Glutamic acid decarboxylase antibodies in neurocritical patients: a culprit or a bystander?

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Abstract
Background Glutamic acid decarboxylase (GAD) is an intracellular enzyme, which is widely expressed in central nervous system (CNS), pancreas, and other organs. GAD antibodies (GAD-Abs) are linked to various neurological disorders. However, the significance of GAD-Abs in neurocritical patients is undetermined.

Materials and methods Patients with serologically positive GAD-Abs and requiring neurocritical care were included. The clinical, laboratory, and outcome data were retrospectively collected.

Results We included 9 patients with serologically positive GAD-Abs. Clinical manifestations involved both CNS and peripheral nervous system (PNS). Six (66.7%) patients had other specific autoimmune antibodies. Non-specific autoimmune responses were observed in 8 (88.9%) patients. All patients clinically responded well to immunotherapy. The titers of GAD-Abs decreased in 7 (77.8%) patients but remained unchanged in the other 2 patients. One (11.1%) patient awoke before the negative conversion of GAD-Abs, and 3 (33.3%) patients remained unconscious and/or under mechanical ventilation for several weeks after the vanishing of GAD-Abs.

Conclusions Most neurocritical patients with serologically positive GAD-Abs had other specific autoimmune antibodies. All patients responded well to immunotherapy, but not parallel to the titers of GAD-Abs. These results indicated that GAD-Abs might be more a bystander than a culprit in neurocritical patients, suggesting that an underlying autoimmune disease should be explored.

Keywords Glutamic acid decarboxylase · Autoimmune · Antibodies · Neurocritical

Contribution to the field statement Glutamic acid decarboxylase antibodies (GAD-Abs) are linked to various neurological disorders that seldom develop into life-threatening conditions; however, advances in the detection of antibodies have identified an increasing number of neurocritical patients that are afflicted by GAD-Abs. In this study, we summarized the clinical features and overlapping autoimmune antibodies in neurocritical patients. We found that neurocritical patients presenting with positive GAD-Abs more likely progressed to acute and subacute coma, status epilepticus (SE), and refractory SE. Additionally, these same patients exhibit a common overlap with other autoimmune antibodies. Most patients appeared to benefit from plasma exchange therapy.

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Introduction

Glutamic acid decarboxylase (GAD) is an intracellular enzyme that is widely expressed in the central nervous system (CNS), pancreas, and other organs [1]. GAD catalyzes the conversion of glutamate to gamma aminobutyric acid (GABA), which is a major inhibitory neurotransmitter. GAD has two subtypes, GAD65 and GAD67. However, only GABA produced by GAD65 plays a role in neurotransmission and neuronal synapses [2]. Accordingly, anti-GAD antibodies (GAD-Abs) that are associated with neurological syndromes are targeted against GAD65, which blocks the conversion of glutamate to GABA and leads to motor and cognitive dysfunction due to the decrease of GABA level.

GAD-Abs are associated with a variety of neurological disorders, including but not limited to stiff-person syndrome (SPS), cerebellar ataxia (CA), epilepsy, oculomotor dysfunction, brain stem involvement, and limbic extra-limbic encephalitis [1–5]. However, it is not entirely clear why one antibody causes different symptoms. As an intracellular enzyme, there is controversial evidence that GAD-Abs play a direct role in the pathogenesis of these disorders [1]. Other autoantibodies, including anti-thyroid antibody, anti-intrinsic factor antibody, antinuclear antibody, anti-ribonucleoprotein antibody, and anti-gliadin antibody, are often detected in the serum of GAD-Ab-positive patients [2], which suggests that GAD-Abs tend to be accompanied by other immune responses.

Although many of the previously known GAD-Ab-related neurological disorders, including SPS and CA, rarely develop into life-threatening conditions, the progress of antibody detection has identified that more and more neurocritical patients are affected by GAD-Abs. These patients may have rapid coma, status epilepticus (SE), or respiratory weakness, which require critical care [6]. What is the role of GAD-Abs in the pathogenesis of these neurocritical disorders? Are GAD-Abs the culprit of these disorders? In order to illustrate the clinical significance of GAD-Abs in neurocritical patients, a retrospective observational cohort study was conducted.

