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Original Article

The effectiveness of the ketogenic diet in drug-resistant childhood epilepsy

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ABSTRACT

Background. We aimed to investigate the effectiveness of ketogenic diet (KD) in children with various types of refractory epilepsy.

Methods. A total of 91 children (49 females) aged 3 to 193 months (median, 52 months) with drug resistant epilepsy who received KD treatment for at least 12 months were enrolled in the study. Seizure frequency, adherence to diet, reason for discontinuation of KD, and adverse effects were recorded. Response was defined as ≥50% improvement in seizure frequency compared to baseline. We also searched for influences of different variables on the outcome.

Results. Intent-to-treat analysis revealed an improvement in seizure frequency for ≥50% in 73.6%, 80.2%, 75.8%, 73.6%, and 70.3% of patients at month-1, -3, -6, -9, and month-12, respectively. Overall, 32 (35.2%) patients remained seizure-free at month-12. There was no significant differences between responders and non-responders in terms of age at onset of epilepsy, age at onset of KD, gender, or etiology. Mild hyperlipidemia was associated with a higher response rate. At the last follow-up (median: 20 months), 38 (41.8%) patients were still maintained on KD. While 15.4% of patients completed the diet with a success in seizure control, remainder discontinued KD due to lack of efficacy (23.1%), non-adharence to diet (11%), intercurrent infection (4.4%), adverse effects (3.3%), and death (1.1%).

Conclusion. Ketogenic diet treatment appears to be effective in about two-thirds of children with various types of drug-resistant epilepsy, including one-third remaining seizure free. Mild hyperlipidemia seems to be associated with a higher response rate. Discontinuation of KD is mostly due to lack of efficacy or non-adherence, and rarely side effects.

Key words: ketogenic diet, drug-resistant epilepsy, effectiveness, tolerability.

Epilepsy is the most common chronic neurologic disorder that requires continued medication for long-term management in children. However approximately 20-30% of all children with epilepsy do not respond sufficiently to antiepileptic drugs (AED), and are considered medically intractable, despite recent development of a number of anticonvulsant agents.[1] The ketogenic diet (KD), defined as a high-fat, adequate-protein, and low-carbohydrate diet, is one of the most effective alternative treatment options for drug resistant epilepsy.[2] It is not a benign therapy, however, being associated with a number of adverse effects.[3] Moreover, compliance with

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diet for both patients and their caregivers appears to be one of the main concerns in KD implementation. Differences in food culture, locally available food, eating habits and children's preferences may affect dietary compliance, and therefore the effectiveness of the diet in various parts of the world. For instance, since Asian diet is predominantly cereal-based and its carbohydrate content is much higher compared to Western diets, it is not surprising that compliance with the diet and, accordingly, the response to treatment in children from East Asian countries is lower than those from Western countries where ordinary diet is based mainly on high-lipid, low carbohydrate foods such as butter and cream.[4,5] In this study, we aimed to investigate effectiveness of KD in different types of drug resistant childhood epilepsy in Turkey where the fat content of ordinary diet consists mainly of olive oil.

Material and Methods

Patients and settings

Hospital charts of children treated with KD at the University of Health Sciences Turkey, Dr. Behçet Uz Children's Education and ResearchHospital between the years 2013 and 2019 were retrospectively reviewed. Patients who had drug resistant epilepsy (defined as failure to ≥2 appropriate antiepileptic drugs), who had more than four seizures per month, and patients who continued KD treatment for at least 12 months were identified. Patients who discontinued treatment before 12 months due to ineffectiveness, side effects or nonadherence to KD were also included into the analysis. Ethical permission for the study was obtained from the institutional ethical committee (2020/08-05).

