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Management of autoimmune temporal lobe epilepsy with GAD65 antibody: four case reports

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ABSTRACT

Aim of study. Glutamate decarboxylase (GAD) enzyme can be a target intracellular antigen in autoimmune focal epilepsy. GAD65 antibody is in found patients diagnosed with drug-refractory temporal lobe epilepsy (TLE). We explore the clinical features of the disease and therapeutic options.

Material and methods. We present the cases of four TLE patients, two of them with type 1 diabetes. All of them were drug-resistant and therefore underwent presurgical evaluation, which revealed GAD65 antibody positivity. We discuss the four GAD65 antibody positive temporal lobe epilepsy patients' electroclinical data, the treatments, and their effectiveness.

Results. One of them became seizure-free after right anterior temporal lobe resection, two of them did not show significant improvement with immunmodulatory agents, and the fourth patient with the shortest duration of disease had significant improvement in seizure status and normalisation of cognitive status with IVIg therapy.

Conclusions and clinical implications. Our cases show that the earlier a GAD65 antibody is detected, the greater the chance of achieving seizure freedom or improvements in both seizure and cognitive status with immunomodulatory agents. However, in some cases, surgery may also bring seizure freedom, but with a risk of cognitive deterioration.

Keywords: GAD 65 antibody, drug-refractory epilepsy, immunomodulation in focal epilepsy, autoimmune epilepsy

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Aim of study

GABA (gamma aminobutyric acid) is the main inhibitory neurotransmitter. It is converted from glutamate by GAD (glutamate decarboxylase). GAD is an intracellular enzyme in neurons and pancreatic beta cells. GAD65 enzyme can be a target intracellular antigen in several diseases, including autoimmune-associated epilepsy. GAD65 antibody is found in patients diagnosed with drug-refractory temporal lobe epilepsy (TLE) [1, 2] and autoimmune encephalitis with acute symptomatic seizures [3, 2]. In reference to current ILAE terminology, the term "autoimmune-associated epilepsy" refers to chronic seizures determined to be secondary to autoimmune brain diseases. These seizures can be proved resistant, and this might occur frequently in patients with intracellular GAD65 antibody, onconeural antibodies (eg.Hu.Ma2), or in Rasmussen encephalitis [2]. In contrast to intracellular antibodies, neuronal cell-surface antibody-mediated encephalitis

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Table 1. Demographic and clinical data of four epileptic patients with GAD 65 antibody

	Case 1	Case 2	Case 3	Case 4
Age/sex/epilepsy onset (years)	33/female/29	31/female/9	41/female/28	36/female/19
Seizures, frequency	FAS 2–6/month GTCS 3x in 2017	FAS 3–4/month GTCS 1x/year	FAS 8–16/month GTCS 1/year	FBAS 1–3/week
GAD 65 antibody titre	> 2,000U/ml both in serum and CSF	> 2,000U/ml both in serum and CSF	> 2,000 U/ml both in serum and CSF	> 2,000 U/ml both in serum and CSF
CSF	No OGP, acellular, total protein normal	No OGP, acellula, total protein normal	No OGP, acellular, total protein normal	No OGP, acellular, total protein normal
Other autoimmune disorders	Hypothyroidism	DM I	Hypothyroidism	Hypothyroidism DM I
MRI with epilepsy protocol before immunotherapy	2020: larger left amygdala; left amygdala and left hippocampus with T2W/FLAIR hyperintensity and mild hippocampal atrophy	2014: normal	2010/2014/2016: normal	2009/2012: right hippocampal sclerosis
Video-EEG monitoring	2020: 1xFAS; bilateral, non-lateralised centro-parieto-temporal seizure pattern interictal: left temporal, mild focal cortical dysfunction	2014: 3 × FASs: left temporal onset seizure patterns 3 × FBAS: non-lateralisable, rather right frontotemporal seizure patterns, interictal: Interictal left and right temporal epileptiform potentials were seen with a 70–30% ratio	2018: 4 FASs → 2 secondary generalised left fronto-central onset seizure patterns	2012: 3 × FBASs: right temporal seizure patterns interictal: right and left temporal epileptiform potentials were detected
First neurocognitive assessment				
Auditory Verbal Learning Test	6	8	5	7
trial	9	11	8	7
trial	13	12	9	12
trial	14	12	10	10
trial	14	13	9	12
trial	6	4	4	4
Interference trial	13	9	8	10
Immediate recall	11	8	7	10
Delayed recall	36	29	36	36
Rey-Osterrieth complex Figure copy	24	11.5	14	18.5
Delayed recall	27 sec	14 sec	28 sec	34 sec
Trail making A	46 sec	1 min. 41sec	65 sec	1 min 36 sec
Trail making B	6	5	6	6
Digit span forward	6	3	4	4
Digit span backward	6	4	5	6
Corsi block tapping forward	4	4	5	4
Corsi block tapping backward	24,19,27	22,1,12	23,7,15	15,19,13
Phonemic fluency (K,A,T)	29	23	27	18
Semantic fluency (animal)	60	60	58	56
Boston Naming Test				
Antiepileptics	LE,V,LTG,CLB	LTG, LEV, VPA, OXC, CBZ, CLN, TPM, BRV, LEV, LCM, GBP	LEV, LTG, LCM, CLB, CBZ	LEV, LTG, CLB, GBP
Epilepsy surgery	no	no	no	right ATLR
Seizure frequency, cognitive status after surgery				- seizure free - verbal learning, visual working memory, phonemic and semantic fluency were impaired