Materials and methods

Patient selection

We retrospectively analyzed consecutive patients with serological positive GAD-Abs who were admitted to our neuro-intensive care unit (NICU) of Nanfang Hospital, Southern Medical University, from May 2017 to February 2019. Positive GAD-Ab was defined as a serum titer over 5 U/mL. This study was approved by the local ethics committee of Nanfang Hospital, Southern Medical University. Informed consent was waived by the institutional review board since this study was observational and retrospective, and all data was fully de-identified.

Demographic information and clinical data were collected from the medical records, including clinical manifestations, cerebral spinal fluid (CSF) test results, serum GAD-Ab titers, other autoimmune antibodies, cranial magnetic resonance imaging (MRI) and/or computed tomography (CT) results, electromyography (EMG) manifestations, immunotherapy, and treatment response.

Detection of GAD-Abs and other autoantibodies

The serum GAD-Ab was detected by enzyme-linked immunosorbent assay (ELISA) with GAD65 autoantibody-specific ELISA Kit (RSR Limited, UK, normal range 0–5 U/mL). The ELISA study was conducted in accord with the manufacturer’s guidelines.

Various methods were used to detect other autoimmune antibodies. Serum and CSF samples were screened for paraneoplastic antibodies (i.e., CV2/CRMP5, Ma2, Ri, Yo, Hu, and amphiphysin) by indirect immunofluorescence assay (IIFT) [7], and neuron surface antibodies by cell-based assay (including N-methyl-D-aspartate receptor (NMDAR), voltage-gated potassium channel (VGKC), voltage-gated calcium channel (VGCC), a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), gamma-aminobutyric acid B receptor (GABABR), gamma-aminobutyric acid A receptor (GABAAR), metabotropic glutamate receptor 1 (mGluR1), contactin-associated protein-like 2 (CASPR2), dipeptidyl peptidase-like protein 6 (DPP6), and leucine-rich glioma-inactivated 1 (LGI1)). Western immunoblotting assay was used to screen serum and CSF antibodies for aquaporin-4 (AQP4), glial fibrillary acidic protein (GFAP), myelin oligodendrocyte glycoprotein (MOG) [8], and ganglioside (i.e., GQ1b, GD1b, GM3, GM1, GT1b, GD1a, GM2). Other serum autoantibodies were also detected, including antinuclear antibodies (ANAs) by immunoblotting, antithyroid peroxidase (TPO) and antithyroglobulin (TG) by electrochemiluminescence assay.

Treatment and follow-up

Immunotherapies included steroids pulse therapy (SPT, methylprednisolone 1.0 g for 5 days), intravenous immunoglobulin (IVIG, immunoglobin 0.4 g/kg/day for 5 days), and plasma exchange (PE, 40 ml/kg for 5 days). In our NICU, once the patient showed serological positive GAD-Ab, immunotherapies were initiated. GAD-Ab titers were recorded according to the test time and compared with the clinical response of the patients. For patients with CNS involvement, the wake-up time was recorded. For patients with peripheral nervous system (PNS) involvement, the time of ventilator weaning was recorded.
Data availability statement

All research data can be obtained on request, and request should be directed to the management team of Nanfang hospital, Southern Medical University.

Results

Patient demographics and clinical spectrum

Between May 2017 and February 2019, nine patients with positive GAD-Abs admitted to our NICU were included. Four of them (44.4%) were males. The median age was 36 (25–71) years (Table 1). Seven of the 9 patients (77.8%) presented with CNS involvement, while 2 (22.2%) presented with PNS involvement. Three cases presented with SE and involuntary movement; 2 cases with refractory SE; 2 cases with complete oculomotor paralysis, limb weakness, and respiratory failure; 1 case with acute coma and recurrent cardiac arrest; and 1 case with subacute progressed coma. Two of the 9 patients had teratoma (case No. 3 and No. 4). One patient had concomitant type 1 diabetes (case No. 4).

