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CASE REPORT

Anti-GAD65 Antibodies Related Refractory Epilepsy Successfully Treated with Tocilizumab: A Case Report and Systematic Literature Review

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Background: Although anti-GAD65 related epilepsy is rare, it needs more attention because it is refractory to the conventional therapies, has poor outcome and high relapse rate. In this study, we intended to report the efficacy of tocilizumab in the treatment of anti-GAD65 antibodies related refractory epilepsy based on our center's experience and literature review.

Methods: The clinical data of the patients managed with tocilizumab at Xiangya Hospital and those from the literature was collected and analysed.

Results: A female child presented at our center with neuropsychiatric symptoms and generalized tonic-clonic seizures (including status epilepticus) at the age of 3 years. She had positive anti-GAD65 autoantibodies. Her initial electroencephalograph showed multi-focal epileptic discharges and an early brain magnetic resonance imaging demonstrated increased intensity in the bilateral hippocampi and right insular cortex. She received several anti-seizures medications (ASMs) and immunotherapies without significant improvement; however, she experienced significant clinical, electrographic and radiological improvement after receiving four cycles of the tocilizumab. Literature review unveiled two more female cases. The mean age of seizure onset for three cases was 7.72 years, and they presented with refractory seizures (n=3), neuropsychiatric symptoms (n=3), ataxia (n=2), and anti-GAD autoantibodies were elevated in both the serum and cerebrospinal fluid (n=3). All three cases tried several combinations of ASMs and immunotherapies before tocilizumab but they remained with refractory epilepsy. Following several cycles of the tocilizumab, all cases had significant positive changes: seizure freedom (n=1), seizure control (n=2), improved-normal cognition (n=3), improved neuropsychiatry symptoms (n=2) and controlled ataxia (n=2).

Conclusion: Tocilizumab seems to be an effective therapy for the refractory anti-GAD65 related epilepsy as it can control seizures, improve cognition and neuropsychiatric symptoms.

Keywords: anti-GAD65 autoantibodies, epilepsy, tocilizumab, efficacy, safety, review

Introduction

Gamma-aminobutyric acid (GABA) is a neurotransmitter produced by the enzyme known as glutamic acid decarboxylase-65 (GAD65).[1] Anti-GAD65 antibodies can cause several neurological disorders such as epilepsy, cognitive impairment, limbic encephalitis, Stiff-person spectrum disorders, cerebellar ataxia, myelopathy and brainstem dysfunction.[1] Despite the fact that anti-GAD65 antibodies are considered as a cause of aforementioned syndromes, high serum titers do not associate with disease severity or response to therapies.[2] Thus, it is still unclear if anti-GAD65 antibodies are pathogenic or only serve as a marker for autoimmune disorders induced by cytotoxic T cells.[2] For the anti-GAD related epilepsy, patients can present with epilepsia partialis continua, refractory status epilepticus,[3] segmental myoclonus and epilepsy[4] and adult onset temporal lobe epilepsy (TLE).[5] There are some evidences from human and

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animal models suggesting the role of the interneurons (including GABAergic interneurons, which have connection with GAD) in the occurrence of epilepsy.[6,7] The loss of principal cells and interneurons and neuroinflammation are among the histopathological features of TLE.[6] There are some evidences that GABAergic interneurons are reduced in the dentate gyrus of patients with TLE and rodent models, therefore, their loss can lower seizure threshold.[6] Moreover, spontaneous recurrent seizures can reduce interneurons during epileptogenesis.[6] Of concern, most of the GAD epileptic manifestations are refractory to the combinations of therapies including immunotherapies and antiseizure medications (ASMs).[2,5,8–11] A recent review also revealed that the prognosis of patients diagnosed with anti-GAD65 related epilepsy is poor, more prone to relapse and can cause more central nervous system (CNS) morbidities than other anti-GAD65 related syndromes.[2,12,13] Recently, tocilizumab was reported as an effective therapy for the epilepsy in two patients.[14,15]

Although anti-GAD65 related epilepsy is rare, it needs more attention because it is refractory to the conventional therapies, has poor outcome and high relapse rate. Therefore, we provide more evidence that tocilizumab is effective and safe therapy for this condition by sharing our treatment experience. To the best of our knowledge, this is the third report about the treatment of the anti-GAD65 related epilepsy with tocilizumab worldwide, and the first case ever in Asia. Along with our cases, we have summarized the information of all reported patients who were treated with this therapy to provide more robust evidence to advocate its use in similar situations.

