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Original Article

The Ketogenic and Modified Atkins Diet Therapy for Children With Refractory Epilepsy of Genetic Etiology

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ABSTRACT

Background: The ketogenic diet is an accepted treatment modality in refractory childhood epilepsy. In this study, we analyzed the efficacy and tolerability of the ketogenic and modified Atkins diets in children with refractory epilepsy of genetic etiology and studied the effect of the diet on seizure frequency.
Methods: The records of children with a genetic etiology for refractory epilepsy treated with ketogenic and modified Atkins diet between September 2005 and July 2016 were reviewed. We documented age of seizure and diet onset, seizure characteristics, and specific genetic etiology. The proportion of children remaining on the diet and responder rates (greater than 50% seizure reduction) were noted at one, three, six, 12, and 24 months after diet initiation. Tolerability and safety profile were also recorded.
Results: Fifty-nine children with a genetic etiology (63% females, median age at diet onset 2.2 years) were initiated on the diet at our center. Fifty-three (90%) were started on a traditional ketogenic diet, whereas six started a modified Atkins diet. The adverse events at the initiation of diet were vomiting (24%), hypoglycemia (15%), and refusal to feed (11%). Three children stopped the diet before discharge because of poor compliance, severe reflux, and ketoacidosis (n = 1 each). The proportion of children remaining on the diet at one, three, six, 12, and 24 months was 95%, 86%, 69%, 64%, and 47%. The responder rates were 63%, 61%, 54%, 53%, and 41% at one, three, six, 12, and 24 months, respectively.
Conclusions: The ketogenic diet is an effective treatment modality in children with refractory epilepsy of genetic etiology.

Introduction

Intractable epilepsy, defined by the International League Against Epilepsy as a failure of adequate trials of two tolerated and appropriately chosen and dosed antiepileptic drug (AED) schedules, is seen in approximately 10% to 20% of children with epilepsy.[1-3] The ketogenic diet (KD) is an important therapeutic option for early onset, medically intractable epilepsy particularly if surgical resection is not an option.[4]

Many of the severe genetic disorders have developmental consequences arising directly from the effect of the genetic mutation, in addition to the potential effect of the frequent epileptic activity on development.[5] Nearly 40% of the causes for epilepsy are now known to be because of genetic factors.[6] Berg et al.[7] reported that genetic testing provided a diagnosis in one-fourth of children whose cause would have otherwise remained unresolved. Although genetic etiology is not an absolute contraindication for resective surgery, many children with genetic mutations have medically refractory epilepsy not amenable for resective, potentially curative surgery. The KD and modified Atkins diet (MAD) are used as an established nonpharmacologic alternative for medically refractory epilepsy.

We analyzed the response to the diet in various genetic etiologies and the difference in response to the diet, if any, that exists between these genetic etiologies, as there is a paucity of such data in the current literature. Most evidence is from studies focusing on one particular etiology. Ko et al.[8] studied the efficacy of KD for specific genetic mutation in 73 children with developmental and epileptic encephalopathy who had a pathogenic mutation and

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found a difference in the seizure response among different mutations. The goal of our retrospective study was to evaluate the efficacy and tolerability of dietary therapy for children with refractory epilepsy of genetic etiology and determine the various factors that may affect the response rates.

Methods

The present study was a single center, retrospective study of children with refractory epilepsy of proven genetic etiology. All children with genetic epilepsy treated at Mayo Clinic, Rochester, in the age group of zero to 18 years at commencement of the KD and MAD between September 2005 and July 2016 were included. We excluded subjects with refractory epilepsy of genetic etiologies resulting in a structural abnormality, such as tuberous sclerosis or lissencephaly. The prospectively maintained KD database at our institution allowed for the complete identification of study subjects. We performed additional chart review of these patients to collect the following data:

