Case Report

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Successfully treated anti-GAD limbic encephalitis in a 15-year-old diabetic boy with intravenous immunoglobulin: case report

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Introduction and importance: Limbic encephalitides (LE) have symptoms and signs of new-onset seizures accompanied by cognitive impairment and signal changes in the MRI of the limbic system in the brain. Numerous antibodies against the neurons and synapses have been detected so far. Of those, antiglutamic acid decarboxylase antibody (Anti-GAD Ab) impairs the gamma amino butyric acid, one of the primary mediators that naturally prevents abnormal neuronal activity causing seizure.

Case presentation: The authors have reported a case of anti-GAD Ab LE in a diabetic male adolescent who responded dramatically to intravenous immunoglobulin and reviewed all similar pediatric cases for 15 years now.

Clinical discussion: The symptoms in children suffering from anti-GAD LE in three categories, systemic, psychiatric, and neurological, are heterogeneous. The most common manifestations were seizures followed by altered mental status and behavioral changes, respectively. The two main clinical scenarios described in GAD65-mediated autoimmune epilepsy are (1) an acute/subacute onset of seizures alone or seizures (including new-onset refractory status epilepticus, NORSE) accompanied by some degrees of cognitive and psychiatric manifestations, including amnesia and mesiotemporal inflammatory involvement consistent with LE and (2) epilepsy without clinical or MRI evidence of active central nervous system inflammation.

Conclusion: Although rare, the neurologist should consider the potential role of anti-GAD ab-associated encephalitis in the presence of diabetes mellitus.

Keywords: antiglutamic acid decarboxylase antibody, case report, epilepsy, intravenous immunoglobulin, limbic encephalitis

Introduction

Limbic encephalitis (LE) is described as acute or subacute onset of seizures accompanied by cognitive and/or memory impairment and psychiatric symptoms compatible with inflammatory changes in MRI of mesiotemporal lobes mainly[1]. Furthermore, there is another term called epileptic encephalopathy. It is defined, according to the International League Against Epilepsy, as 'embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be from the underlying pathology alone'[2]. There are types of viral infective, paraneoplastic, and rarely nonparaneoplastic variants of LE using autoantibodies directly targeting the neuronal cell membranes or enzymes regulating neuronal rest potential activity like glutamic acid decarboxylase. Glutamic acid decarboxylase antibody LE is relatively resistant to immunotherapy. Refractory seizures and cognitive impairments made it with poor outcomes. We have reported a case of anti-GAD Ab LE in a diabetic boy who responded well to intravenous immune globulin (IVIG) and then reviewed the all pediatric cases presented in the medical literature since 21 years now to the best of our knowledge. These pieces of information are summarized in Table 1. For this, we searched the PubMed/Medline, Web of Science, Scopus, and Google Scholar with the key terms of

HIGHLIGHTS

- Limbic encephalitis (LE) is an inflammation of limbic system in the brain almost idiopathic.
- LE presents mainly with seizures and mental status disturbances in children.
- Any factor altering the gamma amino butyric acid (GABA) activity in the brain can lead to seizure.
- Antiglutamic acid decarboxylase antibody (anti-GAD Ab) impairs the GABAergic activity.
- Immunosuppressive therapy by intravenous immunoglobulin can be an effective way for anti-GAD LE in children.

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Table 1

Previously reported pediatric anti-GAD LEs.