Case Report

A normally developed female child presented with status epilepticus and neuropsychiatric symptoms at the age of 3 years and 2 months. She was attended in another hospital two weeks prior to the admission in our unit. The initial manifestations included aggression, biting of people, bad mood, confusion, occasional vomiting, and intermittent low fever. One month later, she experienced fever-related (39.3°C) tonic-clonic seizures for the first time that lasted for 30 minutes (status epilepticus); consequently, she was admitted to the local hospital for 2 weeks. Unfortunately, she developed cognitive decline after seizures and only received symptomatic treatment at this hospital. She experienced a second episode of frequent seizures 13 days later. These seizures continued to the next day, were accompanied with tremor of the upper extremities, and altered level of consciousness during post-ictal phase. She was then transferred to our hospital on the second day of repeated seizures. Initial investigations' results from the first hospital and ours were similar; brain magnetic resonance images (MRIs) showed increased intensity in the bilateral hippocampi and right insular cortex (Figure 1A). The electroencephalographs (EEGs) showed multi-focal epileptic discharges and subclinical seizures (Figure 2A–F). Cerebrospinal fluid (CSF) analysis revealed normal levels of the white blood cells (WBC), protein and glucose. Serum levels of the thyroperoxidase autoantibodies (TPO-A) and thyroglobulin autoantibodies (TGA) were elevated significantly (both > 1000 IU/mL). The whole body screening for tumors via computed tomography (CT) scan was non-remarkable. There was no evidence of pathogenic infection or metabolic disease. Both CSF and serum were screened for the autoantibodies via indirect immunofluorescence on cell-based assays in an independent laboratory (KingMed Diagnostic, Changsha, Hunan). Autoantibodies checked included anti-NMDAR, -GAD65, -LGI1, -CASPR2, -GABABR, -AMPAR1, -AMPAR2, -IgLON5, -DPPX,-mGluR5, -MOG, -GFAP, -GABAAR, -AQP4 and -mGluR1, consequently, there were anti-GAD65 positive antibodies in both serum and CSF (both 1:100). Therefore, the diagnosis of the anti-GAD65 antibodies related encephalitis was reached.

After the admission to our hospital, she was given intravenous immunoglobulin (IVIG, 2g/kg in total) and intravenous methylprednisolone (IVMP pulse, 15 mg/kg/day for 5 continuous days), followed by oral prednisone (2 mg/kg/day) which was tapered off within the following six months. Levetiracetam (LEV) and other symptomatic treatments were prescribed. She got some relief; however, she still had experienced abnormal behavior (hyperactivity and poor cognition), occasional clinical seizures and frequent subclinical seizures according to the EEG monitoring. As a result, within the following 14 months, she took combined immunotherapies as described below. Monthly to bimonthly IVIG (2 g/kg, 10 times); rituximab (750 mg/m^2 twice in 2 weeks interval shortly after the first IVIG plus IVMP pulse; 750 mg/m^2 once, half a year later and 700 mg/m^2 once, one year later). Besides, mycophenolate mofetil (MMF) was added shortly after the first round of rituximab since the improvement of the patient was not satisfactory; IVMP pulse was repeated again in the 9th month of treatment (15 mg/kg/day for five continuous days, which was followed by oral prednisone (1 mg/kg/d) and then tapered off within 1 month). Moreover, lacosamide (LCM) was added in the 14th month of treatment. Despite this long duration of repetitive and