Dietary protocol

A standardized KD with a non-fasting gradual initiation protocol during a 5-day hospital stay was started on a 3:1-ratio. During the inpatient treatment, parents were educated about diet and ways to prepare KD at home. Ketogenic diet was started with full calories. A 1:1 ratio on the 1st day, 2:1 ratio on the 2nd day, and 3:1 ratio thereafter was administered. Continuing adjustments to dietary ratio between 2:1 to 4:1, energy, and protein intake were made while children remained on the diet in order to optimize ketone levels and seizure control, minimize side effects, and maintain appropriate growth. We tried to maintain ketone levels at ≥3+ (50–150 mg/dl) in routine urinalysis or 4–6 mM for serum β-hydroxybutyrate. No water restriction was applied. As there is evidence showing similar efficacy at ratios of 2:1 to 4:1,[6,7] we included all children receiving KD at ratios between 2:1 and 4:1. The recipes were individually prepared with locally available foods, taking into account the preferences of families and the children, and cultural differences. The principal unsaturated fat source of the diet was olive oil (about 80% of all fats in the diet), which is widely used, readily available, and relatively inexpensive in Turkey. Saturated fats including cream, butter, and fatty beef made up about remaining 20% of the fat in the diet, and no other types of fat were used. We tried to manage patients who developed hyperlipidemia using simple dietary modifications such as replacing saturated fats with extra-virgin olive oil, carnitine and/or omega-3 fatty acid supplementation, or reducing the ketogenic ratio gradually down to the level of 2:1, trying not to alter ketosis and seizure control. We had to reduce the KD ratio to 2:1 in only two patients. Omega-3 supplements (docosahexaenoic acid / eicosapentaenoic acid) were given to five patients whose high triglyceride levels persisted despite dietary modifications. Carnitine supplements were given to six patients with low carnitine concentrations, because carnitine supplementation has been reported to reduce triglyceride levels in adults.[8] In order to reach optimum ketone levels, medium-chain triglyceride (MCT) oil was added to the diet in seven children. The initial daily calorie requirement was calculated individually for each patient as the average between their pre-diet intake and their energy requirements for

ideal body weight for children younger than two years of age and ideal body mass index for children aged two years or older (approximately 60 – 80 kcal/kg/day), taking into account their levels of physical activity, and trying to bring patients to their ideal weight. Calories were generally adjusted in increments or decrements of 100 kcal at intervals of at least 2 weeks before any further changes were made in order to optimize ketone levels and seizure control. Protein content was generally calculated according to World Health Organization (WHO) minimum requirements for age (about 1 – 1.5 g/kg/day).[9] All foods and beverages weighed precisely on a gram scale, and the recipes were largely planned with a computer program called "ketodietcalculator" freely released by Charlie Foundation.[10] The amount of fat, carbohydrate, protein, and calories contained in all locally available food and beverages were entered into the programme by our dietitian (Z.A.). A formula with 4:1 ratio produced for KD therapy were added to the diet for formula fed babies. Urine or blood ketone and glucose levels were checked and recorded by parents using ketostix and dextrostix strips twice daily during the first week and as needed clinically thereafter. Medications were changed to carbohydrate free preparations wherever available. Multivitamins were given to all patients, as the KD is not nutritionally complete.

Data collection and variables

Detailed demographic and clinical information including age at onset of seizures, age at initiation of KD, gender, developmental status, etiology, type of seizure and epilepsy syndrome, improvement in alertness, seizure frequency, and treatment history were noted. Seizure types, etiology and epilepsy syndromes were classified, where possible, according to the criteria proposed by the International League Against Epilepsy (ILAE).[11,12] Before the diet was started, each patient underwent detailed metabolic screening in order to rule out disorders contraindicated for KD treatment such as primary carnitine deficiency, fatty acid oxidation disorders, or pyruvate carboxylase deficiency. A thorough laboratory investigation was carried out, as well, including complete blood count, biochemical profile (liver and kidney function tests, fasting lipid profile), and abdominal ultrasonography. Brain magnetic resonance imaging and electroencephalogram (EEG) were performed in all cases.