No	Authors	Year	Age and sex	Clinical presentation	Treatment	Anti-GAD antibody titer and other lab reports	MRI/PET	EEG	Co-existing problems	Outcome
1	Olson *et al.*[3]	2002	6/M	Multifocal right-sided seizures, aphasia and obtundation	Antiepileptic medications Intravenous PRDL Acyclovir Midazolam coma Plasmapheresis	Serum Anti-GAD Ab (UI/ml) = 3484 CSF Anti-GAD Ab (UI/ml) = ND	Nonenhancing left cerebellar lesion A subsequent scan 26 days after presentation revealed lesions of the gray matter involving the occipital and frontal cortex bilaterally and left insular region, which resolved within 2 weeks of initiating therapy	Frequent left-sided epileptiform discharges and slowing	Type 1 DM	No improvement achieved
2	Matá *et al.*[22]	2008	14/F	TLE, anterograde amnesia	IVIG and IV Steroids Plasmapheresis	Serum Anti-GAD Ab (UI/ml) = 87.5 CSF Anti-GAD Ab (UI/ml) = 54.1	Bilateral temporal hyperintensity	ND	ND	2 years improvement then relapse
3	AKMAN *et al.*[23]	2008	16/F	Seizures and confusion after a history of upper respiratory infection	mPSL Lamotrigine Carbamazepine Levetirecetam IVIG Oral PRDL	Serum Anti-GAD Ab (UI/ml) > 300 CSF Anti-GAD Ab (UI/ml) > 300	Bilateral hippocampal hyperintensity in T2-weighted sequences and axial fluid-attenuated inversion-recovery sequences	Complex partial status epilepticus with bilateral temporal onset.	Osteomyelitis, low IgM and IgG in addition to low IgA levels	Decrease in serum anti-GAD titer to 180.13 IU/ml, bilateral mesial temporal sclerosis
4	Korff *et al.*[4]	2011	6/F	Focal seizures with frequent secondary generalization.	mPSL Oral PRDL Plasmapheresis Mycophenolate mofetil Rituximab Clobazam Stiripentol	Serum Anti-GAD Ab (UI/ml) = 3400 CSF Anti-GAD Ab (UI/ml) = 13	Cortical and subcortical atrophy/ diffuse cortical hypometabolism	Multifocal discharges and right frontal electroclinical eizures	Type 1 DM	CSF GAD titer level dropped to 1.8 U/ml after a year and the EEG abnormalities had markedly diminished. The hemoglobinA1c level decreased progressively, from 5.7 to 4.9%.
5	Mishra *et al.*[24]	2014	15/M	Headache, transient memory disturbance, and focal motor seizures of the left leg evolved to general tonic-clonic dysguesia	Levetiracetam Clobazam IVIG Prednisolone Rituximab Sertralin	Serum Anti-GAD Ab (UI/ml) = 1/160 000 titer CSF Anti-GAD Ab (UI/ml) = 1/128 000 titer	High T2/fluid-attenuated inversion recovery signal of the right hippocampus and amygdala, as well as mildly increased signal in the left amygdala	Interictal epileptiform discharges arising independently from right frontotemporal and left posterior head regions	Mild asthma	At least 6 months symptoms-free

