Case Report

Favorable response to classic ketogenic diet in a child with anti-GAD 65 antibody mediated super refractory status epilepticus

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Article info
Article history:
Received 6 March 2022
Revised 30 May 2022
Accepted 5 June 2022
Available online 7 June 2022

Keywords:
Classic ketogenic diet
Super refractory status epilepticus
Autoimmune encephalitis

Abstract
Autoimmune encephalitis refers to a spectrum of inflammatory brain diseases which can present as drug-resistant seizures in children. Hereby, we report a case of anti-GAD-65 antibody encephalitis in a 7-year-old child who presented with superrefractory status epilepticus (SRSE). The traditional management with multiple anti-seizure medications at appropriate dosage and immunotherapy was tried despite which the child continued to have seizures. Hence the child was initiated on a classic ketogenic diet. He achieved ketosis within 48 h of diet initiation and there was a drastic reduction in the seizure frequency followed by a completed remission. Hence, this non-pharmacological intervention was an effective adjunct in achieving seizure control in our patient. A ketogenic diet has been sparingly used for the management of post-encephalitic epilepsy and autoimmune epilepsy. However, the data onthe effectiveness of the ketogenic diet in the management of autoimmune encephalitis is scarce. Starting KD early in the disease course helped not only in seizure control but also preserved the cognitive and neurological well-being of the child.

1. Introduction
Autoimmune encephalitis (AIE) in children usually presents with behavioral changes, drug-resistant seizures, and encephalopathy. Though anti-NMDA receptor antibody is the most common antibody associated with AIE, anti-VGKC antibodies, anti-GABA receptor antibodies, anti-GAD-65 antibodies and others have also been reported in children besides several cases of seronegative AIE [1]. We report a case of anti-GAD65-Ab AIE in a 7-year-old child with superrefractory status epilepticus (SRSE) in whom seizure control could not be achieved despite multiple anticonvulsants and immunotherapy. This case report focuses on the role of a non-pharmacological intervention namely the ketogenic diet which was used to augment the treatment. The management challenges faced during the prolonged duration of hospital stay will be highlighted.

2. Case summary
A 7-year-old developmentally normal boy presented to the emergency room with a low-grade fever of 5 days duration followed by multiple episodes of seizures. The seizure semiology included lip-smacking movements and right upper limb tonic-clonic movements lasting for around 2 min. His sensorium was normal during the period in between the seizures. The child was given intravenous (IV) loading doses of multiple anti-seizure medications (ASM) (in the order of sequence) including levetiracetam (60 mg/kg/day), sodium valproate (60 mg/kg/day), phenytoin (8 mg/kg/day), lacosamide (8 mg/kg/day), clobazam (1.2 mg/kg/day), oxcarbazepine (40 mg/kg/day) and Midazolam infusion at optimal dosages despite which the seizures persisted. Preliminary work up with cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) of the brain with gadolinium contrast were unremarkable. CSF showed no cells, glucose of 71 mg/dl, and proteins of 22.7 mg/dl. Electroencephalogram (EEG) showed bilateral diffuse background slowing suggestive of cerebral dysfunction. Refractory status epilepticus treatment protocol was followed and the child was continued on multiple ASMs, midazolam infusion, intravenous Immunoglobulin (IV Ig) (400 mg/kg/day) for 5 days, and IV pulse methylprednisolone (30 mg/kg/day) for 5 days were given, despite these measures, seizure control could not be achieved. The seizure frequency quadrupled from 3 to 4 episodes/day to 15–20 episodes/day of focal onset seizures. Given persistent seizures and a decline in the Glasgow coma scale, the child was intubated and put on mechanical ventilation. He was then trans-

