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ORIGINAL ARTICLE

Autoimmune encephalitis associated with glutamic acid decarboxylase antibodies: a case series

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Abstract
Antibodies against glutamic acid decarboxylase (GAD) are associated with various neurologic conditions described in patients including stiff person syndrome, cerebellar ataxia, refractory epilepsy, limbic and extralimbic encephalitis. GAD antibodies-related limbic encephalitis cases are well described; reports of extralimbic involvement are limited. We describe four cases of GAD antibody-related autoimmune encephalitis. Three of them had extralimbic involvement and only one had limbic encephalitis.

Keywords Glutamic acid decarboxylase antibody · Autoimmune encephalitis · Children

Introduction

Autoimmune encephalitis (AE) is characterized by an acute to subacute onset of seizures, cognitive impairment, and psychiatric symptoms. AE might be associated with antibodies against neuronal cell surface or synaptic proteins. These antibodies are anti-glutamic acid decarboxylase (GAD), anti-*N*-methyl-D-aspartate-receptor (NMDAR), anti-voltage-gated potassium channels (VGKC) complex, and anti-γ-aminobutyric acid receptor [1].

Anti-GAD antibody (ab)-related AE is classified into limbic and extralimbic subtypes [2, 3]. The LE is defined by characteristic seizures, affective and memory disorders, and mesiotemporal magnetic resonance imaging (MRI) abnormalities. By contrast, the extralimbic encephalitis (ELE) subtype is, clinically and radiographically, heterogeneous syndrome, varying according to the location and extent of extralimbic involvement [2].

There have been reports about cases of LE or ELE subtypes related with anti-GAD ab, but mostly as LE [1–4]. Only few cases with ELE are reported in the literature [2, 4, 5]. We describe four patients with nonparaneoplastic form of AE, associated with anti-GAD ab. Three of them were ELE subtypes, and only one case was LE.

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Case reports

Case 1

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. 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 Babinski sign was negative. 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 analyses, initial and repeat MRI of brain was normal. Interictal electroencephalography (EEG) showed epileptiform abnormalities both temporal regions. Cerebrospinal fluid (CSF) sample revealed normal protein and cellular content. All evaluation of him did not suggest the possibility of infections, neoplasms, or toxic or metabolic etiology. We suspected LE; anti-GAD ab could be performed with highly positive titers. Intravenous immunoglobulin (IVIg) 0.4 g/kg/day was administered for 5 days for the presumed diagnosis of LE. After IVIg treatment, neurological

condition did not improve. Then, we used plasmapheresis (PE) five times daily, followed by three exchanges consecutive days. After PE, IVIg 0.4 g/kg for another 5 days was administered again. After that combined treatment, we determined a dramatic improvement of his neurological symptoms.

Case 2

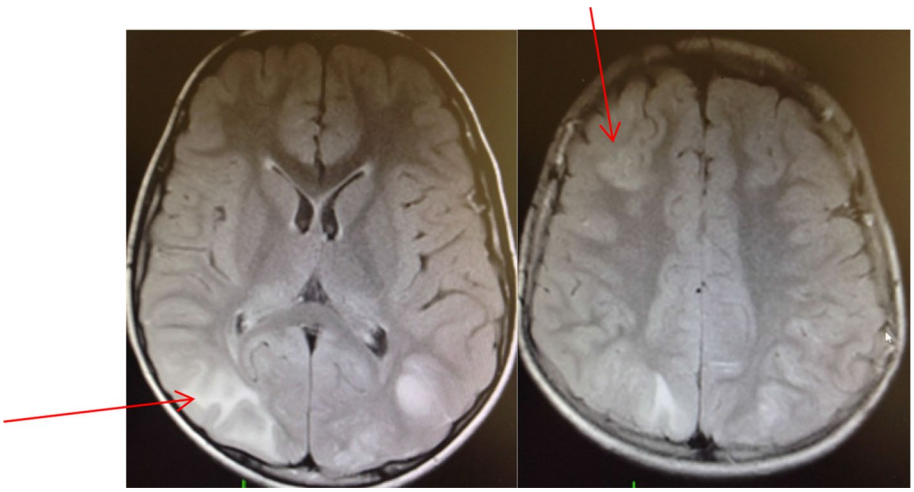
A 8-year-old boy presented with a new-onset headache, focal and secondarily tonic–clonic seizure, and behavioral changes. He had previously healthy and developmentally normal. There was no family history of autoimmune disease. On physical and neurological examination was normal except mild confusion. On laboratory examination, CSF analysis was normal; oligoclonal bands were absent. Serological and CSF assays for infectious agents were negative. The brain MRI showed T2 and fluid-attenuated inversion-recovery (FLAIR) hyperintense lesion in the right anterior frontal lobe, and bilateral occipito-parietal region (Figs. 1, 2). Extensive serum immunological testing, including thyroid studies, antithyroid peroxidase antibody, antinuclear antibodies, anti-double-stranded DNA, antineutrophil cytoplasmic antibodies, and rheumatoid factor, was negative. Serum anti-GAD ab titer was 44.3 IU/mL (normal 2–9 U/mL). ELE associated with anti-GAD ab was diagnosed. The patient was started on levetiracetam and carbamazepine for seizure control. The patient was initially treated with 5 days of IVIg (2 g/kg total), but his neurological condition resolved partially. Then, we started pulse prednisolone treatment (20 mg/kg methylprednisolone/day IV bolus for 3 days), followed by oral prednisolone (1 mg/kg/day). After therapy, his neurological symptoms gradually recovered. Anti-GAD ab titers decreased to less than 5 IU/mL.