→

Table 1 cont. Demographic and clinical data of four epileptic patients with GAD 65 antibody

	Case 1	Case 2	Case 3	Case 4
First immunotherapy	Oct 2020: monthly high dose pulsatile methylprednisolone, 1gr/die for 4 days and plasmapheresis 2 x/month	2015: monthly plasmapheresis 3x/month	2019: plasmapheresis 2x/2 weeks	no
Seizure frequency, neurocognitive status after immunotherapy	after three months (Jan 2021): FASs 0-3/months, no GTCS, normalised cognitive functions — after 6 months (May 2021): FAS 2-4/month) & decrease in verbal memory, executive function again	2021 FAS: unchanged 2021: cognitive status worsened; verbal, visual episodic memory and verbal, visual working memory functions reduction	unchanged	
Second immunotherapy	Jun 2021 IVIG start	Mar 2022 IVIG start	Mar 2021 rituximab (3 × 1,000mg)	No
Seizure frequency, neurocognitive status after second immunotherapy	Nov 2021: FAS reduction: 1–5/3months cognitive status normal again	Unchanged	unchanged	
Follow-up MRI with epilepsy protocol	Feb 2022: slight decrease in amygdala volume, hippocampal sclerosis unchanged	Apr 2021: normal	Dec 2021: normal	2015: post-operative state on right side, no novum

FAS — focal automatism seizure; FABS — focal behaviour arrest seizure; GTCS — generalised tonic-clonic seizure; LEV — levetiracetam; LTG — lamotrigin; LCM — lacosamid; CLB — clobazam; GBP — gabapentin; CBZ — carbamazepin; OXC — oxbarbazepin; TPM — topiramate; BRV — brivaracetam; GAD — gamma-amino-decarboxylase; ATLR — anterior temporal lobe resection; IVIG — intravenous immunglobulin; CSF — cerebrospinal fluid; OGP — oligoclonal gammopathy; DM I — diabetes mellitus type I

e.g. NMDA, LGI-1 respond well to immunomodulation, with most patients becoming seizure-free and requiring no long-term antiseizure medication. These seizures can be considered acute symptomatic seizures secondary to autoimmune encephalitis. Peltola et al. investigated anti-GAD65 titres in patients with pharmacoresistant focal epilepsy, and concluded that antibodies produced against GAD65 antigen may be an underlying cause of epilepsy [4]. GAD65 antibody-associated epilepsy is mostly an autoimmune condition, without underlying malignancy [5]. High GAD65 antibody serum levels are specific for central nervous system involvement [6].

Autoimmunity targeting neuronal antigens leading to inflammation, result in an altered neurotransmission Immunomodulatory agents are used to control autoimmune inflammation, antiepileptics and resective and other palliative (e.g. VNS) interventions are used to eliminate seizures. Many patients respond to antiepileptic drugs, although immunotherapy is needed for the improvement of cognitive dysfunction. An explanation of the efficacy of sodium channel blockers might be the immunomodulatory feature of these medications [7]. Antibody titres do not reflect the duration, frequency, or severity of epilepsy [8], although persistently high levels can be found in patients with poor clinical response [8]. First-line immunosuppressive treatments can be effective [9, 10], but patients frequently need second-line immunosuppressants such as rituximab and/or cyclophosphamide [11].