(1) Demographics, including sex and current age. (Table 1)
(2) Epilepsy characteristics including age at seizure onset, age at KD or MAD initiation, type of seizure(s), epilepsy syndrome (when known), seizure frequency before and after diet initiation, number of AEDs failed before KD initiation, and prior epilepsy surgery. The seizure frequency in the baseline period of one month was determined from the epileptologist's notes, and this was based on the seizure diary maintained by parents in the last month before diet initiation.
(3) Specific genetic etiology was determined through karyotyping, chromosomal microarray, epilepsy gene panels, or whole-exome sequencing.
(4) Developmental milestones before starting the diet: we categorized development as normal or suspect delay, mild delay (defined as an estimated developmental quotient of 50 to 70), and moderate to severe delay (estimated developmental quotient of less than 50), based on the developmental level noted on formal testing, or if that was absent, based on developmental milestones recorded in the chart.
(5) KD and MAD initiation and maintenance details, including the type of diet started (traditional KD or MAD), KD formulation (liquid only [oral or tube fed], combination of liquid and solid, or just solid diet), initiation site (hospital or home), diet ratio at the various time points (Table 2), and complications during diet initiation and maintenance (Tables 3 and 4).
(6) Diet efficacy and duration were assessed at one, three, six, 12, and 24 months follow-up. Response to diet was classified as nonresponders (no response or reduction of seizures by less than 50%), and responders (50% to less than 75% seizure reduction, 75% to less than 90% seizure reduction, 90% to 99% seizure reduction, and complete seizure freedom). The response rate was calculated as a proportion of the total number of patients initially enrolled (n = 59). At each time point, we documented the reported ketosis range, dietary ratio, history of adverse events (AEs), reason for stopping the diet (if applicable), and AED changes made.
(7) Values in the study are expressed as the median with the interquartile range (IQR) or as the number, ratio, and percentage. Comparisons between two groups were performed using chi-square tests for categorical data and values of $P < 0.05$ were considered statistically significant. The software used for analysis was JMP pro version 13.0 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA).

TABLE 1.
Demographic, Seizure, and Genetic Etiology Characteristics

Variable	Frequency and Characteristics
Sex	
Female	37 (63%)
Male	22 (37%)
Median age at seizure onset (years)	0.5 (0.1, 1)
Median age at diet onset (years)	2.2 (1.1, 5.3)
Seizure types at diet initiation	
Focal	32 (54%)
Absence	24 (41%)
GTC	18 (31%)
Myoclonic	18 (31%)
Spasms	15 (25%)
Tonic	13 (22%)
Epilepsy syndromes	32 (52%) had a known syndrome
LGS	10 (17%)
DS	9 (15%)
West	8 (14%)
MMPSI	3 (5%)
EME	1 (4%)
Ohtahara syndrome	1 (4%)
Seizure frequency	
Daily	48 (81%)
Weekly or less	11 (19%)
Development delay at diet onset	
Normal or suspected delay	10 (17%)
Mild delay	26 (44%)
Severe delay	23 (39%)
Genetic etiology	
SCN1A gene mutation	11 (19%)
CDKL5	10 (17%)
SLC2A1	8 (14%)
SCN2A	3 (5%)
MeCP2	2 (3%)
GRIN2A, GABRG2, GABRA1, STXBP1, WWOX, SMC1A, GCH mutations	1 each
Chromosomal abnormalities	18 (31%) (trisomy 21 in 3, 15q11.2 del, isodicentric 15q13 and 4p16.3 del in 2 each; mosaic tetrasomy 5p, 1q4 dup, 22q11 dup, 22q11.21 del, 3p12.3 del, 5q21.1 del, 2q22.3 del, ring chromosome 20 and 11p11.2 del in 1 each)
AED history at diet onset	
Current AED*	2 (1,3)
AEDs failed because of lack of efficacy*	3 (2,4)
Prior epilepsy surgery	None

Abbreviations:
AED = antiepileptic drug
del = deletion
DS = Dravet syndrome
dup = duplication
EME = early myoclonic encephalopathy
GTC = generalized tonic-clonic seizures
LGS = Lennox-Gastaut syndrome
MMPSI = migrating malignant partial seizures of infancy
* Median (twenty-fifth, seventy-fifth percentile).

Results

Fifty-nine patients initiated the dietary therapy for refractory epilepsy of genetic etiology, of which 37 patients (63%) were females. The median age at initiation of the diet was 2.2 years (IQR 1.1 and 5.3 years) (Table 1). Twenty-eight of the 59 patients (47%) remained on the diet at the end of 24 months.

