Clinical Heterogeneity in Acute Symptomatic Seizures due to Autoimmune Encephalitis Related to GAD65 Antibodies

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Keywords

Glutamate decarboxylase 65 antibody · Autoimmune encephalitis · Acute symptomatic seizures

Abstract

Introduction: This study aimed to explore the diversity and clinical features of acute symptomatic seizures due to autoimmune encephalitis related to anti-glutamate decarboxylase (GAD) 65 antibodies. **Methods:** Clinical data of a series of 6 patients positive for anti-GAD65 antibodies were retrospectively analyzed. **Results:** Five of the patients were male and 1 was a female, with a median age of 44.1 years (range 18–70 years). Seizure forms were varied in 6 patients when they were admitted to the hospital: 3 cases of seizures only and 3 accompanied by other symptoms, such as mental disorder, cognitive impairment, cerebellar ataxia, and ocular movement disorder. Three patients (50%) had coexisting systemic autoimmune diseases, including diabetes mellitus, vitiligo, and hyperthyroidism. Five patients (83%) had abnormal brain MRI findings. They were all treated by immunotherapy, 5 of 6 patients improved significantly but relapsed after withdrawing methylprednisolone, and 1 patient got

deteriorated. None of them were diagnosed with tumors.

Conclusions: Clinical features of acute symptomatic seizures related to GAD65 antibodies are diverse, and early and continuous immunotherapy is necessary for patients.

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Introduction

Acute symptomatic seizures are one of the most common symptoms of GAD65 AE. The most recent International League Against Epilepsy (ILAE) supports using the term “acute symptomatic seizures secondary to AE” to refer to seizures occurring in the setting of the active phase of immune-mediated encephalitis and suggests the term “autoimmune-associated epilepsy” to refer to chronic seizures determined to be secondary to autoimmune brain diseases [1]. In this study, the clinical symptoms, auxiliary examinations, treatments, and prognosis of 6 patients with GAD65 antibody-associated acute symptomatic seizure were discussed and analyzed to improve the understanding of the disease.

Table 1. Data of 6 patients positive for GAD65 antibody

Patient	1	2	3	4	5	6
Age, sex	61, M	44, F	18, M	23, M	49, M	70, M
Disease form	Partial sensory and autonomic seizures	GTCS	NORSE	Partial sensory, particle motion	FBTCS, SE	Particle motion, SE
Clinical features	Depression, memory impairment	None	Diplopia, CA	Dysarthria	Conscious disturbance	None
Disease duration	8 months	3 years	7 days	14 days	7 days	12 days
GAD Ab titers						
Serum	1:100	1:320	1:32	1:100	1:32	1:100
CSF	1:100	1:100	1:1	1:32	1:100	1:10
Other autoantibodies	LG11, ICA: (+) AMA-M2: (+) ANA: 1:100	ICA: (+), A-TG: (+), A-TPO: (+)	A-TG: (+), A-TPO: (+), CCP (+), ANA: 1:100	–	–	–
CSF						
Cells, /mm ³	6	7	15	40	34	1
Protein, g/L	0.66	0.71	0.20	0.83	0.80	1.18
Complications						
DM	+	+	–	–	–	–
Grave's	–	+	+	–	–	–
Vitiligo	+	–	–	–	–	–
Neoplasm	–	–	–	–	–	–
Immunotherapy	IVMP + IVIG	IVMP + IVIG	IVMP + IVIG	IVMP + IVIG	IVMP	IVMP
Pre-QOLIE-31	58	55	–	–	–	60
Post-QOLIE-31	89	86	67	72	0	86

F, female; M, male; GTCS, generalized tonic-clonic seizures; SE, status epilepticus; NORSE, new-onset refractory status epilepticus; FBTCS, focal to bilateral tonic-clonic seizures; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; WBC, white blood cell; CSF, cerebrospinal fluid; QOLIE-31, 31-item quality of life in epilepsy.

Materials and Method and Patients

From May 2018 to December 2020, 6 patients, including one with coexistence of anti-leucine-rich glioma-inactivated protein (LG11) antibody, who were positive for anti-GAD65 antibodies were diagnosed and admitted to the Department of Neurology, the Hospital of Jilin University, Changchun, China. The study was approved by the Ethics Committee of China – Japan Union Hospital of Jilin University. All patients were informed and provided informed consent to participate in the study.