In this series of case studies, we present four patients with pharmacoresistant autoimmune temporal lobe epilepsy with GAD65 antibody, and discuss their treatments (Tab. 1).

Case 1

A 33-year-old female with a history of autoimmune hypothyroidism (at age 22), no risk factors for epilepsy, developed focal epilepsy in 2017 at age 29, with generalised tonic-clonic seizures (GTCS), focal automatism seizures (FAS), and epigastric auras. Initial head MRI in 2017 was normal. In August 2020, video-EEG monitoring captured one FAS with bilateral, non-lateralised centro-parieto-temporal seizure pattern on the ictal EEG; repeated head MRI showed enlargement of left amygdala with increased T2/FLAIR signal intensity and left mild hippocampal sclerosis (Fig. 1 C). Immunoassay confirmed a high titre of GAD65 antibody in both serum and cerebrospinal fluid (CSF). There was no oligoclonal gammopathy (OGP) in CSF, and total protein was within normal range and was acellular. Neurocognitive assessment showed a moderate level of memory impairment. Chronic course of autoimmune TLE was diagnosed with GAD65 antibody positivity.

The patient was treated with immunomodulatory therapy, including high-dose intravenous methylprednisolone and plasmapheresis. Her neurocognitive dysfunction initially improved, but seizure frequency increased, and neuropsychological testing showed deterioration again. Head MRI showed

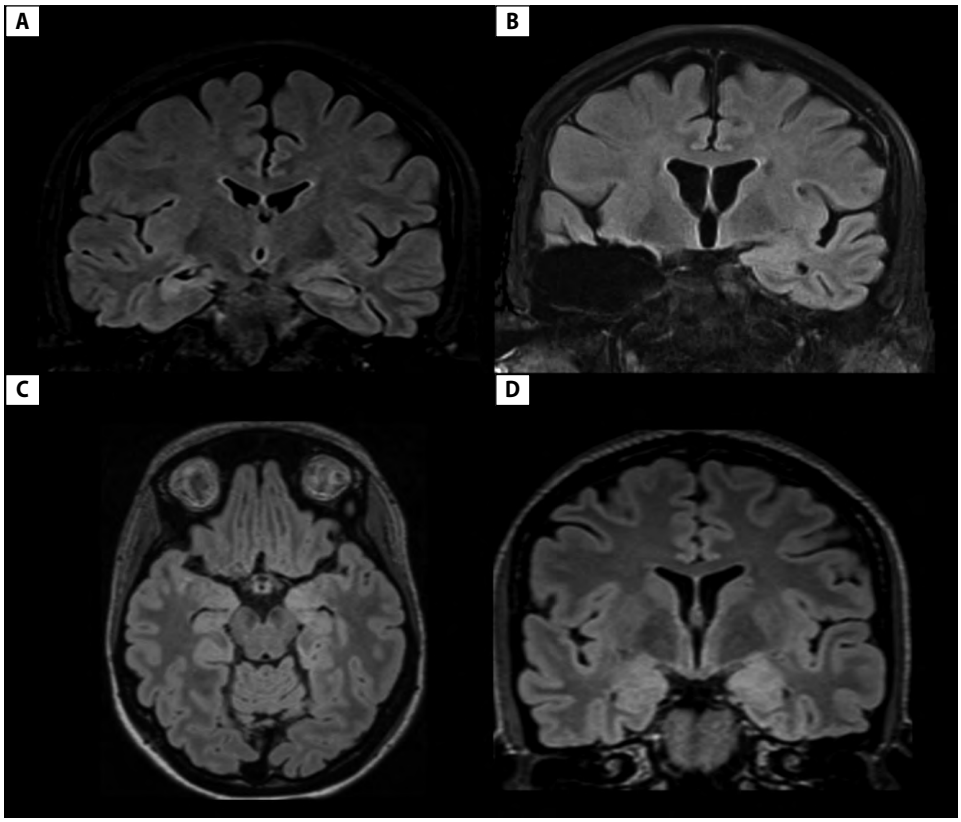

Figure 1. A (Case 4) — (2012) coronal T2W/FLAIR image shows increased signal intensity within right hippocampus, atrophy and disruption of internal structure of right hippocampus; **B (Case 4)** — (2015) follow-up MRI after right anterior temporal lobe resection, coronal T2W/FLAIR shows postoperative state on right side; **C (Case 1)** — (2020) larger left amygdala; left amygdala and left hippocampus with T2W/FLAIR hyperintensity and mild hippocampal atrophy; **D (Case 1)** — (2022) follow-up MRI after immunmodulatory treatment, axial T2W/FLAIR image displays slight decrease in amygdala volume with unchanged T2W/FLAIR hypeintensity, hippocampal appearance unchanged