6	Farooqi *et al.*[25]	2015	19/F	TLE, tonico-clonic seizures	Oral steroids, Mycophenolate Mofetil PE	Serum Anti-GAD Ab (UI/ml) = 115 900 CSF Anti-GAD Ab (UI/ml) = ND	Right temporal hyperintensity	ND	ND	Improvement for a month then relapse
7	Licchetta *et al.*[5]	2014	15/M	Cramps and a muscle disturbance in the limbs and masticatory muscles	IVIG Plasma exchange	Serum Anti-GAD Ab (UI/ml) = ND CSF Anti-GAD Ab (UI/ml) = ND	NL	ND	NL	ND
8	Incecik *et al.*[6]	2015	7/M	Behavioral changes, dysphagia, ptosis, diplopia, and drowsiness after a history of upper respiratory infection	Amoxicillin Levetiracetam IVIG PE	Serum Anti-GAD Ab (UI/ml) = 56900 CSF Anti-GAD Ab (UI/ml) = 475	ND	ND	ND	Improvement
9	Achour *et al.*[7]	2018	9/F	Refractory tonic-clonic seizures and behavioral disturbances,	Sodium Valprovate mPSL IVIG + mPSL Rituximab	Serum Anti-GAD Ab (UI/ml) = Pos. CSF Anti-GAD Ab (UI/ml) = Pos.	ND	Bilateral frontotemporal spike-wave discharges.	ND	Autonomic imbalance, Refractory focal motor seizures, deceased 6 month later
10	Nagai *et al.*[26]	2019	5/F	Epilepsy, altered mental status,	Chemoradiotherapy HSCT IVIG mPSL Tacrolimus	Serum Anti-GAD Ab (UI/ml) = 142000 CSF Anti-GAD Ab (UI/ml) = 238	Hyperintensity of the cerebrum, predominantly in the left hemisphere cerebral laminar necrosis, predominantly Finally diffuse atrophy	Generalized delta activity and no spike waves	Pineoblastoma, Type 1 diabetes melitus	Improve in seizures, ability to do individual tasks, unable to communicate or walk independently
11	Boesen *et al.*[8]	2019	8/M	Generalized tonic-clonic seizure, agitation, problems with sleep and concentration, difficulty socializing with peers, weight gain (10 kg), and episodes of memory loss	Oxcarbamazepine, Levetiracetam, Clobazam, IVIG, Plasma exchange, and Rituximab	Serum Anti-GAD Ab (UI/ml) = 1025 CSF Anti-GAD Ab (UI/ml) = 104	NL	sharp waves and 3–4 Hz slow waves in the right temporal region	ND	Remission during 30 months
12	Boesen *et al.*[8]	2019	5/M	Truncal instability and reduced consciousness	Acyclovir	Serum Anti-GAD Ab (UI/ml) = ND CSF Anti-GAD Ab (UI/ml) = 109 RU/ml	NL	Abnormal background activity but no paroxysms	Chicken pox	Partially improved
13	Boesen *et al.*[8]	2019	2/M	Fever, urinary retention, anorexia, mydriasis, and photophobia	Antibiotics	Serum Anti-GAD Ab (UI/ml) = 25 CSF Anti-GAD Ab (UI/ml) = 109 RU/ml	ND	Diffuse 1–2 Hz activity, but no focal or paroxysmal activity	ND	Partially improved
14	Li *et al.*[9]	2020	3/F	CPS	LEV, discontinuation by herself later IVMP and IVIG, prednisone	Serum Anti-GAD Ab (UI/ml) = 1/100 CSF Anti-GAD Ab (UI/ml) = 1/100	Hypometabolism of L TL	ND	ND	No achievement
15	Douma *et al.*[10]	2021	4/F	Seizure, Behavioral disorders, decreased level of consciousness, orofacial dyskinesia, sleepiness	mPSL IVIG Azathioprine	Serum Anti-GAD Ab (UI/ml) = ND CSF Anti-GAD Ab (UI/ml) = 45	NL	ND	ND	Partial improved during 6 years
16	Douma *et al.*[10]	2021	9/F	Behavioral disorders, decreased level of consciousness, speech disorders, autonomic disturbances, hallucination, sleepiness	mPSL IVIG Rituximab	Serum Anti-GAD Ab (UI/ml) = ND CSF Anti-GAD Ab (UI/ml) = 32	NL	ND	ND	Partial improved during 6 years

Table 1

(*Continued*)

No	Authors	Year	Age and sex	Clinical presentation	Treatment	Anti-GAD antibody titer and other lab reports	MRI/PET	EEG	Co-existing problems	Outcome
17	Douma *et al.*[10]	2021	9/M	Decreased level of consciousness, acute confusional state, visual hallucinations, behavioral disorders, tremor	mPSL IVIG Azathioprine	Serum Anti-GAD Ab (UI/ml) = ND CSF Anti-GAD Ab (UI/ml) = 71	NL	ND	ND	Partial improved during 1.5 years
18	Ren *et al.*[11]	2021	6/F	Intermittent focal seizures, headache, and decreased memory function	mPSL IVIG Levetiracetam Oxcarbazepine and Topiramate	Serum Anti-GAD Ab titer = 1/100 CSF Anti-GAD Ab titer = 1/320	Abnormally high T2 and fluid-attenuated inversion recovery (FLAIR) signals in the bilateral hippocampus in association with swelling	Right hemisphere epileptiform activity	ND	Partially improved over 1.5 years
19	Ren *et al.*[20]	2021	16/F	Remitted focal seizures and memory deficits autonomic imbalance, including dysrhythmia, hypothermia/ hyperthermia, and hyperhidrosis	IVIG mPSL	Serum Anti-GAD Ab titer = 1/10 CSF Anti-GAD Ab titer = 1/32	Bilateral hippocampal hyperintensity in T2-weighted sequences and FLAIR sequences abnormalities in the bilateral frontal lobe, left parietal lobe, right temporal lobe, and insular cortex as well as the subcortical white matter and bilateral hippocampus	Slowed theta rhythm with bilateral temporal spike-wave discharges	Thyroiditis	Depression persistent brain atrophy
20	Ren *et al.*[20]	2021	4/M	Fever, vomiting, headache, and diplopia followed by coma	mPSL IVIG	Serum Anti-GAD Ab titer = 1/100 CSF Anti-GAD Ab titer = 1/320	Multiple diffuse abnormalities in the brainstem, thalamus, basal ganglia, and bilateral cerebral and cerebellar hemispheres on T2-weighted FLAIR imaging without enhancement	Slowed theta rhythm	ND	Full recovery
21	Kern *et al.*[12]	2021	16/F	Headaches, changes in acute mental status, expressive aphasia and auditory hallucinations	Corticosteroids IVIG	Serum Anti-GAD Ab (UI/ml) = Pos. CSF Anti-GAD Ab (UI/ml) = NL	New edema and enhancement of the temporal lobe	Subclinical seizures	New-onset type 1 diabetes mellitus	Recovery