Forty-three patients started the diet during an elective admission for KD initiation. The dietary therapy was started concurrently during an admission for management of status epilepticus in three patients. Seven children initiated the diet in the outpatient setting (Table 2). Six children were already on the diet when initially seen

TABLE 2.
Diet Details at the Time of Initiation

Variable	Frequency
Type of diet	
Traditional KD	53 children (90%)
MAD	6 children (10%)
Median duration of hospitalization*	4 days
Ratio of KD started	2:1 in all patients on traditional KD at full calories without fasting and the ratio was increased by no more than 1.0 per day as tolerated
Median ratio at discharge†	2.5:1 (2:1, 3:1)
Route of feeding	
Oral feeder	45 (76%)
Tube feeder	14 (24%)
KD formulation	
Only liquid formula orally	6 (10%)
Liquid formula through tube feeding	14 (24%)
Combination of liquid and solid ketogenic food	9 (15%)
Solid oral diet	30 (51%)
IV line placed	35 (76%) of the 46 hospitalized patients
Routine glucose checks ordered (every 6-12 hours)‡	40 (87%)
Ketosis attained§	24/46 children (52%) attained ketosis in first 24 hours

Abbreviations:
IV = intravenous
KD = ketogenic diet
MAD = modified Atkins diet
* Median duration was 45 days in children with diet initiation during stay for status epilepticus management.
† Median (twenty-fifth, seventy-fifth percentile).
‡ The rest had glucose checked only with an episode of emesis or intake <2/3 of normal.
§ All except one were ketotic at discharge.

by the pediatric epilepsy team at our center. For these six, we have included only data on efficacy analysis, as we did not have complete details regarding the diet initiation.

Adverse events and complications during diet initiation in hospitalized patients

Twenty of 46 children (43%) hospitalized at our center had complications during diet initiation. Of these, only 10 were significant, i.e., needing intervention or having more than one complication (Table 3).

Long-term efficacy of the diet

Among the 59 children who were started on the diet, three patients stopped within a week of initiation, because of difficulty in preparing KD meals and poor compliance (N = 1), severe ketoacidosis (N = 1), and severe reflux (N = 1). The median follow-up of subjects was 12 months (IQR of 3 and 24 months). The proportion of patients followed through each of the time points was 95% (56/59), 95% (56/59), 83% (49/59), 68% (40/59), and 56% (33/59) at one, three, six, 12, and 24 months, respectively. The proportion of children remaining on the diet at one, three, six, 12, and 24 months was 95%, 86%, 69%, 64%, and 47% respectively. The responder rates were 63%, 61%, 54%, 53%, and 41% at one, three, six, 12, and 24 months, respectively (Table 5). Figure 1 shows follow-up details on diet and Fig 2 shows seizure response.

There was no statistical difference between gender and response to the diet (*P* values = 0.21, 0.5, 0.18, and 0.58 at three, six, 12, and 24 months, respectively). We did not find any association between age at the diet initiation (less than two versus greater than two years) and response to the diet (*P* values = 0.7, 0.64, 0.90, and 0.48 at three, six, 12, and 24 months, respectively).

TABLE 3.
Adverse Events (AEs) and Complications During Diet Initiation in Hospitalized Patients (n = 46)

AE During Diet Initiation in Hospitalized Patients	Severity of AE	Intervention
Emesis (n = 11) 24%	Mild (n = 4) Significant (n = 7)	No intervention 3 with reduction in ratio of diet and IV fluids, 3 with only reduction in ratio, and 1 with IV fluids
Hypoglycemia* (n = 7) 15%	Mild (n = 4) Significant† (n = 3)	Treated with oral apple juice IV dextrose
Food refusal (n = 5) 11%	Mild (n = 2) Significant‡ (n = 3)	No intervention IV fluids, IV dextrose, and reduction in ratio of diet

Abbreviation:
IV = intravenous
* Defined as a serum glucose <50 mg/dL with neuroglycopenic symptoms, or <40 mg/dL in the absence of symptoms.
† Glucose <30 mg/dL or symptomatic. These three subjects also had recurrent episodes.
‡ In these three subjects, food refusal was associated with hypoglycemia in two and emesis in one subject. The two children with food refusal who developed hypoglycemia had glucose levels of 40 and 27 mg/dL, respectively, with the latter having recurrent hypoglycemia.