unchanged left amygdala and hippocampus. Intravenous immunoglobulin therapy was commenced and the patient's condition improved. Seizure frequency decreased from 1–5 episodes of FAS and epigastric aura every month to 1–5 episodes every three months on IVIg. No memory impairment was reported. Head MRI showed a slight decrease in left amygdala volume compared to the last scan, but left hippocampal sclerosis was unchanged (Fig. 1 C, D).

Case 2

A 31-year-old female with a history of type 1 diabetes mellitus from age 9, and no epilepsy risk factors. Focal epilepsy started at age 9 with GTCS, FASs and aspecific auras. Head MRI in 2008 was normal, drug resistance was established. In 2014, her MRI showed no abnormality, no dysfunction on neuropsychological assessment. During video-EEG monitoring, six focal seizures and three isolated aspecific auras were recorded. Two types of focal seizures with different symptomatogenic zones were recorded; FASs with a left temporal onset; focal behaviour arrest seizure (FBAS) with a right frontotemporal seizure pattern, immunoassay confirmed GAD65 antibody positivity in serum. The results suggested chronic autoimmune GAD65 antibody associated TLE. In 2015, monthly plasmapheresis treatment brought about no improvement. Patient stopped treatment of her own free will. In 2021, frequent seizures occurred. GAD65 antibody positivity was confirmed in both serum and CSF. There was no OGP in CSF, total protein was within normal range and was acellular. Neurocognitive testing showed significant impairment, head MRI was normal. Since March 2022, after induction treatment (2 gr/kg body weight, 120 gr), she has received monthly treatment with 60 gr (1gr/kg body weight) IVIg. To date (Dec 2022), seizure and cognitive status are unchanged.

Case 3

A 41-year-old female had been treated for focal epilepsy since 2008 (from age 28), with GTCSs, FASs and deja vu auras. She had a history of autoimmune hypothyroidism from age 17, and no risk factors for epilepsy. Repeated head MRIs (2010, 2014, 2016) were normal. In 2018, her findings of video-EEG included four FASs: two episodes of FAS with secondary generalisation. A seizure pattern with left fronto-central onset was recorded on ictal EEG. Immunoassay confirmed high titre of GAD65 antibodies in both serum and CSF. There was no OGP

in CSF, total protein was within normal range and was acellular. Neurocognitive testing demonstrated moderate impairment. Head MRI was negative. Chronic autoimmune TLE was diagnosed with GAD65 antibody positivity. The patient did not consent to steroid treatment, and plasmapheresis was started with no improvement in seizure or cognitive status. In March 2021, rituximab was administered. She received three courses of 1,000 mg rituximab, with no significant improvement in seizure or cognitive status by Dec 2022, head MRI still normal.

Case 4

A 36-year-old female with a history of type 1 diabetes from age 7, hypertension and autoimmune hypothyroidism (at age 12), no risk factors for epilepsy. She had been treated for focal epilepsy since 2004 (age 19) with FBASs and deja vu auras. Right hippocampal sclerosis was detected in 2009 and 2012 (Fig. 1 A). During video-EEG monitoring (2012), three FABSs were recorded. On ictal EEG, a right temporal seizure pattern was seen. Immunoassay confirmed high titre of GAD65 antibodies in both serum and CSF. There was no OGP in CSF, total protein was within normal range and was acellular. Neuropsychological examination was normal. In 2013, right anterior temporal lobe resection was done (Fig. 1 B). Postoperatively, the patient was seizure-free, although cognitive impairment was depicted.