22	Sivathanu *et al.*[13]	2022	7/M	Low grade fevers and seizures of lip-smacking movements and right upper limb tonic-clonic movements lasting for around 2 min	Midazolam infusion, IVIG mPSL Rituximab	Serum antibody titer: 221 IU/ml (0–17) and CSF AB titer: 218 IU/ml [0–17]	NL	ND	ND	Seizures cessation
23	Our case	2023	15/M	Headaches and focal seizures	Sodium valproate, IVIG	Serum Anti-GAD Ab (UI/ml) = 18 CSF Anti-GAD Ab (UI/ml) = ND	Areas with signal change in the medial of right parietal, temporal, and occipital lobes	Compatible of TLE	DM	2 years disease free

Ab, antibody; CPS, complex partial seizure; DM, diabetes mellitus; EEG, electroencephalography; F, female; GAD, glutamic acid decarboxylase; IV, intravenous; IVIG, intravenous immunoglobulin; M, male, mPSL, methyl prednisolone; ND, non declared; NL, normal; PET, positron emission tomography; PRDL, prednisolone; Pos., positive, TLE, temporal lobe epilepsy.

'Glutamic acid decarboxylase', 'Anti-GAD', 'Limbic encephalitis', and also the references of available literature from 2002 to 2022. The exclusion criteria were adults over 19 years old, extra limbic anti-GAD encephalitis cases and those whose diseases found during autopsy. This work conforms to Surgical CAse REport (SCARE) 2020 criteria[14].

Case presentation

A 15-year-old male with a history of epilepsy and diabetes mellitus presented to the neurology emergency department complaining of vague chronic right temporal constant headaches with exacerbating attacks for about 2 months, not responding well to the over-the-counter painkillers. The patient also had photo and phonophobia but was not accompanied by blurred vision. At times of exacerbation, he was nauseous and vomiting. The boy was on regular and isophane (NPH) Insulin injections. Regarding being diabetic, erythrocytes sedimentation rate and C- reactive protein tests were requested to rule out temporal arteritis in normal ranges. He then underwent DEPAKIN (Sodium valproate) 500 mg daily. In the postcontrast phase, the gyral enhancement was seen in the areas mentioned. Magnetic resonance arteriography and venography were normal. On the third day of admission, he had focal seizures with loss of consciousness for less than 2 min. Immediately MRI (with and without contrast) and venography were requested that revealed areas with a signal change in the medial of right parietal, temporal, and occipital lobes (Fig. 1). The IVIG was initiated with the primary diagnosis of autoimmune encephalitis. Considering diabetes alongside autoimmune encephalitis, we requested an antiglutamic acid decarboxylase (anti-GAD) serum level that was 18 (> five is positive). In a nutshell, we encountered extra limbic anti-GAD autoimmune encephalitis presenting with a headache that has already not been reported in the literature. The seizures were controlled so that he experienced them only in the second month of treatment; otherwise, the 2-year follow-up period was overall uneventful. There was a short episode of seizure shorter than a minute on his sixth month of remission. The school scores were also applicable.