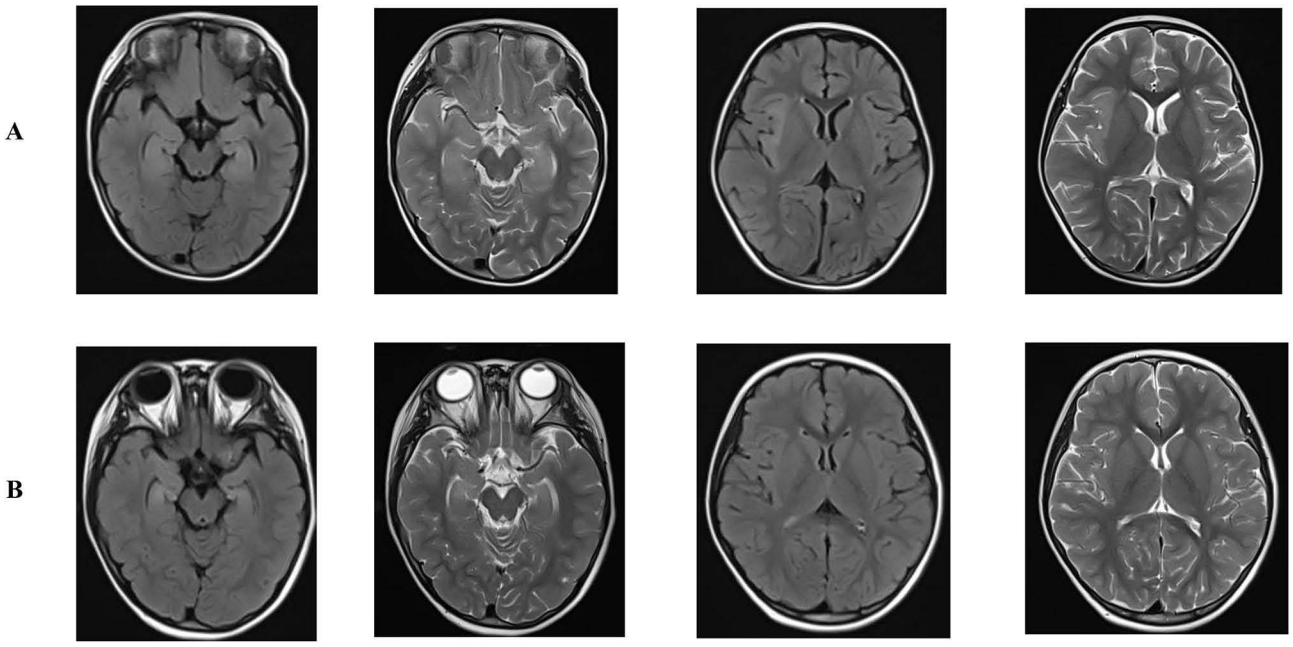

Figure 1 Brain magnetic resonance imaging (MRI) results. (**A**) The initial brain MRI taken on the 2nd month of the disease course; there is an increased intensity and edema in the bilateral hippocampi and right insular cortex. (**B**) The brain MRI taken at last follow up on the 22nd month of the disease course, the edema and lesions in the bilateral hippocampi and right insular cortex improved.

