



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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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 on the 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.

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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 (IVIg) (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-

Abbreviations: ASM, Anti-seizure medications; GAD, Glutamic acid decarboxylase; AIE, Autoimmune encephalitis.

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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-FDGPET-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 (K_D) 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 K_D only traces of the urine ketones were found. Within 48 h

of K_D 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. K_D 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													
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7							
Week 1	Fever	Onset of fever													
	Seizure					Onset of Seizures	3-4 episodes of Lip Smacking Movements & Right Focal Seizures								
	Comments	Child was treated with ASM, pulse Methyl prednisolone 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 D7 of illness. In our hospital, ASM continued and IVIg given for 5 days (400mg/kg/day) and pulse methyl prednisolone (30mg/kg/day) for 5 days													
Week 2	Seizure	Increase in seizure frequency observed from 3-4/day to 15-20/day		Worsening of seizure frequency		A classic 4:1 ketogenic diet(KD) was initiated		Seizure frequency reduced to 1-2 seizures/day							
	Comments	Intubated in view of drop in GCS		Hence Rituximab (750mg/m ²) started		Serial monitoring of nutritional assessment, sugars, blood gas and urinary ketones were monitored		Child achieved ketosis urinary ketones 2+							
Week 3	Seizure	Child was afebrile and seizure control achieved with Multiple ASM, KD, Immunotherapy													
	Comments	Child was seizure free				Tapering of ASM started									
Week 4&5	Seizure	Child was afebrile and seizure control achieved with Multiple ASM and KD													
	Comments	The drug levels of ASM were measured and adjusted appropriately		A mini mental status examination was done serially to assess mental functions which showed an improving trend. KD was continued											
Week 6	Seizure	Child was seizure free and afebrile. Keto diet was liberalized and the patient was discharged. KD was continued for 3 months after discharge and was slowly stopped. No sleep or behavioural disturbances.													

	Fever
	Seizure

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. K_D: ketogenic diet. EEG: electroencephalogram. IVIg: Intravenous immunoglobulin. GCS: Glasgow coma scale.