Patients were assessed through clinic visits at 1, 3, 6, 9, and 12 months, and every 6 months thereafter. At each visit, seizure frequency, adverse events, compliance with the diet, adherence, and the reason for KD discontinuation were recorded. The main measure of efficacy was the decrease in seizure frequency as assessed by parental report and seizure diaries. The average seizure number in one month prior to each visit was compared to the baseline average seizure number in the month before the start of the diet, and expressed as a percentage of reduction. Improvement in seizure frequency was classified into four categories: seizure-free, ≥50% improvement, <50% improvement, or no improvement/ increase in seizure frequency compared to baseline. Response was defined as ≥50% seizure reduction. An intent-to-treat analysis was employed, and patients who discontinued KD for any reason (ineffectiveness, incompatibility, or adverse effects) were counted as non-responders from the point of discontinuation of KD. Assessment of improvement in alertness was based on parental reports and clinical examination; no formal developmental tests were performed. Tolerability and adverse events were assessed with physical examination, laboratory testings, and adverse events spontaneously reported by the parents or the children. Hyperlipidemia was defined as serum total cholesterol levels ≥ 200 mg/dl and/or serum triglyceride levels ≥ 130 mg/dl, and graded as mild, moderate, or severe hyperlipidemia (serum total cholesterol level between 200 - 399 mg/dl; 400 - 599 mg/dl; ≥ 600 mg/dl, and/or serum triglyceride levels between 130 -259 mg/dl; 260 -389 mg/dl; ≥ 390 mg/dl, respectively). Adherence was assessed by direct questioning and by measurement

of serum/urine ketone concentrations. The decision to continue antiepileptic medications was made by the treating physician based on seizure frequency, epilepsy type, and EEG results at each visit.

Statistics

The data were analyzed using SPSS for Windows software package, version 20.0 (SPSS, Chicago, IL). Due to non-parametric distribution of data, Mann—Whitney U and Friedmann tests were used for continuous variables, and Pearson Chi Square, Fisher exact or Cochrane Q tests for categorical variables. A p-value less than 0.05 was regarded as statistically significant.

Results

A total of 91 children (49 females) aged from 3 to 193 months (median, 52 months) at the onset of KD treatment with drug resistance epilepsy due to various types of etiology, who received a KD for at least 12 months were enrolled in the study. Etiologic distribution of study sample is shown in Table I.

Of the 91 patients, 16 (17.6%) stopped KD before 12 months due to lack of efficacy (7 patients), non-adherance to the diet (5 patients), adverse effects (2 patients) and severe intercurrent infection (2 patients), and these patients were counted as non-responders in the analysis. Intent-to-treat analysis revealed an improvement in seizure frequency for ≥50% in 73.6%, 80.2%, 75.8%, 73.6%, and 70.3% of patients at month-1, -3, -6, -9, and month-12, respectively. Overall, 32 (35.2%) patients remained seizure-free at month-12. The median number of AEDs used during this 12-month period decreased significantly (Table II).

The comparative demographic and clinical characteristics of the study sample between responder and non-responder groups are presented in Table III. There was no significant difference between these groups in terms of age at onset of epilepsy, age at onset of KD, gender, and etiology. Mild hyperlipidemia was significantly higher in the responder group compared to non-responders. Number of children with individual syndrome groups was too small for intergroup statistical analysis. However KD appeared to be particularly effective in patients with glucose transporter 1 (GLUT-1) deficiency, pyruvate dehydrogenase deficiency, and Dravet syndrome. At the last follow-up (median: 20 months), 38 (41.8%)

Table I. Etiologic distribution of the patients treated with ketogenic diet.

Etiology	n (%)
Total	91 (100)
Unknown	36 (39.6)
Structural causes	21 (23.1)
Hypoxic ischemic encephalopathy	7 (7.7)
Cortical malformation	4 (4.4)
Encephalitis with unknown etiology	3 (3.3)
Herpes encephalitis	1 (1.1)
Stroke	2 (2.2)
Congenital cytomegalovirus infection	1 (1.1)
Hypothalamic hamartoma	1 (1.1)
Traumatic brain injury	1 (1.1)
Neonatal cerebral hemorrhage	1 (1.1)
Epileptic encephalopathies	23 (25.3)
West syndrome	6 (6.6)
Lennox-Gastaut syndrome	6 (6.6)
Dravet syndrome	3 (3.3)
Rett syndrome	2 (2.2)
SCN1B Encephalopathy	1 (1.1)
CDKL5 encephalopathy	1 (1.1)
KCNB1 related encephalopathy	1 (1.1)
STXBP1 related encephalopathy	1 (1.1)
EMC1 gene mutation related disorder	1 (1.1)
DYRK1A related disorder	1 (1.1)
Metabolic causes	11 (12.1)
Glucose transporter-1 deficiency	3 (3.3)
Pyruvate dehydrogenase deficiency	2 (2.2)
Nonketotic hyperglysinemia	1 (1.1)
Tay Sachs Disease	1 (1.1)
Cobalamin synthesis defect	1 (1.1)
Mitochondrial DNA depletion syndrome type 14	1 (1.1)
Congenital glycosylation defect 1D	1 (1.1)
Hypomyelinating leukodystrophy	1 (1.1)