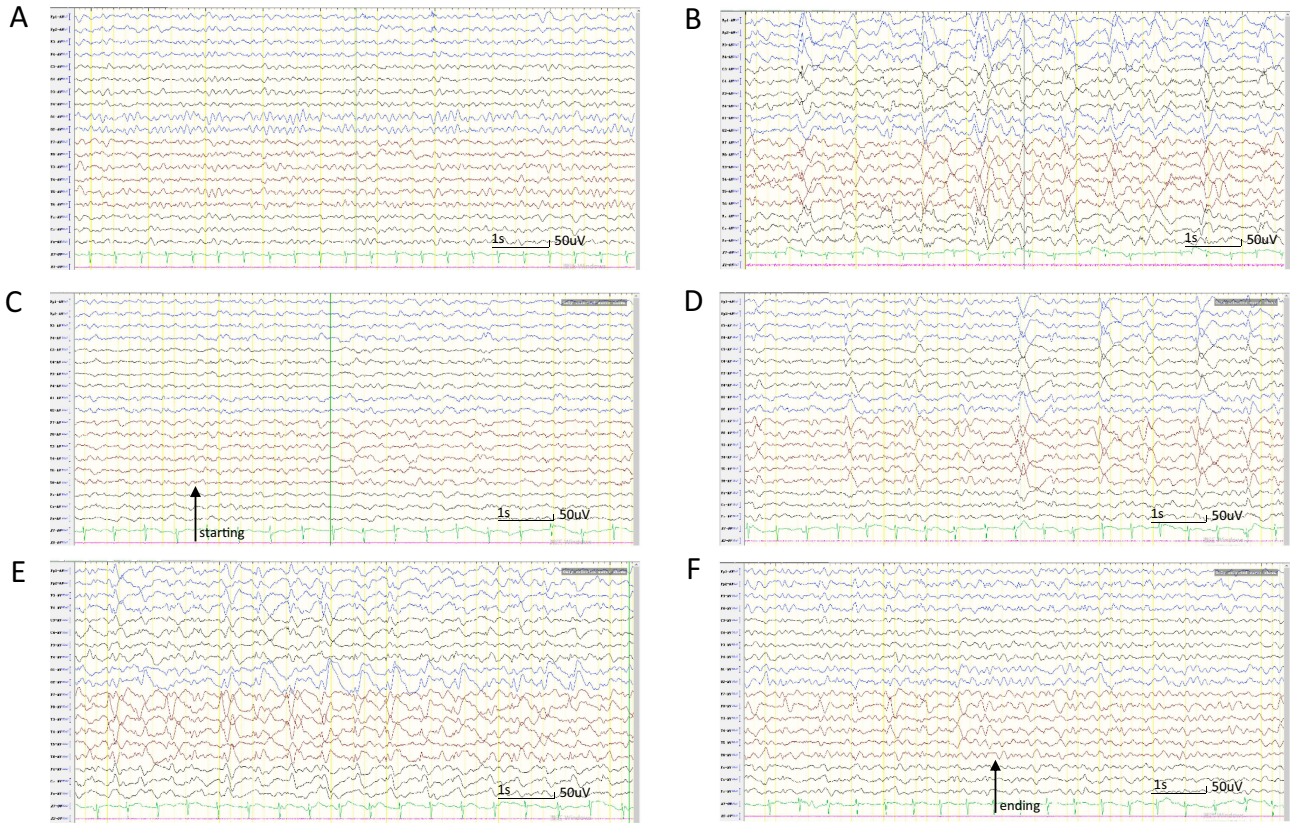

Figure 2 Electroencephalographic findings during the acute phase of the disease. (**A**) Background showing α rhythm in the occipital regions. (**B**) Typical inter-ictal discharges: bilateral multifocal sharp and spike-slow wave complexes of medium-high amplitude, more prominent in the right anterior region. (**C**–**F**) Compound consecutive figures showing one of the subclinical seizures: low-amplitude sharp wave bursts in the right anterior regions evolving into sharp slow wave complexes of medium-high amplitude bursts in the right hemisphere evolving to low-amplitude sharp and spike slow wave complexes bursts mainly in the right frontal and temporal regions with a duration of 81seconds. The arrows indicate the starting and ending of this subclinical seizure, respectively.

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continuous aggressive therapies, she still presented with abnormal behavior (mostly hyperactivity), poor cognition and uncontrolled seizures (her EEG once became normal in the 7th month of the treatment but it became worse later with occasional clinical seizures and frequent subclinical seizures according to the EEG monitoring) (Figure 3A–F).

In the 15th month of treatment, we gave her the first dose of tocilizumab (10 mg/kg), tapered off LCM due to the complained itchy rashes, added clobazam (CLB, 5mg bid) and repeated IVIG (1.5 g/kg in total) once. Her mental status improved obviously after the first dosage of the tocilizumab. Then in the following six months, we gave her another 5 cycles of tocilizumab (10–12 mg/kg), tapered down MMF, maintained the dosage of LEV and CLB and repeated IVIG (1 g/kg in total) once. Her cognition became better and better with the use of the tocilizumab, however, she got an upper respiratory tract infection once in between (after the 3rd cycle of tocilizumab) and regressed a little bit. We continued with tocilizumab and other therapies in the following months. At the end of the 20th month of treatment, she had no clinical seizures or subclinical seizures and the EEG was normal (Figure 4). In the 21st month of treatment, her behavior and cognition had improved significantly. Besides, brain MRI (Figure 1B) was improved too. She got mild side effects (upper respiratory tract infection and reduced Ig levels in the serum) after the third tocilizumab dose.