Discussion

Autoimmune encephalitides (AEs), members of a spectrum of disorders targeting the brain, are common in the nature of abnormal immune responses[15,16]. Antibodies against neuronal cell-surface proteins, ion channels, receptors, synapses, or enzymes that catalyze the formation of neurotransmitters such as (GAD)[17] are responsible for prominent neuropsychiatric symptoms in patients[18]. Gamma amino butyric acid (GABA) plays the role of the main inhibitory neurotransmitter in the mammalian brain. As a cofactor, GAD, accompanied by pyridoxal-5′-phosphate (PLP), is the rate-limiting enzyme in converting glutamate to GABA. In mammals, GAD is found in multiple isoforms expressed in pancreatic β-cells, testis, fallopian tube, liver, kidney, adrenal glands, and central nervous system[19]. This can be a justification for anti-GAD Abs' association with type 1 diabetes (TID) so that anti-GAD Abs may be detected in 87% of patients with type I diabetes, making it a marker for TID[20].

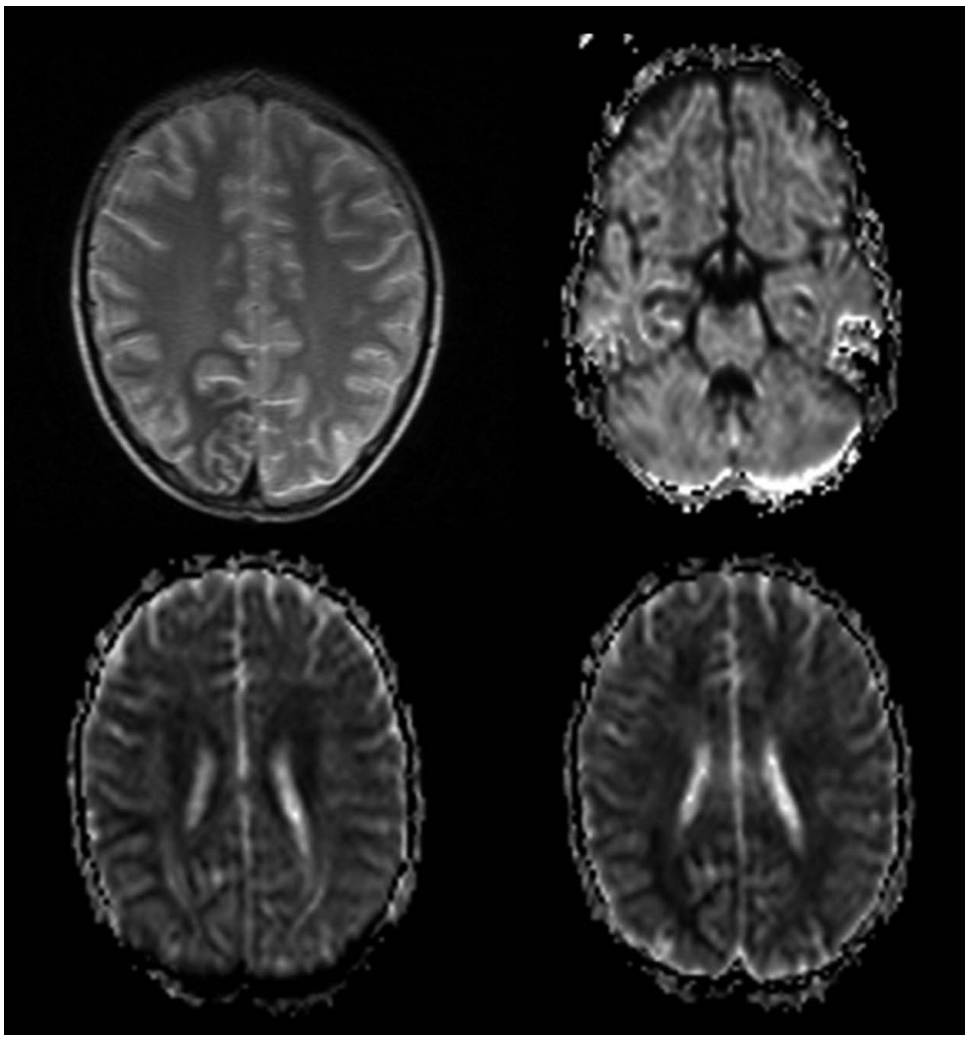

Figure 1. The MRI of the patient at admission showing multiple areas with a signal change in the temporal (right upper), occipital (left upper), and medial of right parietal (right and left inferior) accompanied with diffuse cerebral atrophy.