Method

Complete clinical data were collected after admission including the results of neurological, serum laboratory, cerebrospinal fluid, neuroelectrophysiology, and MRI examinations. Serum and cerebrospinal fluid samples were obtained from all patients for the detection of autoimmune encephalitis (NMDA, LG11, AMPA1, AMPA2, GABA, CASPR2, and GAD65) and paraneoplastic (Ma2, Hu, Yo, Ri, CV2, CRMP5, and amphiphysin) antibodies. All samples were measured using Indirect Immunofluorescence Test (IIFT) kits purchased from EUROIMMUN AG (Lübeck, Germany) and used according to the manufacturer's instructions.

Curative Effect Evaluation

We used the 31-item quality of life in epilepsy (QOLIE) inventory – QOLIE-31 – to assess epilepsy persons's overall wellness including seizure worries, cognitive impact, and social functioning, and details of the scoring system are provided in the QOLIE-31 Scoring Manual [2]. A composite score from 0 to 100 that represents higher scores represent better function.

Results

The clinical data of 6 patients are summarized in Table 1. Five of the patients were males and 1 was a female, with a median age of 44.1 years (range 18–70 years).

Seizure forms were varied in 6 patients; 3 of 6 patients developed fever (37.1–38.2°C) before seizure, and in addition to seizures, they demonstrated other symptoms, such as mental disorder, cognitive impairment, CA, and ocular movement disorder. One patient developed rapidly progressive memory and affective disturbances 4 months after the seizure, while the other 2 pa-

Fig. 1. **a** (Pt 1) The right amygdala hyperintensity and enlargement in MRI FLAIR weighted; the left hippocampal sclerosis and atrophy (**b**). **c, d** (Pt 3) Hyperintense in the bilateral insula cortex in MRI T2 and FLAIR weighted. **e, f** (Pt 4) Hyperintense in the left parietal, temporal, and the insula cortex. **g, h** (Pt 5) Hyperintense in the right temporal, bilateral frontal lobes, and the frontopolar cortex.

tients presented only seizures all the time. Patient 1 had DM and vitiligo, and patient 2 had DM and hyperthyroidism.

We noted coexistence of anti-LGI1 antibodies and anti-GAD65 antibodies in patient 1. Patient 3 had serological evidence of multiple autoantibodies (anti-TPO, anti-nuclear, and anti-cyclocitrulline antibodies), but without any clinical signs of autoimmune diseases. No paraneoplastic antibody was detected in all patients. Brain MRI usually showed hyperintensity and “swelling” in medial temporal structures in T2/FLAIR MRI sequences, hippocampal sclerosis, and atrophy (Fig. 1a–d) and hyperintense cortical/subcortical lesions predominantly affecting the frontal lobes, the frontopolar, temporal cortex with some extension into the insula lobes, and other cortical regions (Fig. 1e–h).

A range of immunomodulatory plans have been used, in addition to the concomitant use of AEDs. Intravenous immunoglobulin at 0.4 g/kg of for 5 days and/or intravenous methylprednisolone at 0.5–1 g per day for 5 consecutive days, with subsequent treatment, was used. Five of 6 patients showed improvement in seizure frequency after receiving immunotherapy but all relapsed after discontinuing methylprednisolone, and one continued to deteriorate and died. Post-QOLIE-31 shows that quality of life of who clinically respond to immunotherapy was improved in the last follow-up, and reduced antibody titers are observed in them but did not disappear.

Discussion

Acute symptomatic seizures related to GAD65 antibodies can be characterized by acute symptomatic seizures secondary to AE and autoimmune-associated epilepsy. Patients present with the former at the onset of the disease and then almost all develop into the latter. The difference is that the latter highlights that not only immune factors but also nonimmune factors (e.g., structural) are also present and may play a role in the development of seizures. Although our study was a small cohort, clinical manifestations range from only seizures to acute explosive encephalitis with new-onset refractory status epilepticus. This indicates the clinical heterogeneity in acute symptomatic seizures due to AE related to GAD65 antibodies.