https://doi.org/10.1016/j.ebr.2022.100557
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ferred to our hospital. He was on six ASMs at maximally tolerated dosages. The switch from levetiracetam to brivaracetam marginally reduced the seizures to nearly 10 episodes a day. An 18-FDG PET-CT (fluorodeoxyglucose-positron emission tomography) of the brain showed hypometabolic changes involving bilateral temporal and parietal lobes. CSF oligoclonal bands, anti-TPO antibodies, ANA, and anti-NMDAR antibody titers were negative. While serum and CSF GAD-65Ab were positive (serum GAD-65 antibody titre: 221 IU/ml [0–17] and CSF GAD-65 AB titre: 218 IU/ml [0–17]). Hence a diagnosis of anti-GAD-65 Ab-associated AIE was made. On day 7, second-line immunomodulation therapy with rituximab (750 mg/m2) was given. Since maximal doses of ASM, adequate first-line immunotherapy, and second-line immunomodulation did not achieve seizure control, a non-pharmacologic therapy in the form of a customized 4:1 proportion classic ketogenic diet (KD) was initiated. A non-fasting protocol was followed. Regular monitoring in the form of serial nutritional assessment, blood sugars, blood gas, and urinary ketones was done. A day after initiation of KD, only traces of the urine ketones were found. Within 48 h of KD initiation, the child achieved adequate ketosis (2+), and the seizure frequency was drastically reduced. The drug levels of the ASMs were checked periodically and dosages were adjusted accordingly. After 12 days of ventilator support and more than 72 h of complete seizure freedom, the child was extubated. KD was continued and tapering of ASMs sequentially was started. The clinical course of the child is depicted in Fig. 1 Seizure frequency depicted in Fig. 2.

A mini-mental status examination was done serially to objectively assess the higher mental functions, which showed a steady and gradually improving trend. The degree of disability and dependence were assessed weekly using the modified Rankin scale. The ketogenic diet was continued for three more months after his discharge and was slowly tapered and stopped over the next 3 months. Currently, the child is only on brivaracetam (1 mg/kg/day), lacosamide (4 mg/kg/day) and clobazam (0.3 mg/kg/day) and on regular follow-up once a month. He is now able to attend regular school with a good scholastic performance and has no sleep or neurobehavioral issues. The child had 2 brief breakthrough sei-

### Timeline of Hospital Events

| Week 1 | Fever, Seizure | Day 1: Onset of Fever | Day 2: Seizures | Day 3: 3-4 episodes of Seizures, Serum, CSF GAD, PSL and IVIg | Day 4: Cessation of Seizures, Serum, CSF GAD, PSL and IVIg | Day 5: Ketosis (2+), Seizure frequency reduced by 2 seizures/day | Day 6: Child achieved ketosis urinary ketones 2+ | Day 7: Child was alert and seizure control achieved with Multiple ASM, KD, Immunotherapy |
|-------|----------------|----------------------|----------------|------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------|
| Week 2 | Seizure        | Day 8: Increase in seizure frequency, observed from 2-4/10 in T1, 2/10/day | Day 9: Worsening of seizure frequency | Day 10: A classic 4:1 ketogenic diet (KD) was initiated | Day 11: Serial monitoring of nutritional assessment, sugars, blood gas, and urinary ketones monitored | Day 12: Child achieved ketosis urinary ketones 2+ | Day 13: Day 14: |
| Comments |                | Child was switched with ASM, pulse methylprednisolone and IVIg in an outside hospital despite which seizures persisted, CSF analysis and MRI brain normal. EEG showed diffuse slowing. Hence child was shifted to our hospital on ITU at illness. In our hospital, ASM continued and IVIg given for 5 days (400 mg/kg/day) and pulse methylprednisolone (30 mg/kg/day) for 5 days |
| Week 3 | Seizure        | Day 15: Child was alert and seizure control achieved with Multiple ASM, KD, Immunotherapy |
| Comments |                | Tapering of ASM started | Day 16: Child was seizure free | Day 17: Child was seizure free and control achieved with Multiple ASM and KD |
| Week 4/5 | Seizure        | Child was seizure free | Day 22-23: Child was seizure free | Day 24-25: Tapering of ASM started |
| Comments |                | The drug levels of ASM were measured and adjusted appropriately | Day 26-27: The mini-mental status examination was done serially to assess mental functions, which showed an improving trend. KD was continued |
| Week 5 | Seizure        | Day 28: Child was seizure free and alert. Child was discharged and the patient was discharged. KD was continued for 3 months after discharge and was slowly stopped. No sleep or behavioral disturbances. |