Overall the response rates in the children with refractory genetic epilepsy (n = 59) were similar to the children with refractory epilepsy of nongenetic etiology [(n = 193), Elaine Wirrell, unpublished data, 2018 from our center].

We had a large number of children with refractory epilepsy because of various chromosomal abnormalities (n = 18). At the end of first and third months, of the 17 still on the diet, the responder rate was 72%. At six, 12, and 24 months, there were 12, 10, and five children still on the diet with responder rates of 56%, 44%, and 28%, respectively. We failed to find any significant difference in response rates between chromosomal (n = 18) and nonchromosomal etiologies (n = 41).

Eleven children with an SCN1A mutation were started on traditional KD. At one and three months, eight (73%) and seven (64%) children, respectively, had more than 50% seizure control and at six and 12 months, six of the nine children still on the diet (55%)

TABLE 4.
Long-Term Adverse Events (AEs) of Dietary Therapy

Type of AE	Time Point	Specific AE
AE leading to diet termination	1 month (n = 2)	Severe gastroesophageal reflux, severe ketoacidosis (n = 1 each).
	3 months (n = 1)	Food refusal and weight loss
	6 months (n = 1)	Food refusal and weight loss
	12 months (n = 1)	Food refusal and weight loss
	24 months (n = 2)	Weight gain, persistent increased triglycerides (n = 1 each)
AE not leading to diet termination	1 month (n = 6)	Weight loss (n = 3), food refusal (n = 2), lethargy and mild hypoglycemia (n = 1)
	3 months (n = 5)	Food refusal (n = 3), mild emesis (n = 1), weight loss (n = 1)
	6 months (n = 5)	Mild emesis (n = 2), pain abdomen (n = 1), weight loss (n = 1), weight gain (n = 1)
	12 months (n = 1)	Mild emesis
	24 months (n = 1)	Constipation

TABLE 5.
Follow-up on the Diet

Variable	Number of Children and Percentage				
	1 month	3 months	6 months	12 months	24 months
Patients followed up to this time point*	56 (95%)	56 (95%)	49 (83%)	40 (68%)	33 (56%)
Patients on the diet*	56 (95%)	51 (86%)	41 (69%)	38 (64%)	28 (47%)
Responder rate*	37 (63%)	36 (61%)	32 (54%)	31 (53%)	24 (41%)
Number of children with seizure freedom†	15 (27%)	11 (22%)	10 (24%)	7 (18%)	5 (18%)
Moderate to large ketosis achieved†	55 (98%)	51 (100%)	41 (100%)	38 (100%)	28 (100%)
Emergence of new seizure types†	1 (2%)	3 (6%)	3 (7%)	3 (8%)	4 (14%)
AED added†	5 (9%)	10 (20%)	7 (17%)	7 (18%)	8 (29%)
AED stopped†	4 (7%)	3 (6%)	6 (15%)	3 (8%)	7 (25%)
Chromosomal abnormalities (n = 18)	13 (72%)	13 (72%)	10 (56%)	8 (44%)	5 (28%)
SCN1A mutation (n = 11)	8 (73%)	7 (64%)	6 (55%)	6 (55%)	5 (45%)
CDKL5 mutation (n = 10)	4 (40%)	4 (40%)	3 (30%)	5 (50%)	5 (50%)
SLC2A1 mutation (n = 8)	7 (88%)	7 (88%)	7 (88%)	7 (88%)	5 (63%)

Abbreviation:
AED = antiepileptic drug
Children were considered responders if they had a seizure reduction of >50% from baseline.
* Includes all 59 subjects who were started on the diet.
† Calculated on the basis of children remaining on diet at that time point.

were responders. At the end of 24 months, we had six children on the diet and five of them (45%) were responders.

Of the 10 children with CDKL5 mutation initiated on the diet in our study, eight remained on the diet at the end of first and third months, and four were responders with a responder rate of 40%. At six, 12, and 24 months there were five children remaining on the diet with response seen in three children (30%) at six months, and all the five children (50%) at 12 and 24 months, respectively.