Being in the differential diagnoses of other inflammatory brain diseases, infections, metabolic diseases, psychiatric disorders, and problems communicating with younger children to describe their symptoms make the diagnosis a challenge in a child's growing brain. It is evident that AE in a child urges fast and proper intervention to prevent permanent neurocognitive deficits. Of note, a specific autoantibody can be detected in not all children with a clinical phenotype of AE[16]. Epileptic seizures following fever and headaches, probably with the underlying mechanism of blood-brain barrier dysfunction, are the common manifestations of AEs[21].

The symptoms in children suffering from anti-GAD LE in three categories, systemic, psychiatric, and neurological, are heterogeneous. The most common manifestations were seizures in 15 cases[3,4,7–11,13,22–26], followed by altered mental status[3,6,8,10,23] and behavioral changes[6–8,10] in nine and seven patients, respectively Table 2.

There is a strong association between antibody-mediated encephalitis and epilepsy. Two main clinical scenarios have been described in GAD65-mediated autoimmune epilepsy. (1) an acute/subacute onset of seizures alone or seizures (including new-onset refractory status epilepticus, NORSE) accompanied by some degrees of cognitive and psychiatric manifestations, including amnesia and mesiotemporal inflammatory involvement consistent with LE[27]. (2) Epilepsy without clinical or MRI evidence of active central nervous system inflammation. Patients may have only some minor psychiatric symptoms[5]. However, these pieces of information are extracted from adult studies. In our study, 11 epileptic cases showed abnormalities in brain MRI T2-weighted and FLAIR sequences, especially in mesiotemporal, hippocampal, and amygdala. In two of three cases with normal neuroimaging but seizures, agitation, problems with sleep, and behavioral disorders, have been observed.

In most reported cases, whether pediatric or adult, the imaging findings depend upon the time of the disease onset. Generally, there is little detailed neuroimaging data on anti-GAD patients in the literature, often revealing normal findings in seven out of 23 cases[8,13,28] in the initial phase or some minor abnormalities[29]. We have extracted 11 patterns of brain tissue involvement in the MRI of pediatric anti-GAD LE cases to the best of our knowledge (Fig. 2): (A) bilateral temporal[12,22], (B) bilateral hippocampal[23], (C) bilateral amygdala and right hippocampus[24], (D) right

Table 2

Frequency of clinical manifestations by mentioning the cases in the Table 1

Presentation	Frequency
Seizure	15
Altered mental status	10
Behavioral changes	6
Memory disturbances	5
Headache	5
Sleeping disturbances	3
Fever	3
Hallucination	3
Speech disorder	3
Diplopia	2
Autonomic disturbances	2
Gait and truncal instability	2
Dyskinesia	2
Urination problems	1
Anorexia	1
Mydriasis	1
Cramps and muscle disturbances	1
Dysphagia	1
Ptosis	1
Weight gain	1
Photophobia	1
Aphasia	1
Vomiting	1

temporal[25], (E) left hemisphere[26], (F) normal[8–10,13], (G) bilateral frontal, left parietal, right temporal, and insular cortexes accompanied with bilateral hippocampal[11], (H) brain stem, thalamus, basal ganglia, bilateral cerebral, and cerebellar[11], (I) our case with mesial of right parietal, temporal and occipital, (J) left cerebellar and bilateral occipital[3], and (K) global cortical-subcortical atrophy[4].

There electroencephalogram (EEG) in those with GAD Ab-associated epilepsy is usually nonspecific. Temporal, fronto-temporal regions, generalized delta activity, abnormal background activity but no paroxysm, and slowed theta rhythm were the EEG patterns in our review. Temporal involvement, as in our study, was predominant[30]. The study aims to reduce immune responses to enhance GABAergic activity to prevent seizures as much as possible. The first line treatment plan frequently used and suggested is 0.5–1 g per day intravenous methylprednisolone for five consecutive days followed by monthly pulsatile treatment or oral prednisone, a 5-day course of IVIG at 0.4 g/kg for 5 days, with or without subsequent treatment, and plasma exchange are considered the first line treatments.

