Sequential Treatment with Modified Atkins Diet and Low Glycemic Index Treatment for Drug-Resistant Epilepsy in Children

Aparna Mulyan[1] Jaya Shankar Kaushik[1,2] Surekha Dabla[3]

[1] Department of Pediatrics, Pt. B. D. Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India
[2] Department of Pediatrics, All India Institute of Medical Sciences, Guwahati, Guwahati, Assam, India
[3] Department of Neurology, Pt. B. D. Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India

Address for correspondence Jaya Shankar Kaushik, MD, DM, Department of Pediatrics, All India Institute of Medical Sciences, Guwahati, Guwahati, Assam 781101, India (e-mail: jayashankarkaushik@gmail.com).

Neuropediatrics 2024;55:289–293.

Abstract

Objectives The present study was designed to study the efficacy of sequential dietary therapy with a modified Atkins diet (mAD) followed by low glycemic index treatment (LGIT) in treating drug-resistant epilepsy in children.

Methods This interventional study was conducted from February 2021 to February 2022 among children aged 6 months to 5 years who had failed to respond to more than two conventional and correctly chosen antiseizure medications. The primary endpoint was the proportion of good responders, that is, children with more than 50% seizure reduction. Secondary outcome measures were the proportion of children with seizure freedom, $>$ 90% seizure reduction, and the nature of parent-reported adverse events.

Results A total of 45 children were recruited for the study, with 6 children being lost to follow-up at 12 weeks. At 12 weeks, 30 of 39 (76.9%) children were good responders with more than 50% seizure reduction. Of these 30 children, 11 (24.4%) had more than 90% seizure reduction, with 9 (20%) achieving complete spasm freedom. Constipation was the most common side effect of the diet among the enrolled subjects.

Conclusion Clinicians can consider sequential dietary therapy with a mAD in the first month followed by LGIT in the next 2 months for treating children who could not tolerate mAD beyond 1 month.

Keywords
- infantile spasms
- Lennox–Gastaut syndrome
- drug-resistant epilepsy
- ketogenic diet

Introduction

Dietary therapy has been an established therapy for the management of drug-resistant epilepsy. Dietary therapy is indicated among those with drug-resistant epilepsy where two appropriately chosen antiseizure medications have failed.[1] Various dietary options include the classic ketogenic diet (KD), modified Atkins diet (mAD), low glycemic index treatment (LGIT), and medium chain triglyceride diet. The traditional KD is a medically supervised high-fat, low-carbohydrate, and restricted protein diet that maintains a chronic state of ketosis.[2] The classic KD is high in fat, appropriate protein (1 g/kg), and low in carbohydrates.[3] The fat-to-protein plus carbohydrate ratio (by weight) is often 1:1 initially and then increased to 4:1 or 3:1.[1] The mAD restricts the carbohydrate to 10 g daily, and the fat is encouraged.[4] The mAD allows meals containing 60% fat, 30% proteins, and 10% carbohydrates, thus being a nearly balanced diet compared with KD.[5] LGIT, in contrast, focuses on the glycemic index of the food rather than strict ratios of fats to carbohydrates and protein.[6]

received
March 23, 2024
accepted after revision
May 21, 2024
article published online
June 21, 2024

DOI https://doi.org/10.1055/s-0044-1787744.
ISSN 0174-304X.

The mAD has demonstrated an efficacy of 60% seizure reduction, and 50% of children on LGIT achieve > 50% seizure reduction.[7] LGIT is a less restrictive diet, with patients showing better compliance when compared with mAD. Considering poor compliance with mAD, authors stipulate that those of mAD can be shifted to LGIT without loss of efficacy. Despite data on the effectiveness and safety of the mAD and LGIT, there is no evidence to assess the efficacy of combined or sequential dietary therapy when we switch from one dietary therapy (mAD) to a less restrictive diet (LGIT). With this background, the present study was conducted to study the efficacy and safety of combined dietary treatment using the mAD in the first month, followed by LGIT.

Methods

This study was conducted in a tertiary care referral center's department of pediatrics and neurology. The data was collected from February 2021 to March 2022. We obtained ethical approval from the Institutional Ethics Committee [BREC/Th/20/Peds011]. The patient information sheet was provided to the parents or legal guardians before obtaining the written informed consent.