In CSF examination, 3 (33.3%) patients showed normal CSF, 3 (33.3%) cases showed slightly elevated white blood cells with lymphocytes predominant, 2 (22.2%) cases had increased protein, and the remaining 1 (11.1%) patient had slightly decreased glucose and increased protein.

Imaging findings from these 9 patients were not characteristic. The CT scan showed low-density lesions in the bilateral midbrain and the thalamus in the patient presented with acute coma and recurrent cardiac arrest (case No. 1). The patient with subacute progressive coma (case No. 5) showed lesions in the left pons, bilateral midbrain, bilateral pallidum, and peri-diencele on cranial MRI (Fig. 1). The other 5 patients with CNS involvement had slight encephalatrophy, or presented with normal cranial MRI imaging. The EMG of two patients with PNS involvement showed axonal injury.

Specific diagnostic antibodies and unspecific antibodies

Six of the 9 patients (66.7%) had specific diagnostic antibodies (Table 1): two with NMDAR-IgG, one with GFAP-IgG, one with both NMDAR-IgG and GFAP-IgG, one with AQP4-IgG, and one with GQ1b, GD1b, and GT1b. Eight of the 9 patients (88.9%) had positive ANAs and elevated antithyroid antibodies. The patient with positive GAD-Ab, NMDAR-Ab, and GFAP-Ab also had concomitant type 1 diabetes and teratoma (case No. 4). None of the patients had positive paraneoplastic antibodies.

Treatment response and dynamic GAD-Ab titers

All patients received immunotherapy. Among them, 6 cases were treated with SPT, 9 with IVIG, and 9 with PE. All patients responded well to immunotherapy. The time of wake-up and ventilator weaning was illustrated in Table 2.

The GAD-Ab titers ranged from 12.42 to more than 2000 U/mL on admission. Seven (77.8%) patients were negative in GAD-Ab test after immunotherapy. The other two patients' GAD-Ab titers remained unchanged after clinical recovery. One patient regained consciousness before GAD-Abs gradually vanished. Three (33.3%) patients remained unconscious and/or under mechanical ventilation for several weeks, even after GAD-Ab titers became negative (Table 2).

Discussion

In this study, we illustrated the clinical features of 9 neurocritical patients with GAD-Abs. According to the detected specific autoimmune antibodies, anti-NMDAR encephalitis, GFAP astrocytopathy, neuromyelitis optica (NMO), and Guillain-Barre Syndrome (GBS) could be diagnosed in 6 (66.7%) patients. All patients responded well to immunotherapy, though not parallel to the titers of GAD-Abs, which indicated that GAD-Abs might be more like a bystander than a criminal in neurocritical patients. A potential autoimmune disease was worth exploring.

In our study, the clinical manifestations of the neurocritical patients with GAD-Abs involved both CNS and PNS. Two patients presented with complete oculomotor paralysis and limb weakness, accompanied by respiratory failure and axonal injury. The cranial images of the 2 patients were normal. One of the patients had concomitant presence of GQ1b, GD1b, and GT1b, and the other case had typical clinical manifestations and prominent CSF albuminocytologic dissociation, which confirmed the diagnosis of GBS. A variety of oculomotor abnormalities have been reported in patients with autoimmunity associated with GAD-Abs, either isolated or formally quantified in patients that have presented with SPS or CA [1]. In addition, Miller-Fisher Syndrome (MFS), a subgroup of GBS, has been reported in a few patients with positive GAD-Abs [9, 10]. Moreover, Albert et al. found a high GAD-Ab titer in a patient with myasthenia gravis, a progressive neuromuscular junction disease [4]. Considering the selective expression of GAD enzyme in the CNS and pancreas, we found it challenging to explain the involvement of PNS and neuromuscular junction. Interestingly, in our patient with GBS (case No. 9), another round of PE after the negative conversion of GAD-Abs further improved respiratory muscle strength and cough reflex, thus contributing to successful weaning. These observations implied that in addition to the

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formally confirmed presence of GAD-Abs, there might be other underlying autoimmune pathogenesis.

