anti-GAD Abs typically include seizures that are usually partial, originating in the mesial temporal areas, and often drug resistant; there is associated memory and affective impairment. One patient presented with subacute short-term memory and language deterioration and developed epilepsy 5 years after disease onset, but the diagnosis of LE was questionable owing to the normality of brain MRI findings. The outcome of anti-GAD Abs–related LE is largely unfavorable in both adults and children because drug-resistant seizures and cerebral atrophy are very frequent.

In our patient, clinical symptoms were extremely subtle at onset with only mood and behavioral changes, mim-
icking a psychiatric disorder. However, 5 months following disease onset, she developed cerebellar signs such as nystagmus, ataxia, and gait impairment requiring a wheelchair. Brain MRI disclosed rapid evolution into cerebral atrophy. Remarkably, she never had epileptic seizures at any time during follow-up. Cerebellar ataxia has a known association with anti-GAD Abs–related neurological disorders, but it has never been described in patients with LE associated with anti-GAD Abs.

To our knowledge, this is the first report of an association between cerebellar ataxia with nystagmus and anti-GAD Abs–related LE. This observation supports a pathogenetic role of anti-GAD Abs in cerebellar dysfunction. In conclusion, this article expands the spectrum of the clinical presentation of anti-GAD Abs–related LE. Testing for anti-GAD Abs should be performed in all patients with clinical suspicion of LE, even in cases of sudden-onset, isolated behavioral changes and in the absence of any seizure disorder.

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