Written informed consent was obtained from the parents to have the case details and any accompanying image published and the study was approved by the ethical committee of Xiangya Hospital, Central South University according to the tenets of the Declaration of Helsinki. The institutional approval from the ethical committee of Xiangya Hospital, Central South University (approval number 202310892) was given to publish the case details.

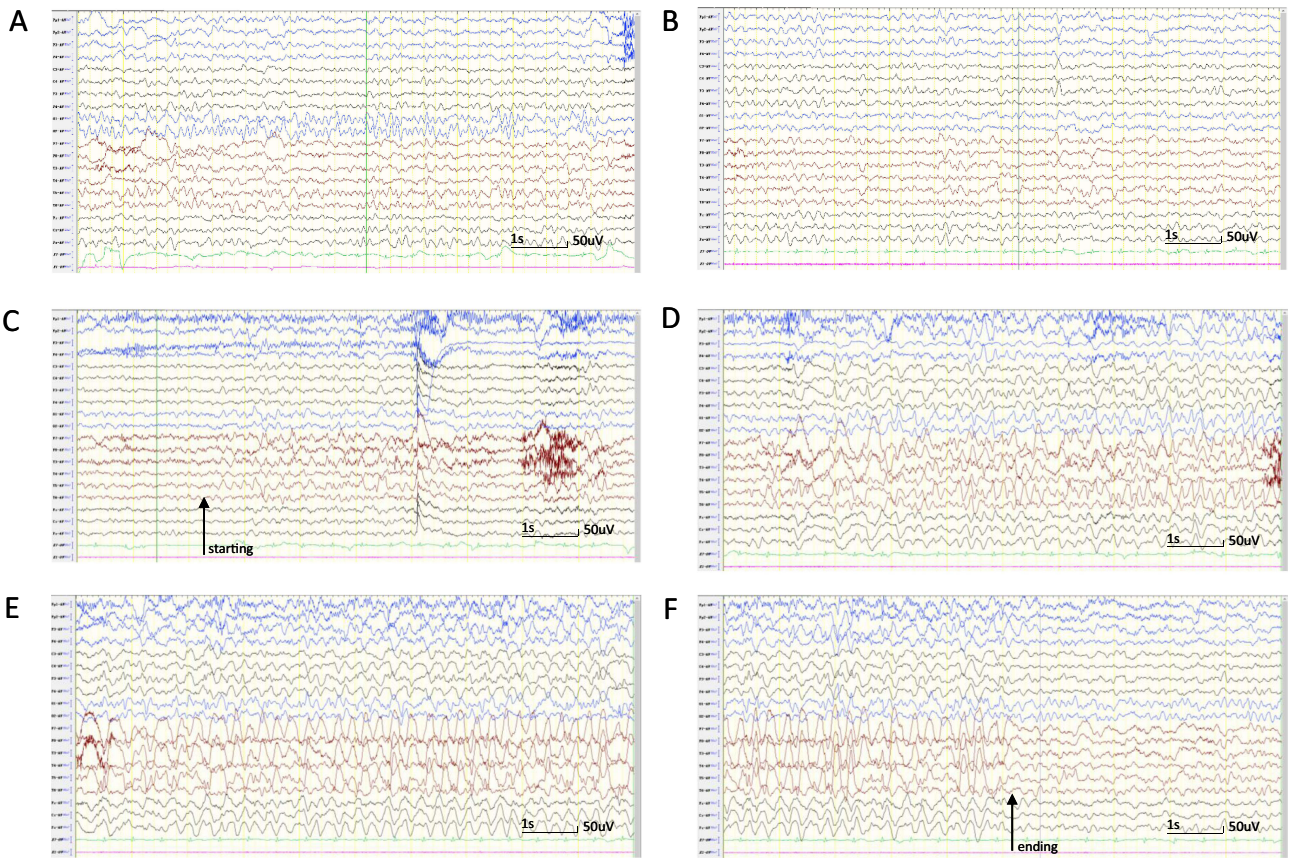

Figure 3 Electroencephalographic findings before tocilizumab treatment. (**A**) Background showing α rhythm in the occipital regions. (**B**) Typical inter-ictal discharges; multifocal sharp and spike-slow wave complexes prominent in the frontal and temporal lobes. (**C**–**F**) Compound consecutive figures showing one of the subclinical seizures: low-medium amplitude sharp or sharp-slow wave complex rhythms located in either left or right temporal regions, which spread to ipsilateral frontal region or hemisphere with a duration of 44 seconds. The arrows indicate the starting and ending of this subclinical seizure, respectively.