Children aged 6 months to 5 years with drug-resistant epilepsy were consecutively enrolled in the study. Drug-resistant epilepsy was defined as a failure (seizure persisting daily or > 7/week) of adequate trials of two well-tolerated and appropriately chosen antiseizure medication schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[8] Children with known or suspected inborn errors of metabolism,[1] systemic illness, severe acute malnutrition, and those having motivational and psychosocial issues in the family were excluded from the study. Children with surgically remedial lesions like tumors, cortical dysplasia, and mesial temporal sclerosis were also excluded from the study.

The baseline demographic and clinical details were recorded, including the frequency of seizures, the nature of antiseizure medications, and their doses. Medications were changed to carbohydrate-free preparations. A baseline electroencephalogram (video EEG whenever possible) was performed during enrolment. Eligible participants were administered mAD for the first month and subsequently shifted to LGIT for the next 2 months. The LGIT was introduced gradually 1 week before the schedule of 1 month so that the transition could be gradual and not sudden and the parents and the children could adjust to the new diet.

In the mAD, carbohydrate was restricted to 10 g/day (18–60 months of age) and 5 g/day (9–18 months of age).[9] The carbohydrate content of daily food was explained to parents, and the exchange list was provided. Fats (cream/oil/butter/ghee) were encouraged. Clear carbohydrate-free fluids were not restricted. A list of recipes from locally available food was provided. A list of dietary options with a glycemic index of less than 50 was provided in the LGIT group. The LGIT diet consisted of an increased intake of carbohydrates with a specific goal of 40 to 60 g per day.[10] Calcium and multivitamin supplementation were prescribed in the form of tablets.

The parents of enrolled participants were encouraged to maintain a daily seizure log in the seizure diary for a 1-week observation period. Medications were changed to carbohydrate-free preparations, wherever available. Steroid/ hormonal therapy, if any, was tapered. All children were reviewed as outpatients every 2 weeks. At each follow-up visit, a 24-hour dietary intake chart was reviewed, and compliance with the prescribed diet was reinforced. Weight was checked at each visit. Parents were asked to measure urine ketones at least twice weekly.

The tolerability of the diet was evaluated using parental interviews at each visit. Parents were questioned for the presence and frequency of the following symptoms: vomiting, lethargy, poor appetite, refusal to feed, and constipation. Any other parental concerns were also recorded. A 2-mL fasting venous blood sample was drawn for liver and renal function tests and lipid profile at baseline and repeated at the end of 12 weeks. A 30-minute EEG record (video EEG whenever possible), including at least one sleep-wake cycle, was performed at baseline and repeated at 12 weeks.

The primary outcome measure was the proportion of patients who were "good responders" at the end of 12 weeks. Good responders were considered as those patients with > 50% seizure reduction (seizure frequency measured as average seizure per week in the preceding 4-week period) from the baseline.[11] Secondary outcome measures included the proportion of children who achieved seizure freedom at 12 weeks and the description and proportion of parent-reported adverse effects.

All data collected were entered in Microsoft Excel. Data were analyzed using the SPSS 21.0 version. All categorical variables were expressed in numbers (percentage), and all continuous variables were expressed as median (interquartile range). The laboratory parameters were compared between the baseline and 12 weeks using paired *t*-tests, and a *p*-value of < 0.05 was considered significant.

Results

Seventy-five children with drug-resistant epilepsy visited the center between February 2021 and February 2022. Out of these 75 patients, 53 agreed to participate in the study. Of these 53 willing participants, 45 children were enrolled (excluded [$n = 8$]: a suspected inborn error of metabolism [$n = 1$], hepatic dysfunction [$n = 1$], severe acute malnutrition [$n = 3$], surgically remedial causes of epilepsy [$n = 1$], and motivational issues in family [$n = 1$]). Six children were lost to follow-up, of whom 4 were lost within the first month of mAD, and the remaining 39 children completed the 12-week follow-up. All six children were diagnosed with West syndrome, and their demographic and clinical characteristics were comparable to those who continued follow-up till 12 weeks.

The baseline characteristics of enrolled participants are enumerated in ►**Table 1**. Most of the enrolled children had West syndrome ($n = 35$ [77.7%]), and the rest had possible evolution to Lennox–Gastaut syndrome ($n = 10$ [22.2%]). Etiology was secondary to perinatal insult in all enrolled children, with perinatal asphyxia (26 [57.7%]) being the most common cause.