There were eight children with SLC2A1 mutation who started the diet. At the end of the first and third months, seven (88%) were responders with 50% attaining seizure freedom. At the end of six months, we had lost one child to follow-up and the remaining

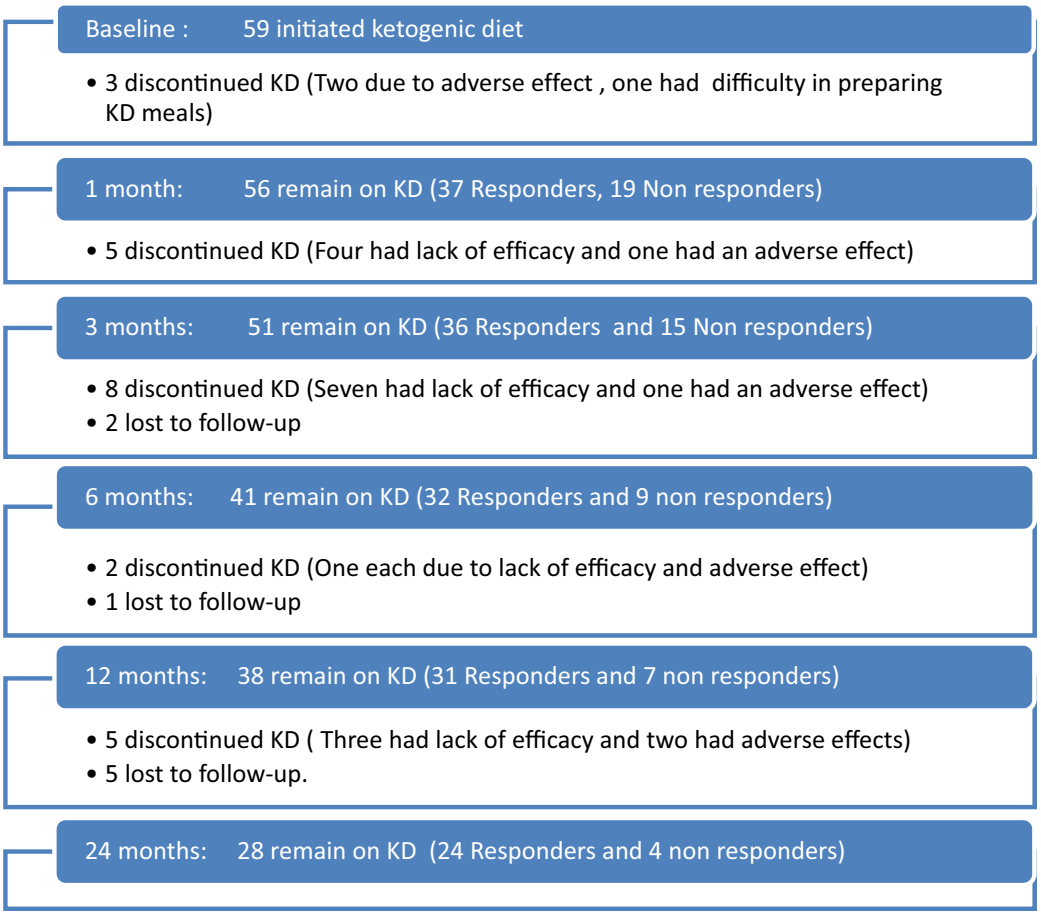

FIGURE 1. Overview of patient details at various time points. The color version of this figure is available in the online edition.