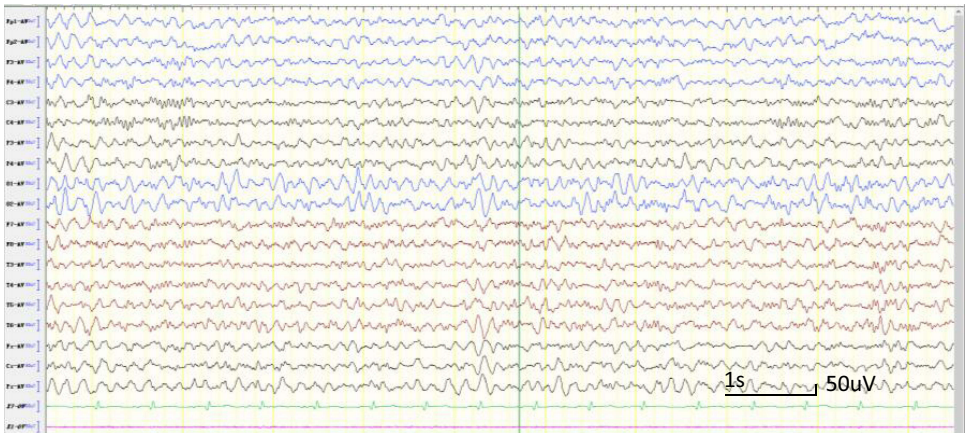

Figure 4 Electroencephalograph findings after 4 cycles of tocilizumab; the background with θ and α rhythm in the occipital regions without inter-ictal discharges.

Literature Review

A literature search was carried out in the PubMed. The key words for searching included: GAD AND (encephalitis OR epilepsy OR tocilizumab). Two published reports were retrieved.[12,13] Two cases with anti-GAD antibodies encephalitis treated with tocilizumab have been reported so far. Thus, we now have three cases if we add our patient. All three cases were females and the mean age of seizure onset was 7.72 years. They all presented with refractory seizures including status epilepticus in two cases, and altered mental status. Two cases presented with ataxia. Anti-GAD autoantibodies were elevated in both the serum and CSF for all cases. Two cases had abnormal brain MRI findings. All three cases had tried several combined ASMs and immunotherapies before tocilizumab but patients remained with refractory AE. ASMs tried included LEV, LCM, CLB: clobazam, phenytoin (PHT), clonazepam (CZP), sodium valproate (VPA), midazolam (MDZ), topiramate (TPM), ketogenic diet (KD), perampanel, phenobarbital (PB), intravenous propofol and ketamine. Immunotherapies used included several cycles of long-term use of IVIG, IVMP, rituximab, plasma exchange (PE) and MMF. Following several cycles of the tocilizumab, all cases had significant improvement; seizure freedom (n=1), seizure control (n=2), improved-normal cognition (n=3), improved neuropsychiatry symptoms (n=2) and controlled ataxia (n=2). Table 1 summarizes the clinical data of our case and patients from the literature.

Discussion

Our patient along with the two previous reported cases[14,15] provide more evidences that tocilizumab is effective and safe for the refractory anti-GAD antibodies related epilepsy. Our patient is the youngest in comparison to the other two. She presented with altered mental status and generalized tonic-clonic seizures, which started as status epilepticus, which is somehow similar to the presentation of one of the two reported cases.[14] Likewise, other studies of the anti-GAD related epilepsy treated with other therapies unveiled that patients can present with epilepsia partialis continua and refractory status epilepticus.[3] Prior to the use of tocilizumab, all three cases (including ours) received several combinations of ASMs, steroids and other immunotherapies, which led to temporary seizure control without improvement of other associated symptoms which concur with the current understanding of this condition.[2,5,8–11] However, the introduction of the tocilizumab to all cases led to the quick control of seizures as well as improvement of cognition, neuropsychiatric symptoms and ataxia. Tocilizumab has been reported as an effective therapy for other types of the refractory autoimmune encephalitis (AE) including anti-CASPR2 encephalitis,[16,17] anti-NMDAR encephalitis[18] as well as anti-LGI1 encephalitis.[19] In addition, there are some evidences that tocilizumab is effective to some refractory epileptic syndromes including new-onset refractory status epilepticus (NORSE)[20–24] and febrile infection-related epilepsy syndrome (FIRES).[25–27]