Table 1 Baseline characteristics of enrolled participants ($n = 45$)

Characteristic	Observation
Age in months, median (IQR)	18 (12.50, 24.0)
Age at onset of epilepsy, median (IQR)	5.0 (3,7)
Male gender	28 (62.2%)
Perinatal and postnatal history, *n* (%)	
Asphyxia	26 (57.7)
Meningitis	11 (24.4)
Hyperbilirubinemia	2 (4.4)
Hypoglycemia	6 (13.3)
Microcephaly	38 (84.4)
Type of seizure	
Epileptic spasms, *n* (%)	28 (62.2)
Other seizure types, *n* (%)	17(37.8)
Antiseizure medication	
Valproate	45 (100)
Clonazepam	44 (97.8)
Vigabatrin	25 (55.6)
Levetiracetam	29 (64.4)
Lamotrigine	4 (8.8)
Zonisamide	1 (2.2)
Topiramate	13 (28.9)
EEG	
Hypsarrhythmia	20 (44.4)
Multifocal	22 (48.7)
Generalized	1 (2.2)
Normal	2 (4.4)

Abbreviations: EEG, electroencephalogram; IQR, interquartile range.

At the end of 4 weeks, 17 of 45 (37.7%) children were good responders. At 12 weeks, 30 of 39 (76.9%) children were good responders with more than 50% seizure reduction. Seizure frequency at baseline and at 12 weeks are shown in ►**Fig. 1**. Of these 30 children, 11 (24.4%) had more than 90% seizure reduction, with 9 (20%) achieving complete spasm freedom. Constipation was the most common side effect of the diet among the enrolled subjects. Lethargy was the second most common adverse effect (►**Table 2**).

Table 2 Outcome measures of enrolled participants

Outcome measure	Observation
> 50% seizure reduction (good responders)	30 (66.7%)
Seizure freedom	9 (20%)
> 90% seizure reduction	11 (24.4%)
Adverse effects	$N = 45$
Constipation, *n* (%)	28 (62.2)
Lethargy, *n* (%)	3 (6.7)
Vomiting, *n* (%)	9 (20.0)
Severe adverse effects, *n* (%)	1 (2.2)

Ketosis achieved by the enrolled participants at the end of 12 weeks was classified as trace (3 [6.7%]), mild (5 [11.1%]), moderate (17 [37.8%]), and large (14 [31.1%]). There was a statistically significant fall in hemoglobin level with an increase in serum glutamic pyruvic transaminase, serum glutamic-oxaloacetic transaminase, and serum cholesterol levels on laboratory parameter monitoring. Still, all the values were within the standard, acceptable range (►**Table 3**).

Discussion

The present study assessed the efficacy of sequential mAD followed by LGIT among children under 5 years with drug-resistant epilepsy. This noncomparative study revealed that 76.9% of children achieved > 50% reduction in seizures with sequential dietary therapy at the end of 12 weeks. The diet was well tolerated, with the majority having constipation.

In the present study, most enrolled children were diagnosed with West syndrome with a median age of 21 months at the time of enrolment. The predominant etiology was perinatal asphyxia. Previous studies have also demonstrated the predominance of perinatal insult in the etiology of West syndrome.[12] Most of them had failed to respond to

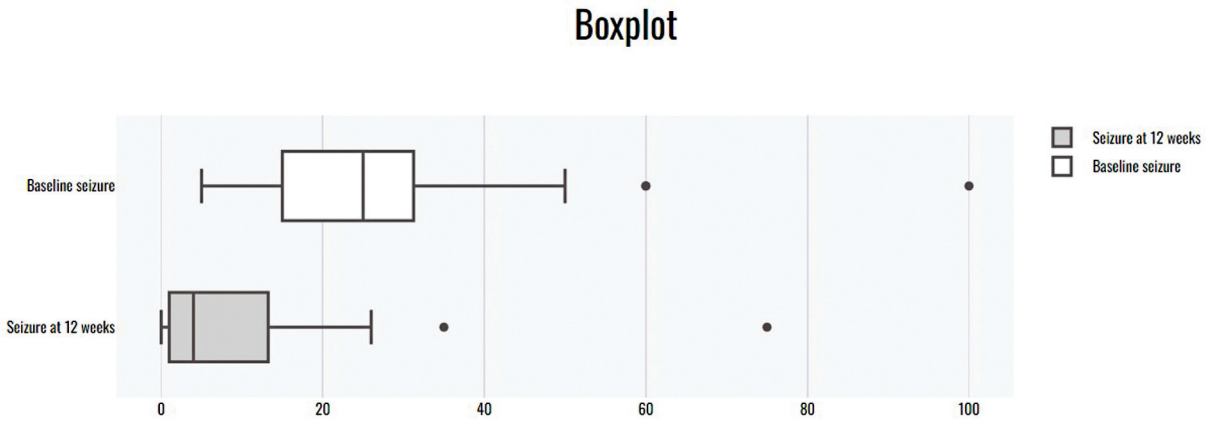

Fig. 1 Box and whisker plots of seizure frequency at baseline and at 12 weeks.