The other 7 patients presented with CNS disorders, including two with NMDAR antibody, one with GFAP antibody, one with both NMDAR and GFAP antibodies, and one with AQP4 antibody. Therefore, the 5 patients were diagnosed as anti-NMDAR encephalitis, GFAP astrocytopathy, and NMO respectively. Flanagan et al. reported that several patients with

| No. | Age range (years) | Symptoms | CSF results | Other antibody | Image/EMG features | Immunotherapy and outcome |
|-----|-------------------|----------|-------------|----------------|-------------------|--------------------------|
| 1   | 55–60             | Hyperpyrexia, acute coma, recurrent cardiac arrest | Glu 2.48 mmol/L, Pro 3.23 g/L | GFAP | Low density of bilateral midbrain and thalamus | IVIG and PE; awoke |
| 2   | 25–30             | SE, involuntary movement, severe mental disorders | Normal | NMDAR, ANAs, TG, TPO | Slight atrophy (MRI) | SPT, IVIG, and PE; awoke |
| 3   | 25–30             | Fever, SE, involuntary movement, teratoma | WBC 50/μL, lym% 90% | NMDAR, TG, TPO, ANAs | Normal (MRI) | SPT, IVIG, and PE; awoke |
| 4   | 25–30             | Fever, SE, involuntary movement, teratoma, type I diabetes | WBC 30/μL, lym% 90% | NMDAR, GFAP, TG, TPO, ANAs | Slight atrophy (MRI) | IVIG and PE; awoke |
| 5   | 45–50             | Subacute progressed coma | WBC 12/μL | AQP4, ANAs, TG, TPO | Left pons, bilateral midbrain and pallidum, peri-diacele | SPT, IVIG, and PE; awoke |
| 6   | 35–40             | RSE, pregnant | Normal | ANAs, TPO | Slight atrophy (MRI) | SPT, IVIG and PE; awoke |
| 7   | 25–30             | Fever, RSE | Pro 0.59 g/L | ANAs, TG, TPO | Slight atrophy (MRI) | IVIG and PE; awoke |
| 8   | 35–40             | Oculomotor dysfunction, limb weakness, respiratory failure | Normal | GQ1b, GD1b, GT1b, ANAs, TPO | EMG: axonal damage | SPT, IVIG and PE; weaning |
| 9   | 70–75             | Oculomotor dysfunction, limb weakness, respiratory failure | Pro 1.1 g/L | ANAs, TG, TPO | EMG: axonal damage | SPT, IVIG, and PE; weaning |

ANAs, antinuclear antibodies; AQP4, aquaporin-4; CT, computed tomography; EMG, electromyography; FOUR, Full Outline of UnResponsiveness; GFAP, glial fibrillary acidic protein; Glu, glucose; IVIG, intravenous immunoglobin; MRI, magnetic resonance image; NMDAR, N-methyl-D-aspartate receptor; PE, plasma exchange; Pro, protein; RSE, refractory status epilepticus; SE, status epilepticus; SPT, steroids pulse therapy; TG, anti-thyroglobulin; TPO, anti-thyroid peroxidase