Tocilizumab is an interleukin-6 (IL-6) inhibitor. IL-6 is a molecule produced by T cells and is vital for the modulation of the antibodies' synthesis by B cells.[28] Besides, IL-6 can also be produced by astrocytes and neurons[29] and there is an evidence that high levels of the IL-6 in the brain can cause astrocytosis and neurodegeneration.[30] It has been reported that that high serum anti-GAD65 antibodies titers do not associate with disease severity or response to therapies.[2] However, the two

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Table 1 Demographics, Clinical and Treatment Information of the Patients Before After Receiving Tocilizumab

Clinical Feature	Our Case	Randell RL et al 2018[15]	Jaafar F et al 2020[14]
Age of onset	3 years and 2 months	12 years	8 years
Sex	Female	Female	Female
Clinical manifestations	Altered mental status, abnormal behaviors and generalized tonic-clonic seizures including status epilepticus, refractory subclinical seizures (multi-focal)	Refractory seizures, ataxia, altered mental status and psychiatric symptoms.	Focal seizures including status epilepticus, altered mental status and ataxia
Preceding manifestations	None	None	Febrile gastroenteritis
Concurrent disease Investigations	None	Type 1 diabetes mellitus and celiac disease	None
Evidence of pathogenic infection after screening	No	No	No
CSF analysis (autoantibodies)	GAD65 (1:100)	GAD (23 nmol/L)	GAD (303.1 U/mL)
Serum analysis (autoantibodies)	GAD65 (1:100)	GAD (398 nmol/L in serum)	GAD (303.1 U/mL)
Paraneoplastic screening	Negative	Unknown	Normal
CSF cells	Normal	Normal	Pleocytosis, 125 WBCs and the presence of 3 RBCs.
CSF protein	Normal	Unknown	Normal
CSF glucose	Normal	Unknown	Normal
Initial electroencephalograph	Multi-focal epileptic discharges, subclinical seizures	Multifocal complex seizures	Right temporal electro-clinical seizures
Initial brain MRI	Increased intensity in the bilateral hippocampi and right insular cortex	Brain atrophy in frontal and parietal lobes	Normal
Treatment and outcome before tocilizumab	Combinations of LEV and LCM were used but seizures were not controlled. The long-term aggressive immunotherapies were prescribed. Two cycles of IVMP pulse (continued with oral prednisone for 6 and 1 month separately); 11 cycles of IVIG (2g/kg, monthly to bimonthly). Moreover, 3 cycles of rituximab as well as MMF were given. However, she still had refractory subclinical seizures as well as abnormal behavior and poor recognition after these treatments.	Steroids, IVIG and rituximab improved ataxia and cognition and decreased seizure frequency. The dosages were increased and MMF was added, as a result, she experienced slow and partial clinical improvement over the two years. However, the patient deteriorated later; she developed refractory AE. The report did not indicate the use of ASMs	Combinations of ASMs including LCM, LEV, PHT, CZP and VPA was given without success. Due to refractory status epilepticus, she was given MDZ, CLB, TPM and perampanel, IVIG and IVMP. However, her seizures remained refractory so propofol, ketamine and PB was given and caused a partial seizure reduction. Five sessions of PE and KD were initiated but the patient remained with refractory seizures.
Consecutive EEGs	Frequent and refractory subclinical seizures (multifocal)	Unknown	Frequent electrographic multifocal seizures mainly from right and left temporal areas.