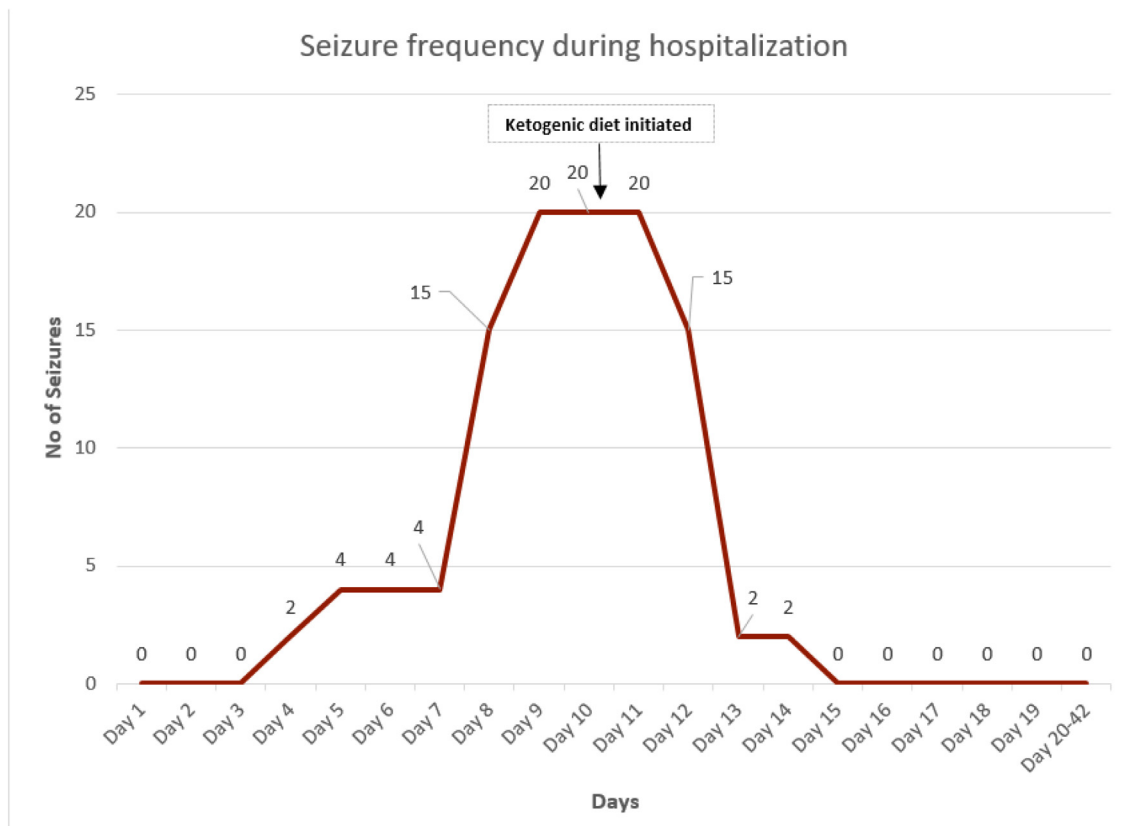


Fig 2. Seizure frequency during hospitalisation.

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 titers of anti-GAD Ab positivity, and all 6 of them presented with focal seizures [4].

The treatment modalities available for the management of pediatric AIE 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 ASM 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].

KD is a non-pharmacological treatment modality used worldwide in people with drug-resistant epilepsy [6]. The exact mechanisms by which KD exerts an anti-seizure effect are still under investigation. Many anti-inflammatory mechanisms of KD have been proposed. Majorly KD 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-kB) 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 glutamergic transmission leading to reduced neuronal excitability resulting in anti-epileptic action. The majority of children achieve a significant reduction in seizure burden on KD.

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-

Table 1

AUTHOR AND YEAR	AGE/SEX	PRESENTATION	MRI	EEG	ANTI GAD	TREATMENT	OUTCOME
Nedia Ben Achow 2018	9y/F	-refractory seizures -behavioural 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 -EEG bilateral temporal epileptiform abnormalities -All infective workup negative	MRI brain normal	Bilateral temporal epileptiform abnormalities	Serum anti-GAD highly positive	Levitracetam IVIG 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 Oral steroids	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 slowed 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	MRI normal	EEG showed slowed theta rhythm	-Serum GAD 1:100CBA and CSF 1:320CBA	IVIG Methyl prednisolone Oral steroids	Complete recovery
Olson JA 2002	6y/M	-epilepsia partialis continua, apahsia	MRI gray matter changes	EEG showed left sided epileptiform discharges and slowing	Serum GAD 19610U/ml and CSF 3325U/ml	High dose steroids IVIG Plasma exchange	Seizure free
Akman CI 2009	16y/F	-focal seizures and status epilepticus -declining academic performance		-EEG shows bilateral temporal abnormalities	Serum and CSF GAD greater than 300 IU/ml	Methyl prednisolone IVIG	Refractory seizures
Korff CM 2011	2y/F	-refractory seizures, memory impairment, developmental regression, ataxia	-MRI normal	-EEG shows multifocal discharges and right frontal seizures	-Serum GAD 3400 IU/ml and CSF 13U/ml	Methyl prednisolone Plasma exchange MMF Rituximab 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 discharges arising from right frontotemporal region	-Serum GAD 1:160000CBA and CSF 1:128000CBA	Rituximab Rituximab Prednisolone	Excellent seizure control, improvement in transient global amnesia like episodes
Incecik F 2015	7y/M	-behavioural changes -drowsiness	-MRI normal	-EEG shows bilateral temporal epileptiform abnormalities	-Serum and CSF GAD positive	IVIG Plasma exchange	Complete recovery
Current case	7 yr/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 Rituximab Ketogenic diet	Complete recovery

ications like phenobarbital, topiramate, immunoglobulin, steroids, and plasmapheresis has got limited success [11]. In such children, K_D proves to be more effective as per a paper by Singh et al [12].

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 K_D therapies may be feasible and safe in the management of chronic PE and AAE. In our child, classic 4:1 K_D was successfully used for achieving seizure remission in anti-GAD65 encephalitis.