Table 3 Comparison of laboratory parameters from baseline to 12 weeks

Parameter	Baseline	At 12 weeks	*p*-Value
Hemoglobin (g/dL)	9.75 (1.6)	9.25 (1.27)	0.02
Blood sugar (mg/dL)	98.97 (17.90)	94.33 (15.77)	0.12
Serum sodium (meq/L)	140.46 (3.75)	141.56 (4.204)	0.27
Serum potassium (meq/L)	4.27 (0.45)	4.34 (0.379)	0.39
Serum calcium (mg/dL)	9.436 (0.76)	9.63 (0.714)	0.26
Aspartate aminotransferase (IU/L)	30.36 (13.30)	37.13 (11.37)	< 0.01
Alanine aminotransferase (IU/L)	27.69 (13.26)	35.67 (11.28)	< 0.01
Blood urea (mg/dL)	20.74 (5.36)	20.82 (5.69)	0.93
Serum cholesterol (mg/dL)	40.51 (29.51)	151.72 (25.51)	< 0.01
High-density lipoprotein (mg/dL)	47.08 (10.08)	47.72 (7.59)	0.72
Low-density lipoprotein (mg/dL)	78.15 (22.31)	82.51 (21.37)	0.16

prednisolone or adrenocorticotropic hormone and vigabatrin. Hence, the results of the present study cannot be extrapolated beyond this relatively homogenous population of drug-resistant epilepsy. Moreover, many authors have used various definitions for drug-resistant epilepsy. Reports range from failure of three antiepileptic drugs by Tonekaboni et al,[13] occurrence of more than four spasm clusters per month despite treatment with two or more than two antiepileptic drugs by Sondhi et al,[9] or daily infantile spasms persisting more than 6 weeks with at least one cluster per day and EEG evidence of hypsarrhythmia and failure of hormonal treatment and vigabatrin by Sharma et al.[2]

Most studies, however, have shown an efficacy of 50 to 60% with mAD.[10] The primary outcome measure for the present study was considered good responders per the parental reports at 12 weeks. In the present study, 30 out of 39 children who completed the 12-week follow-up had achieved $> 50\%$ seizure reduction, accounting for nearly three-fourths of children being good responders with this sequential treatment. These findings are consistent with previous studies quoting 70 to 77.8% efficacy of LGIT on seizure reduction of more than 50%.[11,14–18]

In a study by Sondhi et al,[9] the median change with KD was 60%, mAD was 45%, and LGIT was 54%. In a study by Tonekaboni et al,[13] 67% of children on mAD had $> 50\%$ seizure reduction, like the present study. Hence, the comparable results of the sequential dietary therapy with isolated LGIT revealed that the sequential dietary treatment does not improve the efficacy of the dietary therapy.

Although the diet was well tolerated, nearly two-thirds of the children complained of constipation. Other reported adverse effects included vomiting in almost 20% and lethargy. This was similar to the study conducted by other authors, in which constipation was the most common adverse effect in children on mAD.[1,6,14] However, severe adverse effects have not been reported with LGIT.[18]

The present study was a descriptive study providing a novel insight into the combined sequential dietary therapy with mAD in the first month, followed by LGIT in the subsequent 2 months. The present study shows that shifting from mAD to LGIT is safe after 1 month of mAD. This might be useful for those facing mAD compliance issues. The present study has limitations of not having a comparative group, a small sample size, and a 3-month follow-up period. Attrition rates in the present study (6 out of 45 children) need to be kept in mind while interpreting the results of the present study. The majority (4 out of 6) of dropouts was in the first month of mAD, and their clinical characteristics were like those who continued in the study. Attrition rates with LGIT are minimal, forming the basis for the present study to shift from mAD to LGIT.

Further research is needed to study the long-term outcome of the diet on seizure control, growth, and biochemical parameters. In addition, a comparative trial of sequential treatment with mAD alone could provide more meaningful results.