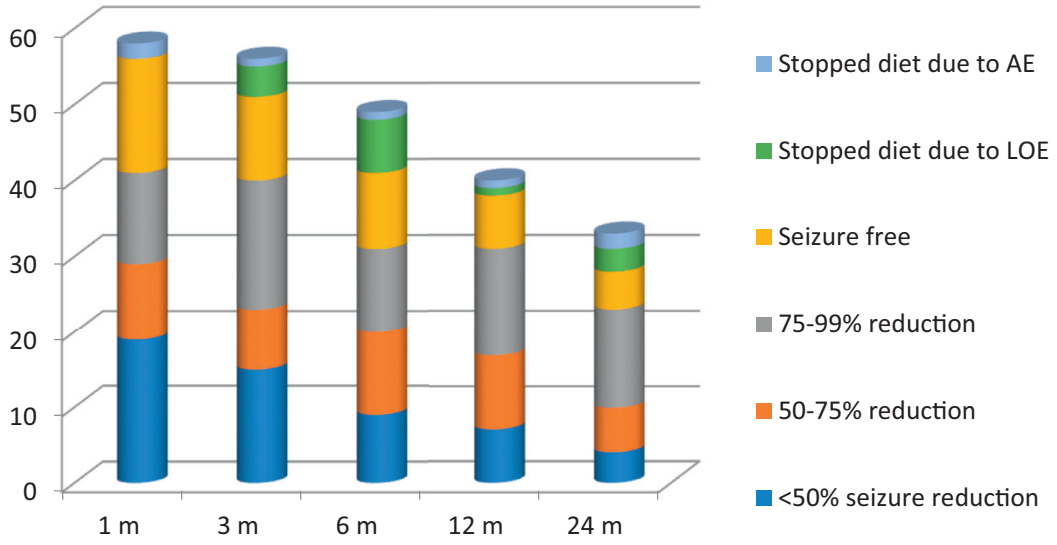

FIGURE 2. Seizure response and dropouts. AE, adverse event; LOE, lack of efficacy. *Y*-axis denotes number of subjects followed through at that particular time point. *X*-axis denotes various time points. The color version of this figure is available in the online edition.

seven children (88%) were responders with three remaining seizure free. At the end of 12 months, the response rate was similar to that at six months. By the end of 24 months, we lost two more children to follow-up (both were earlier seizure free) and all the remaining five children were responders with one child being seizure free.

We analyzed response rates among these four subgroups, i.e., chromosomal abnormalities, SCN1A, CDKL5, and SLC2A1 gene mutations and found no differences.

Long-term adverse effects of dietary therapy

We divided AEs into those which led to diet termination or and those which did not (Table 4). Seven of the 59 children (12%) terminated the diet because of AEs.

Discussion

The KD and MAD are important therapeutic options for children with refractory epilepsy secondary to genetic etiologies. Mutations in the genes coding for ion-channel components (SCN1A, SCN1B, SCN2A, KCNQ2, and so forth) are the basis of development of several epilepsy syndromes.[9] Several non–ion-channel proteins may also be causal (PCDH19, CDKL5, and STXBP1).[10] Nearly 500 different chromosomal abnormalities have been described to be associated with seizures of which certain chromosomal abnormalities show a greater association with epilepsy, for example, Wolf-Hirschhorn (del 4p16), Miller-Dieker (del 17p13.3), Angelman syndrome (del 15q11-q13), inversion duplication 15, and ring chromosomes 14 and 20.[11]

In our study, the dietary therapy was found to be effective with responder rates at one, three, six, 12, and 24 months being 63%, 61%, 54%, 53%, and 41%, respectively. Studies have reported that between 30% and 70% of children achieved greater than 50% seizure reduction after three months on the diet.[12-16] In their randomized controlled trial, Neal et al.[17] showed that 38% of patients in the diet group had greater than 50% seizure reduction compared with 6% control subjects, and 7% in the diet group had more than 90% seizure reduction compared with no control subjects.

We found no difference in efficacy of dietary therapy across different age groups, gender, and specific genetic etiologies, similar to a meta-analysis by Henderson et al.[18] However, Agarwal et al.[19] studied predictors of seizure outcome in 63 children on the diet for refractory epilepsy and concluded that later age of seizure onset, female gender, higher KD ratio, and nonfasting induction were associated with better odds of improved seizure outcome. We did not study the association between the ratio of diet and response to seizure control and also all our patients started diet in the nonfasting status. We also did not analyze the association between seizure type and the dietary efficacy in our study because most patients had multiple seizure types when the diet began.

We assessed the difference in response rates among the four most common genetic etiologies in our study, i.e., chromosomal abnormalities, SCN1A, CDKL5, and SLC2A1 mutations, but found no significant difference among these groups. Although the patients with SLC2A1 mutation (GLUT1 deficiency) appeared more responsive to the diet in our study, as expected, the small patient number precludes statistical significance. In a study by Ko et al.[8] of individuals with developmental and epileptic encephalopathy due to various pathogenic mutations, patients with SCN2A, STXBP1, KCNQ2, and SCN1A mutations in particular showed better responses to KD, with responder rates of 100%, 100%, 83.3%, and 77.8%, respectively. However, no patient with a CDKL5 mutation was among the responders at three months. More prospective studies or randomized controlled trials with a larger cohort may be required to know if there actually is a difference in response among various genetic etiologies.