Outcome and treatment after or during tocilizumab	Her mental status as well as EEG improved obviously after the first dosage of the tocilizumab and she continued to improve with the following tocilizumab doses, but regressed a little bit after an upper respiratory tract infection once in between. She eventually reached the point of having significant improved behavior and EEG after 6 cycles of tocilizumab. The dose of MMF was decreased after the use of tocilizumab. LCM was stopped due to the possible side effects (rashes) but CLB was added at the same time then kept at the same dose, while LEV was maintained. At last follow up, patient had no seizures and cognition was normal	Tocilizumab was initiated due to refractory AE. Within 3 weeks of initiation of tocilizumab patient experienced reduction of seizure frequency, energy, mood, and daily functioning. Tocilizumab dosage was increased; consequently, seizures and psychiatric symptoms were improved two weeks later. Repeated CSF showed the decreased GAD titer to 4 nmol/L. At last follow up, she had maintained improvement however, her seizures had not fully resolved	Tocilizumab was initiated due to refractory AE. Tocilizumab was administered and she became seizure-free 24 h after the first dose of tocilizumab and three days following the initiation of KD. Ketamine and MDZ infusions were weaned and discontinued. She had rapid and significant clinical improvement. At 1 month of follow up, patient was symptom-free except for infrequent seizures, on three ASMs (PB, LEV and perampanel) and on a monthly tocilizumab infusion. Serum GAD antibody titer repeated three weeks later decreased to 30 U/mL
Repeated EEG	Normal	Unknown	Burst-suppression pattern on EEG.
Repeated MRI	Reduced intensity in the bilateral hippocampi and right insular cortex	Unknown	Mild parenchymal brain atrophy

Abbreviations: ASMs, antiseizure medications; AE, autoimmune encephalitis; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LCM, lacosamide; CLB, clobazam; LEV, levetiracetam; MRI, magnetic resonance imaging; PHT, phenytoin; CZP, clonazepam; VPA, sodium valporate; MDZ, midazolam; CLB, clobazam; TPM, topiramate; KD, ketogenic diet; PB, phenobarbital; PE, plasma exchange; EEG, electroencephalograph; MMF, mycophenolate mofetil.

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previous reported cases[14,15] treated with tocilizumab showed the reduction of the antibodies. It is unfortunate that we did not monitor the antibodies titer changes in our case since she recovered well. Currently, it is still unclear if anti-GAD65 antibodies are causative or only serve as a marker for AE induced by cytotoxic T cells,[2] nevertheless, based on the reported two cases, we speculate them to be pathogenic. Although we could not check and monitor IL-6 levels in the serum and CSF, we speculate that this cytokine might play a role in the pathogenesis of this type of AE as evidenced by the improvement of the three cases following the use of tocilizumab. Notably, a recent report showed that elevated plasma IL-6 are related with high GAD titers in epileptic patients.[31] Future studies are needed to explore the signaling pathways involved in the pathogenesis of anti-GAD65 related encephalitis connecting production of cytokines, chemokines and synthesis of auto-antibodies. Epilepsy in children represents an important problem and is associated with significant morbidities such as cognitive impairment, mood disorders (anxiety and depression) and attention deficit/hyperactivity disorder.[32,33] Therefore, it is crucial to identify therapies that can control seizures and minimize the comorbidities.

Conclusively, although anti-GAD65 antibodies related epilepsy is rare, it is a complex disease because it is difficult to manage even with multiple combinations of the ASMs, steroids and other immunotherapies. However, tocilizumab seems to be an effective therapy for the refractory anti-GAD65 related epilepsy as it can control seizures, improve cognition and neuropsychiatric symptoms. This case report supports the treatment with interleukin-6 inhibitors in similar cases of autoimmune encephalitis.

Study Limitations

We assessed our patient retrospectively hence; the study might be prone to the information bias. It is hard to tell the long-term outcome of the patient since we have followed her for a short period.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

The study including all methods adhered to the tenets of the Declaration of Helsinki and received approval from the Institutional Review Board and Research Ethics Committee of Xiangya Hospital, Central South University, Changsha, Hunan. Written consent was obtained from the parents of the subject, which were approved by the Institutional Ethics Committee of Xiangya Hospital, Central South University.

Consent to Publication

The consent for publication was obtained from the parents of the subject.

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We thank the participating patients and their families.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

None of the authors has any conflict of interest to disclose for this work.

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