**ASMs**: Anti-seizure medications  
**KD**: ketogenic diet  
**EEG**: electroencephalogram  
**IVIg**: Intravenous immunoglobulin  
**GCS**: Glasgow coma scale

**Fig. 1.** Graphic representation of the in-hospital clinical course. ASMs: anti-seizure medications. KD: ketogenic diet. EEG: electroencephalogram. IVIg: Intravenous immunoglobulin. GCS: Glasgow coma scale.
zures, nearly-one-year after discharge which were triggered by fever and lack of sleep. His Modified Rankin scale was 1 at the last follow-up visit.

3. Discussion

Autoimmune encephalitis is a significant cause of encephalopathy in children [2]. Early initiation of appropriate immunosuppressive therapy leads to good cognitive and neurodevelopmental outcomes. In a review by Cellucci et al, the typical clinical features in children with anti-GAD encephalitis include memory loss, cognitive impairment, cerebellar ataxia, and temporal lobe seizures [3]. However, our child did not have memory loss or cerebellar ataxia.

Majority of children with autoimmune encephalitis present with seizures in the form of status epilepticus (SE) or super refractory status epilepticus (SRSE). SRSE is the SE that fails to terminate more than 24 h of anesthetic infusion or recurs on weaning of the infusion. This child also presented with SRSE following a mild prodromal illness.

In a study by Lilleker et al of 112 patients with unexplained adult-onset patients, 6 patients had high titters of anti-GAD Ab positivity, and all 6 of them presented with focal seizures [4].

The treatment modalities available for the management of pediatric AE are highly variable and patient-specific and include the usage of immunotherapy along with ASM whenever indicated. This child presented with SRSE which was not controlled even on multiple ASMs and benzodiazepine infusion. Since complete seizure freedom and preservation of the neuro-cognitive status of the child was our ultimate goal, a classic ketogenic diet (KD) was attempted in addition to the rational usage of ASMs and immunotherapy. The literature on the role of early KD therapy in pediatric AIE is scarce although its use in post-encephalitic epilepsy has been described [5].

$K_D$ is a non-pharmacological treatment modality used worldwide in people with drug-resistant epilepsy [6]. The exact mechanisms by which $K_D$ exerts an anti-seizure effect are still under investigation. Many anti-inflammatory mechanisms of KD have been proposed. Majorly $K_D$ improves mitochondrial function and decreases oxidative stress. One of the major ketone bodies namely B-hydroxybutyrate has been shown to reduce the production of reactive oxygen species (ROS), improving mitochondrial respiration. It also stimulates the cellular endogenous antioxidant system with the activation of nuclear factor erythroid-derived 2-related factor 2 (Nrf2) and modulates the ratio between the oxidized and reduced forms of nicotinamide adenine dinucleotide (NAD+/NADH). Furthermore, the ketogenic diet performs anti-inflammatory activity by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and leucine-rich-containing family thereby improving memory encoding [7].

KD is a long chain triglyceride-based, low carbohydrate diet. A classic 4:1 ketogenic ratio means 4 g of fat for every-one gram of protein and carbohydrate. Modified Atkins Diet (MAD) is one in which the ketogenic ratio is 1:1 which is usually home regulated [8]. In the absence of glucose, the brain utilizes ketone bodies as the fuel source [9]. Due to various mechanisms, it leads to an increase in GABAergic and a decrease in glutaminergic transmission leading to reduced neuronal excitability resulting in antiepileptic action. The majority of children achieve a significant reduction in seizure burden on $K_D$.

Febrile infection-related epilepsy syndrome (FIRES) is a form of pseudo-encephalitic epileptic encephalopathy that presents with drug-resistant status epilepticus in developmentally normal healthy children [10]. Treatment of FIRES with anti-seizure med-
The study concluded that KD therapies may be feasible and safe in the management of chronic PE and AAE. In our child, classic 4:1 KD was successful in reducing seizures greater than 50% reduction in seizures [5]. The study concluded that KD therapies may be feasible and safe in the management of chronic PE and AAE. In our child, classic 4:1 KD was successful in reducing seizures greater than 50% reduction in seizures [5].