Table II. Seizure outcomes and number of antiepileptic drugs currently used at 1, 3, 6 and 12 months after initiation of the ketogenic diet.

	Baseline N:91	Month 1 N:91	Month 3 N:91	Month 6 N:91	Month 9 N:91	Month 12 N:91	p
Responders, %, (n)		73.6 (67)	80.2 (73)	75.8 (69)	73.6 (67)	70.3 (64)	0.086
Seizure free		18.7 (17)	25.3 (23)	27.5 (25)	30.8 (28)	35.2 (32)	
Reduction ≥50%		54.4 (50)	54.9 (50)	48.4 (44)	42.9 (39)	35.2 (32)	
Non-responders, %, (n)		26.4 (24)	19.8 (18)	24.2 (22)	26.4 (24)	29.7 (27)	
Reduction <50%		11.0 (10)	8.8 (8)	6.6 (6)	8.8 (8)	8.8 (8)	
No change		15.4 (14)	11.0 (10)	17.6 (16)	17.6 (16)	20.9 (19)	
Number of AEDs currently used, n±S.D, (median)	2.96±1.01 (3)	2.71±0.98 (3)	2.54±1.03 (3)	2.43±1.11 (3)	2.37±1.15 (2)	2.34±1.1 (2)	<0.0001

AEDs: antiepileptic drugs, SD: standard deviation.

Table III. Comparison of variables between Responders and Non-responders at month-12.

Characteristics	Total	Responders	Non-responders	p
Patients enrolled, n (%)	91	64 (70.3)	27 (29.7)	
Gender				0.479
Female, n (%)	49 (53.8)	36 (56.3)	13 (48.1)	
Male, n (%)	42 (46.2)	28 (43.7)	14 (51.9)	
Age at onset of epilepsy, yr; mean ± SD	12.0 ± 20.4	12.3 ± 21.4	11.3 ± 18.1	0.885
Duration of epilepsy at onset of KD, mon; mean ± SD	51.9 ± 42.4	52.9 ± 40.3	49.3 ± 47.8	0.414
Age at onset of KD, yr; mean ± SD	64.5 ± 49.6	65.7 ± 48.8	61.7 ± 52.1	0.578
Patients under the age of 2 years, n (%)	25 (27.5)	17 (26.6)	8 (29.6)	0.765
Patients under the age of 6 years, n (%)	56 (61.5)	40 (62.5)	16 (59.5)	0.772
Patients under the age of 12 years, n (%)	79 (86.8)	55 (85.9)	24 (88.9)	0.498
Duration of KD at last follow up, mon; mean ± SD	25.8 ± 17.0	29.7 ± 15.6	16.6 ± 16.9	<0.001
Improvement in alertness	76 (84.4)	59 (93.7)	17 (63.0)	0.001
Continuation of the ketogenic diet at month 12	75 (82.4)	63 (98.4)	12 (44.4)	0.001
Constipation during KD treatment, n (%)	22 (24.2)	15 (23.4)	7 (25.9)	0.800
Constipation at baseline, n (%)	17 (18.7)	11 (17.2)	6 (22.2)	0.574
Renal stone, n (%)	11 (12.1)	8 (12.5)	3 (11.1)	0.853
Hyperlipidemia	69 (75.8)	52 (81.3)	17 (63.0)	0.063
• Mild	47 (51.6)	39 (60.9)	8 (29.6)	0.006
• Moderate	11 (12.1)	6 (9.4)	5 (18.5)	0.292
• Severe	11 (12.1)	7 (10.9)	4 (14.8)	0.726
Ambulant, n (%)	57 (62.6)	40 (62.5)	17 (63.0)	0.967
Number of AEDs at baseline, mean ± SD	2.96±1.01	2.91±1.05	3.07±0.92	0.473
Number of AEDs at month 12, mean ± SD	2.34±1.16	2.09±1.18	2.96±0.84	0.002

Table III. Continued.