Case 3

A 10-year-old girl was admitted to the hospital because of headache, confusion and generalized tonic–clonic seizures. One week before the onset of her complaints, she had an upper respiratory tract infection. There was no fever. Other past medical history was unremarkable; she had no family history of seizures, neurological, or immune disorders. On neurological examination, she had agitation and confusion. The remainder of the physical and neurological examination was normal. On laboratory examination, complete blood count, renal and liver function tests, and thyroid function tests were normal. MRI of the brain revealed T2 and FLAIR hyperintense lesion in the left frontal lobe and in the right temporooccipital region. The EEG was normal. Levetiracetam was started for seizures. CSF analysis was normal. All evaluation of her did not suggest the possibility of infections, neoplasms, or toxic or metabolic etiology. Very high titers of serum anti-GAD ab (33.7 U/mL) were found. We diagnosed ELE associated with anti-GAD ab. A dose of IVIg 0.4 g/kg/day was administered for 5 days. After IVIg treatment, neurological condition resolved partially. Then, we used pulse prednisolone treatment (20 mg/kg methylprednisolone/day IV bolus for 3 days), followed by oral prednisolone (1 mg/kg/day). After therapy, her neurological symptoms gradually recovered. We detected anti-GAD ab titers as 3.5 IU/mL.

Case 4

The patient who presented with acute onset of headache, confusion, and focal seizures is a 6-year-old, previously healthy and developmentally normal girl. On neurological examination, she had mild agitation and confusion. The remainder of the physical and neurological examination was



Figs. 1, 2 Cerebral magnetic resonance imaging showed hyperintense lesion in the right anterior frontal lobe, and bilateral occipito-parietal region

normal. On laboratory examination, CSF revealed normal protein and cellular content. Serological and CSF assays for infectious agents were negative. All evaluation of her did not suggest the possibility of neoplasms, or toxic or metabolic etiology. MRI of the brain revealed hyperintense lesions in the right parieto-occipital region. Very high titers of serum anti-GAD ab were detected. ELE associated with anti-GAD ab was diagnosed. A dose of IVIg 0.4 g/kg/day was administered for 5 days. After IVIg treatment, neurological condition did not completely improve. Then, we started pulse prednisolone treatment (20 mg/kg methylprednisolone/day IV bolus for 3 days), followed by oral prednisolone (1 mg/kg/day). After therapy, her neurological symptoms gradually recovered.

Discussion

Anti-GAD ab-associated neurological disorders are an increasingly recognized central nervous system disease in the literature [1–5]. It includes stiff person syndrome, cerebellar ataxia, refractory epilepsy, palatal myoclonus, LE and ELE [6].

LE-associated anti-GAD ab is a rare inflammatory brain disease characterized by subacute memory loss, seizures, psychiatric symptoms, and sometimes with imaging changes involving the mesial temporal lobes and other areas of the limbic system. It is considered relatively resistant to immunotherapy and is associated with poor outcomes due to refractory seizures and memory impairment. Besides that the neurologic spectrum of anti-GAD autoimmunity also includes brainstem, extrapyramidal, and spinal cord syndromes [7]. ELE subtype is heterogeneous syndrome with clinically and radiographically, varying according to the location and extent of extralimbic involvement.

To our knowledge, there have been previously reported children with anti-GAD ab-associated LE [1, 3, 6, 7], but ELE is uncommon and has been demonstrated only in a limited number of reports [2, 4, 5]. Kojima et al. reported a case of encephalitis with extralimbic involvement associated anti-GAD ab [5]. In another study, Najjar et al. described two cases of isolated ELE-related anti-GAD ab [2]. We detected four patients of anti-GAD ab-associated AE. Three of them had ELE and one patient had LE.

Glutamic acid decarboxylase is an intracytoplasmic, rate-limiting enzyme that converts the excitatory neurotransmitter glutamate into the inhibitory GABA [6]. Two glutamic acid decarboxylase isoforms (65 and 67 kDa) are found. GAD 65 is highly expressed in CA1 and the hippocampal dentate gyrus [8]. 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 [9]. A similar mechanism could be implicated in epileptogenesis in anti-GAD LE.

Treatments for anti-GAD ab-associated AE include intravenous methylprednisolone, IVIg, PE, and other immunosuppressive agents, such as azathioprine, cyclophosphamide, mycophenolate mofetil and rituximab [1–5]. The response of anti-GAD ab-related AE to immune therapy varies. After IVIg treatment, our patients did not completely improve. We used combined treatment to all the patients, and their neurological symptoms gradually recovered. There is a consensus that early immune treatment of cases with suspected and confirmed AE has better outcomes [2, 3]. Most clinicians use first-line therapy (steroids, intravenous immunoglobulin, plasma exchange) and, if severe or refractory, second-line therapy (rituximab, cyclophosphamide) [1–5]. When AE is suspected, methylprednisolone treatment is advised as the first-line therapeutic choice. We think that this consideration may have an important practical implication.

In conclusion, although anti-GAD ab-associated LE is rare, ELE is much more rare entity. Anti-GAD ab-associated ELE should be included in the differential diagnosis for a child presenting with AE.

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Compliance with ethical standards

Conflict of interest The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the parents of the child included in the study.

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