**Table 1**

| AUTHOR AND YEAR | AGE/SEX | PRESENTATION | MRI | EEG | ANTI GAD | TREATMENT | OUTCOME |
|-----------------|---------|--------------|-----|-----|----------|-----------|---------|
| Nedia Ben Achow 2018 | 9y/F | refractory seizures, behaviour disturbances, severe intractable autonomic disturbances, dysrhythmia, tachy/bradycardia, increased or reduced BP, hypo/hyperthermia | MRI normal | EEG showed slowed theta rhythm and bilateral fronto temporal spike wave discharges | Anti GAD65 antibody positive | Two doses of IVIG, methyl prednisolone, rituximab | Died due to autonomic dysfunction after onset (fatal dysautonomia) |
| Haberlandt 2014 | 8y/F | Behavioural changes | MRI normal | Temporal lobe epilepsy | Anti GAD65 antibody positive | Steroids, IVIG | Restitution |
| Farunk Incicek 2014 | 7y/M | Behavioural changes, drowsiness, preceding URI a week prior | MRI normal | Bilateral temporal epileptiform abnormalities | Serum anti-GAD highly positive | Levitracetam, plasma exchange, IVIG | Improved |
| Chanhong Ren 2021 | 6y/F | Seizures, headache, memory deficit | MRI brain normal | EEG right sided epileptiform discharges | Serum GAD 1:100CBA and CSF 1:320CBA | IVIG, methyl prednisolone, rituximab | Refractory focal seizures |
| Chanhong Ren 2021 | 16y/F | Seizures, memory deficit, depression, dysautonomia, On 5 year followup parenchymal atrophy | MRI B/L hippocampal changes | EEG showed theta rhythm with bilateral temporal spike wave discharges | Serum GAD 1:32CBA and CSF 1:32CBA | IVIG, methyl prednisolone, oral steroids, rituximab | Persistent memory impairment and refractory focal seizures |
| Chanhong Ren 2021 | 4y9m/F | Vomiting, headache, confusion, epilepsy partialis continua, apalhia | MRI normal | EEG showed slowed theta rhythm | Serum GAD 1:100CBA and CSF 1:320CBA | IVIG, methyl prednisolone, oral steroids, rituximab | Complete recovery |
| Olson JA 2002 | 6y/M | Epilepsy partialis continua, apalhia | MRI gray matter changes | EEG showed left sided epileptiform discharges and slowing | Serum GAD 19610U/ml and CSF 3325U/ml | IVIG, methyl prednisolone, oral steroids, plasma exchange, IVIG, methyl prednisolone, IVIG | Seizure free |
| Akman CI 2009 | 16y/F | Focal seizures and status epilepticus, declining academic performance | MRI normal | EEG shows bilateral temporal abnormalities | Serum and CSF GAD greater than 300 IU/ml | IVIG, methyl prednisolone, plasma exchange, MMF, rituximab | Refractory seizures |
| Korff CM 2011 | 2y/F | Refractory seizures, memory impairment, developmental regression, ataxia | -MRI normal | -EEG shows interictal epileptiform abnormalities arising from right frontotemporal region | Serum GAD 1:16000CBA and CSF 1:128000CBA | Rituximab, plasma exchange, methyl prednisolone, IVIG | Clinical improvement but had refractory seizures |
| Bigis 2015 | 15y/M | Headache, memory disturbances, seizures, behavioural change | -MRI showed mildly increased signal in left amygdala and right hippocampus | -EEG shows interictal epileptiform abnormalities | Serum and CSF GAD positive | IVIG, methyl prednisolone, plasma exchange, MMF, rituximab | Excellent seizure control, improvement in transient global amnesia like episodes |
| Incecek F 2015 | 7y/M | Behavioural changes, drowsiness | -MRI normal | -EEG shows bilateral temporal epileptiform abnormalities | Serum and CSF GAD positive | IVIG, methyl prednisolone, plasma exchange, MMF, rituximab | Complete recovery |
| Current case | 7y/M | Refractory seizures, Lip-smacking movements and right upper limb | MRI brain normal | EEG diffuse background slowing | Serum and CSF GAD positive | ASM, IVIG, methyl prednisolone, ketogenic diet | Complete recovery |