In our study, the children with chromosomal abnormalities had a responder rate of 72% at one and three months after diet initiation. There are isolated case reports of the use of KD in certain chromosomal abnormalities.[20,21]

In the subset of patients with SCN1A mutations, we observed 64%, 55%, and 45% efficacy at three, 12, and 24 months, respectively. Dressler et al.[22] in their retrospective study on 32 children with Dravet syndrome on the KD reported overall response to KD of 70% and 60% at three and 12 months, respectively. There was a strong consensus that the KD should be considered a second-line therapy in Dravet syndrome, with a classical KD at less than two years of age, an MAD after 12 years of age, and either form of the diet in the ages in-between based on the child's and family's abilities and preferences.[23,24]

Our study showed a 40% efficacy at the end of three months in patients with CDKL5 mutation, which was in contrast to some other

studies that showed poor response in CDKL5 patients to KD.[8,25] In our study, seizure response was defined as greater than 50% seizure reduction from baseline, whereas in the study by Ko et al., the cut off was set at greater than 90% seizure reduction. In a questionnaire-based study in 104 children in Australia with refractory epilepsy due to CDKL5 gene mutation, parents of nearly 59% children reported favorable outcome to KD.[26]

In the subset of children with SLC2A1 mutation, the responder rates were as high as 88% and this was comparable to the largest study of KD in this cohort.[27] In our study, 50% attained seizure freedom by three months.

Overall, the diet appeared safe and with few side effects. During diet initiation, complications were seen in less than one-third of the patients, with vomiting being the most common. The children who developed symptomatic severe hypoglycemia were all aged less than two years and hence, it is imperative to start diet in the hospital for young infants, without fasting and secure an intravenous line and order six to 12 hourly glucose checks, which is in keeping with the consensus on the KD guidelines for infants with refractory epilepsy.[28,29]

Adverse effects while on the diet occurred in just over one-third of the children, which mostly comprised emesis, refusal to feed, loss of weight, weight gain, and loose stools. Most of these were managed by lowering the ratio, changing the consistency of meals, and increasing or decreasing the calorie content. Neal et al.[17] noted that just under a quarter of the 55 children who were on a KD for three months developed problems such as vomiting, lack of energy, or hunger; slightly fewer reported diarrhea, abdominal pain, or taste problems at some point during treatment.

In our study, among the 31 children who discontinued the diet, nearly half did so because of lack of efficacy. We do not have details of eight children who were lost to follow-up as they went back to their hometown for continuation and management of diet. Only 12% had AEs that warranted stopping of the diet. The AEs seen were severe reflux, ketoacidosis, persistent hypertriglyceridemia, weight gain, weight loss in one each, and refusal to feed with weight loss in two subjects. Mackay et al.[30] showed in their study that 62% of patients stopped diet because of poor initial response or loss of efficacy and only 12% stopped diet because of side effects.

There were some study limitations. First, eight subjects were lost to follow-up, and details of their response to the diet or side effects are unavailable and there is no way to determine whether they were responders. Second, there are inherent limitations typified by a retrospective study, such as inability to interpret with certainty if seizure reduction was because of the diet or response to concomitant or new AEDs. Concurrent AEDs are usually not changed in the first weeks after diet initiation to determine diet efficacy. However, there were instances when because of intractability of seizures, AEDs were added in addition to the diet and it was difficult to know if seizure control was because of the diet or the addition of AED. Third, we did not evaluate the effect of diet on neurocognitive development.

The diet is indeed an effective modality in treating refractory childhood epilepsy of genetic etiology. It has good tolerability and relatively few side effects, which can be managed with close monitoring and follow-up. It is recommended to start the KD in the hospital for younger children aged less than two years as they need frequent glucose monitoring. The diet was found to be efficacious irrespective of the specific genetic etiology, gender, or age of onset of seizures. More randomized controlled trials and prospective studies with a larger cohort are necessary to ascertain these findings. The diet has to be considered earlier on while treating these children with high care burden and multiple comorbidities, to minimize issues seen with multidrug therapy like high cost, drug interactions, and side effects.

Conclusion

The diet is an effective modality for treating refractory epilepsy of genetic etiology and is well tolerated among children.

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