K_D 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_D 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_D for management of SRSE in paediatric 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_D 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_D in autoimmunity 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_D either by the oral or nasogastric route. It concluded that nine (56%) children experienced significant seizure improvement within 3 days of starting K_D , with three children becoming seizure-free during the K_D . Hence it was suggested that a non-fasting K_D 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_D 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_D .

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_D 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_D .

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.

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References

- [1] Hacoen Y, Wright S, Waters P, Agrawal S, Carr L, Cross H, et al. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. *J Neurol Neurosurg Psychiatry* 2013;84(7):748–55.
- [2] Garg D, Mohammad SS, Sharma S. Autoimmune encephalitis in children: An update. *Indian Pediatr* 2020;57(7):662–70.
- [3] Cellucci T, Van Mater H, Graus F, Muscal E, Gallentine W, Klein-Gitelman MS, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm* 2020;7(2):e663.
- [4] Lilleker JB, Biswas V, Mohanraj R. Glutamic acid decarboxylase (GAD) antibodies in epilepsy: diagnostic yield and therapeutic implications. *Seizure* 2014;23(8):598–602.
- [5] Husari KS, Cervenka MC. Ketogenic diet therapy for the treatment of post-encephalitic and autoimmune-associated epilepsies. *Front Neurol* 2021;12:624202.
- [6] Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group. *Epilepsia* 2009;50(2):304–17.
- [7] Pinto A, Bonucci A, Maggi E, Corsi M, Businaro R. Anti-oxidant and anti-inflammatory activity of ketogenic diet: new perspectives for neuroprotection in Alzheimer's disease. *Antioxidants (Basel)* 2018;7(5):63.
- [8] Sharma S, Jain P. The ketogenic diet and other dietary treatments for refractory epilepsy in children. *Ann Indian Acad Neurol* 2014;17(3):253–8.
- [9] Lin KL, Lin JJ, Wang HS. Application of ketogenic diets for pediatric neuro critical care. *Biomed J* 2020;43(3):218–25.
- [10] Mikaeloff Y, Jambaqué I, Hertz-Pannier L, Zamfirescu A, Adamsbaum C, Plouin P, et al. Devastating epileptic encephalopathy in school-aged children (DESC): a pseudo encephalitis. *Epilepsy Res* 2006;69(1):67–79.
- [11] Van Baalen A, Häusler M, Plecko-Startinig B, Strautmanis J, Vlaho S, Gebhardt B, et al. Febrile infection-related epilepsy syndrome without detectable autoantibodies and response to immunotherapy: a case series and discussion of epileptogenesis in FIRES. *Neuropediatrics* 2012;43(04):209–16.
- [12] Singh RK, Joshi SM, Potter DM, Leber SM, Carlson MD, Shellhaas RA. Cognitive outcomes in febrile infection-related epilepsy syndrome treated with the ketogenic diet. *Pediatrics*. 2014;134(5).
- [13] Wang X, Gao X, Lu G, Lu Z, Zhou S, Wang Yi, et al. The ketogenic diet for paediatric patients with super-refractory status epilepticus in febrile infection-related epilepsy syndrome. *Acta Epileptologica* 2020;2(1).
- [14] Breu M, Häfele C, Glatzer S, Trimmel-Schwahofer P, Golej J, Male C, et al. Ketogenic diet in the treatment of super-refractory status epilepticus at a pediatric intensive care unit: A single-center experience. *Front Neurol* 2021;12:669296.
- [15] Prasoppokakorn T, Jirasakuldej S, Lakananurak N. Medium-chain triglyceride ketogenic diet is effective for treatment of an adult with super-refractory status epilepticus: a case report and literature review. *Eur J Clin Nutr* 2019;73(12):1594–7.
- [16] Alameen Ali H, Muthaffar O, AlKarim N, et al. The efficacy of non-fasting ketogenic diet protocol in the management of intractable epilepsy in pediatric patients: a single-center study from Saudi Arabia. *J Internat Med Res*. 2022.
- [17] Kossoff EH, Laux LC, Blackford R, Morrison PF, Pyzik PL, Hamdy RM, et al. When do seizures usually improve with the ketogenic diet? *Epilepsia* 2008;49(2):329–33.