**Table 2**

In a case series of ten patients by Husari et al, MAD was used in patients with post-encephalitis (PE) and autoimmune associated epilepsy (AAE) with a 70% responder rate and more than 50% reduction in seizures [5]. The study concluded that KD therapies may be feasible and safe in the management of chronic PE and AAE. In our child, classic 4:1 KD was successfully used for achieving seizure remission in anti-GAD65 encephalitis.


K\textsubscript{0} may be effective for the management of seizures in autoimmune-associated epilepsy and post encephalitis because of the anti-seizure properties and also by anti-inflammatory mechanisms of action. This could explain the high response rate seen in the patients [5].

Many prospective and retrospective studies have been done to evaluate the use of K\textsubscript{0} in the treatment of SRSE of various etiologies. But most of these studies are adult based. A few studies have reported the effectiveness of K\textsubscript{0} for management of SRSE in pediatric patients due to various etiologies specifically FIRES [13, 14]. In a case report with literature review by Prasoppokakorn et al, medium chain triglyceride based K\textsubscript{0} was reported to be beneficial in young adult patients with SRSE and AI encephalitis [15]. However to the best of our knowledge no study reports the utility of K\textsubscript{0} in autoimmune mediated SRSE in a child which makes this case report unique in its own way.

In a Saudi Arabian-based study by Ali HA et al, the benefits of a non-fasting protocol of ketogenic diets have been described. In their study, 16 children with drug-resistant epilepsy were chosen and all were hospitalized and started on K\textsubscript{0} either by the oral or nasogastric route. It concluded that nine (56 %) children experienced significant seizure improvement within 3 days of starting K\textsubscript{0}, with three children becoming seizure-free during the K\textsubscript{0}. Hence it was suggested that a non-fasting K\textsubscript{0} protocol is a safe and effective option for children with intractable epilepsy [16].

Data extrapolated from children suggests that most responders experience a reduction in seizures on K\textsubscript{0} within 14 days from initiation of the diet [17]. However, in our case, the child had a significant reduction in seizure frequency in just 48 h after initiation of K\textsubscript{0}.

To achieve complete clinical and electrographic seizure freedom, the ketogenic diet was used as an adjunct which turned out to be successful. The cognitive status of the child was preserved probably due to aggressive management early in the course of the disease.

This case report highlights the role of the utility of the classic ketogenic diet as an adjunct to ASM in children who fail to respond to immunotherapies in successfully managing a child with SRSE and anti-GAD65-Ab AIE. The child is on regular follow-up for more than a year. A serial clinical examination with developmental assessment is being performed at every visit. He remains seizure-free and can attend regular school with good scholastic performance. His Modified Rankin score was 1 at the last follow-up.

4. Limitations

This is a single case report based on a retrospective review. The natural history of SRSE in children would have been more evident in a case series. Serum ketones were not done and serial EEG monitoring could not be performed which we quote as limitations to our study.

5. Review of literature

A brief review of literature about the management of anti-GAD-65 Ab encephalitis in children is summarized in Table 1. It can be inferred that a trial of K\textsubscript{0} was not reported in any of them. This literature review shows that the management of anti-GAD 65 Ab encephalitis in children can be highly variable. The table below contains the summary of reported cases of pediatric anti-GAD-65 autoimmune encephalitis.

6. Conclusion

Anti-GAD-65 Ab encephalitis is a rare entity in children and requires aggressive management in the initial stages to elicit a favorable outcome. To the best of our knowledge, this is the first case of successful termination of SRSE in a child with anti-GAD autoimmune encephalitis. It is the need of the hour to systematically study the natural course of the disease and formulate treatment protocols incorporating newer treatment strategies including K\textsubscript{0}.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank the PICU team, electrophysiology department, nutritionist of Sri Ramachandra Institute of Higher Education and Research, Chennai, India, and the patient’s family members for their consent.

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