Characteristics	Total	Responders	Non-responders	p
Etiology, n (%)				
• Unknown	36 (39.6)	28 (77.8)	8 (22.2)	0.208
• Structural causes	21 (23.1)	13 (72.9)	8 (27.1)	0.335
° Hypoxic ischemic encephalopathy	7 (7.7)	4 (57.1)	3 (42.9)	0.419
° Cortical malformation	4 (4.4)	1 (25)	3 (75)	0.077
• Epileptic encephalopathies	23 (25.3)	14 (73.5)	9 (26.5)	0.251
° West syndrome	6 (6.6)	2 (33.3)	4 (66.7)	0.061
° Lennox-Gastaut syndrome	6 (6.6)	3 (50)	3 (50)	0.357
° Dravet syndrome	3 (3.3)	3 (100)	0	
° Rett syndrome	2 (2.2)	1 (50)	1 (50)	
• Metabolic causes	11 (12.1)	9 (68.8)	2 (31.2)	0.496
° GLUT-1 deficiency	3 (3.3)	3 (100)	0	
° Pyruvate dehydrogenase deficiency	2 (2.2)	2 (100)	0	

AEDs: antiepileptic drugs, GLUT-1: glucose transporter 1, KD: ketogenic diet, mo: months, SD: standard deviation, yr: years.

Table IV. Continuation of Ketogenic Diet at month-12 and at the last follow up.

Characteristics	n (%)
Patients enrolled	91
Continuation of KD at month 12	75 (82.4)
Reason for discontinuation of KD at month 12	
Lack of efficacy	7 (7.7)
Completion of treatment	
Nonadharence to KD	5 (5.5)
Adverse effects	1 (1.1)
Nephropathy	1 (1.1)
Intercurrent infection	3 (3.3)
Continuation of KD at last follow up (median 20 months)	38 (41.8)
Reason for discontinuation of KD at last follow up (median 20 months)	
Lack of efficacy	21 (23.1)
Completion of treatment	14 (15.4)
Nonadharence to diet	10 (11.0)
Adverse effects	3 (3.3)
Nephropathy	2 (2.2)
Elevation of liver enzymes	1 (1.1)
Intercurrent infection	4 (4.4)
Death	1 (1.1)

KD: Ketogenic diet

patients were still on the KD. While 14 (15.4%) patients completed the diet due to success in seizure control, remainder stopped KD due to lack of efficacy (23.1%), nonadharence to diet (11%), adverse effects (3.3%), intercurrent infection (4.4%), and death (1.1%) (Table IV).

Discussion

Due to the difficulties in developing a blinded placebo-controlled prospective trial of the KD, so far, no placebo-controled study has been conducted for the efficacy of KD in children with

drug resistant epilepsy. Few randomized non-placebo-controlled trials provided an overall low to very low-quality evidence for the efficacy of KD due to the limited number of studies and small sample sizes.[2] Furthermore, except for one study that provided data on 12-month outcomes.[13] all other randomized controlled trials reported outcome measures for short periods ranging from 3 to 6 months.[2] On the other hand, many more observational studies have provided evidence of the effectiveness of KD for longer periods.[14] However most of these studies are heterogenous in terms of patient population, age, and duration of follow-up.[14] Therefore, more studies are still needed to address the effectiveness and safety of KD in daily clinical practice. The present study, although observational, provides outcome measures at different time points including short and long term data, and showed that about 70% of the children with various types of drug-resistant epilepsy, including one third of all patients remained seizure free, achieved ≥50% improvement in seizure frequency. Our rates are higher than those of most of studies reporting 50% or greater reduction in seizure frequency from 18 to 53%[4,5,13,15,16], and are comparable to others with reported response rates between 63 and 72%.[17,18] Various factors, such as differences in eating habits, culinary culture and traditional dishes, heterogeneity of study samples in terms of age at onset of KD or etiology may contribute to the wide range of effectiveness rates. Our high response rate, likely due in part to high retention rate, may be partly explained by the high olive oil content in the customary diet, which seems slightly more similar to KD than, for instance, cereal based high-carb Asian diet. Low retention rates from Asian countries reported between 24 and 46% at 12 months support this hypothesis.[4,16] Our retention rate at month 12 (82%) was even higher than those of many Western countries (55%)[5,13], suggesting olive oil based KD might be more palatable regarding KD. Similar to previous reports, lack of effectiveness was the most common reason for dietary withdrawal in our series.[3-5,16] However, unlike previous studies that reported discontinuation rates due to non-compliance between 14-23%[4,16], in the present study, only 6% of children stopped the diet due to non-adherence, which underlines the importance of individualized diet preparation taking into account various factors such as the families and the child's preferences, cultural differences, close follow up and rapid changes in recipes in case of refusal to eat.