Coexistence of anti-GAD65 and anti-LGI1 antibody is rare, and this results in the variability in the clinical and radiographic features. The tongue stiffness during

the seizure indicates dystonia of the tongue muscle, and maybe it is a specific manifestation of faciobrachial dystonic seizure, which is a special feature of LGI1-AE [3]. Most patients with LGI1-AE can achieve seizure free without AEDs within 3–12 months after receiving immunotherapy [4]. Some scholars believe that anti-GAD65 Abs may coexist with additional cell-surface antibody, and at this time, these antibodies might directly be pathogenic to cells, and anti-GAD65 antibodies might rather be a bystander effect generated by blood-brain barrier permeability. But, the dependence on the glucocorticoids suggests that anti-GAD65 antibodies may also play roles in the development and progression of the disease.

Different clinical characteristics were noted in different patients. We noted that diabetes in patient 1 and patient 2 showed a significant difference in prognosis even though they received the same treatment. Researchers [5] measured the antibody affinity of GAD65 antibody with DM and found that the responsiveness of GAD65 antibody was usually heterogeneous; this difference in antibody response may derive from different immune events, and this is what leads to different clinical characteristics in different patients.

Although there is a certain prevalence of positive antibodies and related diseases in the general population, the probability of positive antibodies and related diseases in AE patients is much higher than the background prevalence [6]. Previous studies [7] have shown that 1 AD increases the chance of another AD. In this study, in 2 patients, 2 ADs coexisted that tested this theory to some extent. Some scholars [8] speculate that vitiligo may be a clue to an autoimmune cause for AE; improvement of AE and vitiligo (Fig. 2a, b) after immunotherapy in patient 1 verifies the possibility.

Brain MRI of 2 patients in our cohort showed invasion of both the limbic lobes and cerebral cortex, which was inconsistent with the previous conclusion [9] that only the limbic lobes can be involved. Patient 2 who had no detection in repeated examinations explains that a negative brain MRI cannot rule out the disease.

A viral infection prodrome may precede the symptoms of AE. Niehusmann et al. [10] showed that the occurrence of GAD65 AE was related to human herpesvirus 6B infection, which may be caused by viral infection causing the central nervous system epitope to be recognized by antibodies after exposure, resulting in the destruction of the body's autoimmune tolerance and the production of anti-GAD65 antibodies. In our study, 3 patients had infection before seizure, which may trigger the occurrence of

Fig. 2. a (Pt 4) The skin defect on the right forearm before immunotherapy. (Pt 4) The skin defect was improved 6 months after immunotherapy **(b)**.

GAD65 AE. For patients with highly suspected autoimmune factors which caused the seizure, such as suspected viral encephalitis, adequate antiviral treatment is ineffective; immunotherapy can be applied experimentally before antibody positive detection.

The persistence of seizures after immunotherapy suggests an enduring predisposition, and this determines that long-term immunotherapy is required. This is consistent with what was mentioned earlier “autoimmune-associated epilepsy.” There was no association between GAD65 antibody titer level and clinical severity of patients. We noted a decrease in antibody titers in patients who responded to immunotherapy but did not disappear in follow-up examination, which is similar to previous studies [11]. We suggest that the evaluation of clinical symptoms is more important in adjusting treatment.

In conclusion, our study reported clinical heterogeneity in acute symptomatic seizures due to AE related to GAD65 antibodies. It is necessary for patients to screen endocrinologic abnormalities and receive continuous immunotherapy.

Statement of Ethics

The study was approved by the Ethics Committee of China – Japan Union Hospital of Jilin University. All patients were informed of the study and provided informed consent to participate in the study. Ethical Reference No. 20200008. Subjects (or their parents or guardians) have given their written informed consent.

Conflict of Interest Statement

None of the authors has any conflicts of interest to disclose.

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Author Contributions

S. Liu contributed to conception and design; S. Wang and Y. Zhu contributed to collection and assembly of data; X. Fan and X. Li contributed to data analysis and interpretation; X. Fan contributed to writing of the manuscript; X. Han contributed to final approval of the manuscript.

Data Availability Statement

The data that support the findings of this study are openly available in PubMed at <http://www.pubmed.net>. All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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