Conclusion

This review indicated the importance of neuroimaging in new-onset seizures in the pediatric population once more, on the one

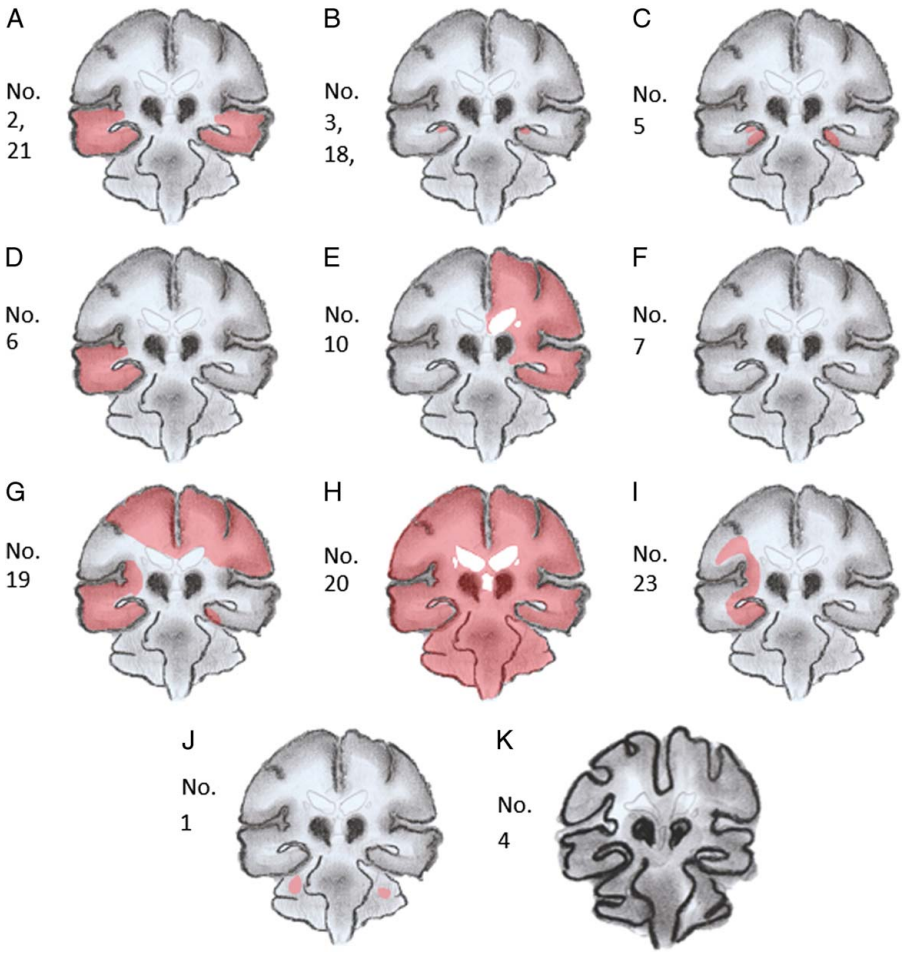

Figure 2. Anatomic patterns of involved cases, from A to K according to the study and the prevalence of the involved areas.

hand. On the other hand, although rare, the neurologist should consider the potential role of anti-GAD ab-associated encephalitis in the presence of diabetes mellitus. MRI low quality could be considered as limitation of our case report.

Ethical approval

Considering that this is a case report study and does not contain new drug or therapeutic approach trial, the authors assumed that there was no need to take ethical code. The corresponding author on behalf of all authors guarantees the principles of confidentiality.

Consent

Written informed consent was obtained from the patient's legal guardians who are the parents for review by the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

G.F.A., was the treating physician of the patient who applied IVIG, got success, proposed preparing this manuscript, and in the role of supervision; A.S.K., prepared the manuscript draft as case report and literature review, painted the picture, illustrated the graphics, and in the role of corresponding author to communicate with the journal; M.J. and D.M.: helped writing the draft and grammatical revision besides table design; P.S.K.: helped get information regarding immunologic and molecular basis of the disease.

Conflicts of interests disclosure

The authors declare there are no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Successfully Treated Anti-GAD Limbic Encephalitis in a 15-Year-Old Diabetic Boy with IVIG: Case Report.
2. Unique identifying number or registration ID: researchregistry9605.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked). https://www.researchregistry.com/browse-theregistry#home/registrationdetails/652904736fc68f0026fefa37/.

Guarantor

Ali Samady Khanghah accepts full responsibility for the work and approves the whole process from designing the study to publication.

Data availability statement

Data sharing is not applicable to this article.

Provenance and peer review

Not commissioned, externally peer reviewed.

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