Few data, limited to case reports or small case series, are available on the effectiveness of KD by etiology.[16,19-21] In our series there was no difference between main etiologic groups in terms of effectiveness. Although the effectiveness of the KD treatment for individuals with a specific etiology could not be determined due to the small numbers of patients in each specific group in our series, KD appeared to be particularly effective in patients with GLUT-1 deficiency, pyruvate dehydrogenase deficiency, hypoxic ischemic encephalopathy, and Dravet and Rett syndrome, in line with previous reports.[4,6,15,19,20] It is also noteworthy that KD treatment was found to be safe and effective in some single cases for which the effectiveness and tolerability of KD have not been previously reported including SCN1B encephalopathy, hypotalamic hamartoma, hypomyelinating leukodystrophy, cobalamin synthesis defect, EMC1 encephalopathy, KCN1B encephalopathy, DYRK1A related disorder, STXBP1 related encephalopathy, congenital glycosylation defect 1D, and nonketotic hyperglysinemia. However an infant with Tay-Sachs syndrome did not respond to KD treatment, and another infant with a diagnosis of mitochondrial DNA depletion syndrome type 14 developed severe pneumonia and we stopped KD during the initiation period.

Age at onset of KD did not have any effect on effectiveness in our series similar to some studies[15,16,21,22], but contrary to the others that demonstrated higher effectiveness in younger ages.[4,5,23,24] One of the suggested explanations for the question of why KD treatment in older children is less effective, is the longer duration of epilepsy.[25,26] This has been supported by

the observation that KD was more effective in patients with shorter duration of epilepy before epilepsy becomes intractable.[22] However this explanation was not supported by our study where the duration of epilepsy had no effect on effectiveness. Thus, the lower efficacy of KD in older children may be due to decreased compliance to the diet rather than the longer duration of epilepsy or age of the patients, as suggested before.[24]

Improvement in cognition and alertness has been reported as an additional therapeutic effect in children receiving KD.[24,27] This was also remarkable in our series, in which parents of more than 90% of responders, and also about two third of patients who did not achieve improvements in seizure frequency reported improvement in alertness which was the most important reason for continuation of diet for non-responders.

Our rates of adverse effects were comparable to those of previous reports.[3,6,13,28] Among more than 40 known categories, the most commonly reported side effects of KD therapy include gastrointestinal disturbances, hyperlipidemia, and kidney stones.[3,6,15] Consistent with previous reports, constipation was the most frequently observed advers effect in our series affecting about a quarter of the children at any time during the KD therapy.[3,6,13,15,20] However, 19% of our patients already had constipation prior to the onset of KD, and in line with published studies, no patient stopped the diet because of constipation.[3,15] Thus, it appears that patients with drug resistant epilepsy are prone to having constipation but this problem can be managed by increasing dietary water and fibers, enema, or polyethylene glycol.