Ethical Approval

An institutional ethical approval was obtained before the commencement of the study.

Authors' Contributions

J.S.K.: Concept and design of the study; A.M., S.D., J.S.K.: data collection, analysis, and interpretation of data; J.S.K., A.M.: drafting the manuscript and review of literature; J.S.K., S.D., A.M.: critical review of the manuscript for intellectual content and final approval of the version to be published; J.S.K.: clinician-in-charge, critical review of the manuscript for intellectual content, final approval of the version to be published, and will act as guarantor for the paper. All authors approve of the final version.

Funding

None.

Conflict of Interest

None declared.

Acknowledgment
We wish to thank Prof. (Col) Vishal Sondhi for suggesting this concept of sequential dietary therapy.

References

1 Kossoff EH, Zupec-Kania BA, Auvin S, et al. Charlie Foundation Matthew's Friends Practice Committee of the Child Neurology Society. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open 2018;3 (02):175–192
2 Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. Epilepsia 2013;54(03):481–486
3 Miranda MJ, Mortensen M, Povlsen JH, Nielsen H, Beniczky S. Danish study of a modified Atkins diet for medically intractable epilepsy in children: can we achieve the same results as with the classical ketogenic diet? Seizure 2011;20(02):151–155
4 Kossoff EH, Dorward JL. The modified Atkins diet. Epilepsia 2008; 49(Suppl 8):37–41
5 Kossoff EH, Cervenka MC, Henry BJ, Haney CA, Turner Z. A decade of the modified Atkins diet (2003–2013): Results, insights, and future directions. Epilepsy Behav 2013;29(03):437–442
6 Grocott OR, Herrington KS, Pfeifer HH, Thiele EA, Thibert RL. Low glycemic index treatment for seizure control in Angelman syndrome: a case series from the Center for Dietary Therapy of Epilepsy at the Massachusetts General Hospital. Epilepsy Behav 2017;68:45–50
7 Sondhi V, Sharma S. Non-pharmacological and non-surgical treatment of refractory childhood epilepsy. Indian J Pediatr 2020;87(12):1062–1069
8 Krauss GL, Sperling MR. Treating patients with medically resistant epilepsy. Neurol Clin Pract 2011;1(01):14–23
9 Sondhi V, Agarwala A, Pandey RM, et al. Efficacy of ketogenic diet modified Atkins diet, and low glycemic index therapy diet among children with drug-resistant epilepsy: a randomized clinical trial. JAMA Pediatr 2020;174(10):944–951
10 Park EG, Lee J, Lee J. Use of the modified Atkins diet in intractable pediatric epilepsy. J Epilepsy Res 2018;8(01):20–26
11 Kim SH, Kang HC, Lee EJ, Lee JS, Kim HD. Low glycemic index treatment in patients with drug-resistant epilepsy. Brain Dev 2017;39(08):687–692
12 Kaushik JS, Patra B, Sharma S, Yadav D, Aneja S. Clinical spectrum and treatment outcome of West Syndrome in children from Northern India. Seizure 2013;22(08):617–621
13 Tonekaboni SH, Mostaghimi P, Mirmiran P, et al. Efficacy of the Atkins diet as therapy for intractable epilepsy in children. Arch Iran Med 2010;13(06):492–497
14 Muzykewicz DA, Lyczkowski DA, Memon N, Conant KD, Pfeifer HH, Thiele EA. Efficacy, safety, and tolerability of the low glycemic index treatment in pediatric epilepsy. Epilepsia 2009;50(05):1118–1126
15 Gupta S, Dabla S, Kaushik JS. Modified Atkins diet vs low glycemic index treatment for drug-resistant epilepsy in children: an open label, randomized controlled trial. Indian Pediatr 2021;58(09): 815–819
16 Karimzadeh P, Sedighi M, Beheshti M, Azargashb E, Ghofrani M, Abdollahe-Gorgi F. Low glycemic index treatment in pediatric refractory epilepsy: the first Middle East report. Seizure 2014;23 (07):570–572
17 Lakshminarayanan K, Agarawal A, Panda PK, et al. Efficacy of low glycemic index diet therapy (LGIT) in children aged 2-8 years with drug-resistant epilepsy: a randomized controlled trial. Epilepsy Res 2021;171:106574
18 Coppola G, D'Aniello A, Messana T, et al. Low glycemic index diet in children and young adults with refractory epilepsy: first Italian experience. Seizure 2011;20(07):526–528