Fig. 1 Cranial CT and MRI scan of reported cases. Cranial CT image of case No. 1 showed low-density lesions of bilateral midbrain and thalamus (a). Cranial MRI T2-weighted image (case No. 5) showed lesions of the left pons, bilateral midbrain, bilateral pallidum, and peri-diacele (b). CT, computed tomography; MRI, magnetic resonance imaging
GFAP astrocytopathy had coexisting GAD65-antibodies [11]. In our study, we found that patients with anti-NMDAR encephalitis were more likely to have GAD-Abs, followed by GFAP astrocytopathy. In anti-NMDAR encephalitis patients with GAD-Abs (cases No. 3 and No. 4), the patients remained unconscious until the titers of NMDAR-IgG decreased, weeks after GAD-Abs diminished, which indicated that NMDAR-IgG was predominantly involved in the pathogenesis other than GAD-Abs. This result was consistent with previous studies. GAD-Abs were found to be associated with neurological disorders, and the antibodies against cell surface antigens might be associated with disease pathogenesis along with the presence of GAD-Abs [12]. Two female patients who had two concomitant antibodies (NMDAR-IgG and GAD-Abs) and three concomitant antibodies (NMDAR-IgG, GAD-Abs, and GFAP-IgG) presented with teratoma respectively, which was consistent with the study by Flanagan et al. [11].

We found ANAs and antithyroid antibodies in most patients (88.9%), consistent with previous reports. All patients clinically responded well to immunotherapy. There are few randomized trials to assess the efficacy of immunotherapy in patients with GAD-Abs. The efficacy of IVIG had been established in a small group of SPS [13], and a partial response to IVIG was observed in CA [14–16]. Epilepsy related to GAD-Abs was reported to have a partial response to steroids, IVIG, and PE [17], and early initiation of immunotherapy seemed to improve the overall prognosis [18]. In addition, aggressive immunotherapy is recommended in patients with encephalitis [19]. Nevertheless, little evidence has been derived from critically ill patients. In our study, after immunotherapy, GAD-Abs of 7 patients converted to be negative, whereas 2 patients had unchanged titers despite a clinical recovery. Moreover, one patient awoke before GAD-Abs gradually vanished and 3 patients remained unconscious and/or under mechanical ventilation for several weeks after GAD-Ab titers became negative, indicating that the clinical response was not parallel to GAD-Ab titers. These results suggested that GAD-Abs might not be directly involved in the pathogenesis of neurological disorders. Experimental studies based on the passive transfer of GAD-Abs from patients with GAD-Ab-associated neurological disorders to rats or mice also showed diverse findings [12, 20–22], which also cast doubt on the pathogenic role of GAD-Abs.

**Conclusions**

Neurocritical patients with positive GAD-Abs had a broad spectrum of clinical presentations, involving both CNS and PNS. Most of these patients had other specific diagnostic autoimmune antibodies. All patients responded well to immunotherapy, but not parallel to the titers of GAD-Abs. These results suggested that GAD-Abs might be more a bystander than a culprit in neurocritical patients, indicating that an underlying autoimmune disease deserved to be explored.

**Authors’ contributions** Shengnan Wang and Yongming Wu contributed to study conception and design. Dongmei Wang and Kaibin Huang participated in study conception and design and data analysis and helped to draft and revise the manuscript. Zhenzhou Lin and Yongfang Zhang collected data. Guanghui Liu helped in revising the manuscript. All authors made substantial contribution. All authors read and approved the final version of the manuscript.

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**Data availability** All of the data derived from this research can be obtained on request. Requests should be directed toward the management team of Nanfang Hospital, Southern Medical University.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This study was approved by the local ethics committee of Nanfang Hospital, Southern Medical University.

### Table 2 Dynamic titers of GAD-Abs (U/mL) and time of clinical recovery

| No. | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  |
|-----|----|----|----|----|----|----|----|----|----|
| 0   | 68.32* | 325.95 | 247.03 | > 2000 | 156.73* | 12.42* | > 2000 | 190.28 | 63.63* |
| 2w  | 31.54 | Awake | 518.04 | Negative; awoke | > 2000 | Weaning | Negative |
| 4w  | Awoke | Negative | 
| 6w  | Negative | 127.5 | 21.10 | > 2000 awoke | Negative | Negative | Weaning |
| 8w  | 64.98 | Negative | Negative | Negative | Negative | Negative | Negative |
| 15w | Awoke | Awoke | Negative |

*Immunotherapies had been administrated before patients were transferred to our NICU
Consent for publication  Informed consent was waived by the review board because this study was an observational and retrospective analysis and all data were fully de-identified.

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