Discussion

The cases described are in accordance with the literature [12, 13]. They feature young women with autoimmune thyroid diseases or type 1 diabetes presenting with later-onset seizures in patients with pharmacotherapy-resistant temporal lobe epilepsy. The earlier the clarification of autoimmune aetiology (GAD65 antibody positivity), the higher the chance of an effective immunomodulatory treatment. Immunomodulatory treatment is predominantly started with first-line agents, switching to second-line agents in cases of ineffectiveness. Some cases in a previous study found that immunotherapy was most effective when commenced within 10 months of epilepsy onset. In one case, seizure freedom was achieved with VNS implantation; in this patient immunotherapy was initiated eight years after epilepsy onset, followed by unsuccessful selective amygdalohippocampectomy [12]. The literature suggests that resective surgery has a worse seizure outcome compared to non-autoimmune TLE, but can be performed in selected cases, especially if immunomodulatory treatment is ineffective [9, 12, 13].

In the first of our four cases, IVIg proved effective in reducing seizure frequency and normalising cognitive status. In the other two cases, the delay between the onset of disease and the initiation of immunotherapy reduced the effectiveness of treatment. Successful immunotherapies have been described even after long disease duration, plasmapheresis started seven years after epilepsy onset [14], and basiliximab treatment [15] in another case report proved to be effective. Induced T cell cytotoxicity is assumed to cause neuronal damage. Direct therapeutic interventions against the antibodies might be ineffective, whereas attenuation of the cytotoxic T cell response may be effective.

It is hypothesised that GAD65 antigen can also be expressed on the cell surface after binding to the HEAT shock cognate 70 protein and then to a synaptic vesicle, and thus can be expressed on the cell surface during exocytosis, explaining the efficacy of plasmapheresis. No OGP or elevated total protein was detected in any of the patients, all samples were acellular, and previous case studies showed that OGP was not detected in CSF in one third of cases [12]. In a study of 19 GAD65 antibody positive patients, nearly one third showed no relevant MRI abnormalities and only 30% showed hippocampal signal abnormalities. In the first patient, head MRI showed left amygdala enlargement, increased T2/FLAIR signal intensity and mild hippocampal sclerosis three years after the onset of epilepsy. Dubey et al. screened adult-onset epileptic patients of unknown aetiology for an autoimmune aetiology and found that 12.5% were GAD65 antibody positive [16]. They recommended that patients should be screened for GAD65 antibody, especially young women with unknown aetiology [16]. Therapeutic treatments for autoimmune inflammation associated with GAD65 antibody positivity can evoke seizure-free status and restore cognitive deficits. The effectiveness of immunotherapies varies, and surgery can achieve seizure-free outcomes.

The results in the literature suggest that the efficacy of the immunomodulatory treatments used is highly variable, and this is likely to be related to the fact that the timing of the initiation of immunomodulatory treatments is also highly variable, often coming after the acute phase with marked T cell-mediated cytotoxicity has passed, several years after the onset of the disease. In a recent excellent study, detailed immunohistological processing of samples from 15 adult epileptic patients with GAD-65 antibody positivity and therapy resistant TLE who underwent temporal lobe resection was performed. In samples from the GAD65-TLE early group (disease duration ≤ 6.3 years), CD 8 + T cells, granzyme B positive cells, CD 8 + cell pathways were overrepresented. Immunohistochemical examination of samples from patients with onset of disease within the last six years showed a higher number of plasma cells, but without signs of antibody-mediated tissue damage, and a strong CD8 + cytotoxic T cell infiltration and local proliferation, some of which correspond to antigen-specific resident memory T cells. In contrast, based on the results of the GAD65-TLE late group samples (disease onset > 6 years), an immunologically inactive or low activity phase is likely.

These findings suggest that the immunotherapy should primarily target T cell-mediated cytotoxicity and will have a much higher efficacy within one year of disease onset than beyond [17].

Conclusions and future directions

In TLE associated with GAD65 antibody positivity, the clinical presentation often does not exhibit the typical features of classic, acute limbic encephalitis (e.g. cumulative seizures, psychiatric symptoms, severe cognitive deficits), and diagnosis is often delayed. In focal epilepsy of unknown aetiology and/or with female adult onset, in pharmacotherapy-resistance, GAD 65 antibody screening and immunotherapy are recommended.

More experience is needed on various immunotherapies, including agents like basiliximab.

Early diagnosis has shown an increase in the effectiveness of immunotherapy on both seizure rate and cognitive status. In selected therapy-resistant cases, palliative interventions should be considered.

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