Hyperlipidemia, another frequently reported adverse effect in children receiving KD, was also observed in approximately three quarters of the patients in our series.[3,15,29] However, as expected, most of them had mild hyperlipidemia and none needed antilipidemic medication. Since children with mild hyperlipidemia were found to be more likely to respond to KD therapy in our series, it would be more appropriate to call it a desired effect rather than an adverse effect. Severe hyperlipidemia were observed in 12% of our patients and similar to a previous report, it was successfully managed by reducing KD ratio and/or the amount of saturated fat in the diet.[30]

Ketogenic diet has been associated with a reported incidence of kidney stones between 2.2 and 6.7%, which rarely leads to cessation of KD therapy.[4,5,30,31] Although the incidence of kidney stones, which was 12% in our study, was slightly higher than those in previous studies, no child had to terminate the diet because of stones.[5,31] Following potassium citrate supplementation and increasing fluid intake, the size of the stones decreased in two patients, remained unchanged in most, and one patient required lithotripsy. In addition, a patient who had kidney stones before starting diet successfully received KD without any renal complications. Surprisingly two patients stopped the diet due to grade II nephropathy detected on ultrasonography, which was very rarely reported[32], and none of these patients had calculi on ultrasonography. Nephropathy might have developed due to chronic acidosis and dehydration since these two children admitted emergency room with poor food and fluid intake, severe acidosis, persistent vomiting, and dehydration. Therefore hydration with larger amounts of water should be encouraged to prevent the formation of renal calculi, dehydration, acidosis and nephropathy.

In our series, the most common reason for discontinuation of KD therapy was a lack of efficacy, in line with previous studies reporting that up to half of patients stopped the diet due to limited efficacy.[3,5,6,16] Conversely, patients likely remain on diet for as long as they respond to treatment.[5] Indeed, nearly all patients in our series who showed more than 50% improvement in seizure frequency continued on the diet for more than 12 months; this is comparable to the 80% probability rate of remaining on the diet at 12 months reported previously.[5] Similar to previous reports, being

too restrictive for patients or parents, and refusal to eat was the second most common reason for diet cessation.[3,5,7,16] In agreement with previous reports, side effects and intercurrent ilnesses were not common causes of KD discontinuation in our study.[3,5,30] Except for two patients with acidosis, dehydration and nephropathy and one patient with elevated liver enzymes, most of the complications in our series were transient and improved with conservative management, and as reported previously, did not require cessation of the KD.[30] Consistent with previous studies, the cause of death of one patient in our series was attributed not to KD but to severe global developmental delay, malnutrition, and severe infection.[3,5]

Limitations

The main limitations of this study are its retrospective nature and the heterogeneity of the study sample. There is also a risk of subjective error due to the use of parental or caregiver seizure records and determination of certain parameters, including improvement in alertness, based on verbal expressions of the parents. Our inability to evaluate the effectiveness of KD treatment for individual syndromes due to the small number of patients in each group was another significant limitation. In this study, the effectiveness of olive oil-based (approximately 80% of dietary fats) KD in daily clinical practice was investigated. To reflect the results of our daily clinical practice, we included all children who received KD between 2:1 and 4:1 ratios; children whose diets differed slightly in olive oil content, and also children who had dietary modifications such as replacing saturated fats with unsaturated fats or medium-length chain triglycerides, carnitine and/or omega-3 fatty acid supplementation, or changing olive oil content or KD ratio during the study period, to optimize ketone levels, minimize adverse effects or normalize serum lipid concentrations. Thus, this is not a study of the effectiveness of well-controlled olive-oil-based KD, but a study that reflects the results of daily clinical practice of olive-oil-based KD. Future comparative studies are needed for the effectiveness of well-controlled olive oil-based KD.

In conclusion, individualized olive oil-based KD appears to be effective in about two-thirds of children with various types of drug-resistant epilepsy, including one-third who remain seizure free. Mild hyperlipidemia seems to be associated with a higher response rate. Although the small number of patients with specific etiologies did not allow us to provide evidence for effectiveness, KD appears to be particularly effective in patients with GLUT-1 deficiency, pyruvate dehydrogenase deficiency, and Dravet Syndrome. Discontinuation of KD is mostly due to lack of efficacy or nonadherence to diet, and rarely side effects.

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Ethical approval

This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the Dr. Behçet Uz Children's Education and Research Hospital Clinical Research Ethics Committee on May 21, 2020 (Number: 2020/08-05).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SE, ÜY; data collection: ZA, YG, GG, BTB, SS, SP, HHK, MY; analysis and interpretation of results: SE, ÜY, MK, AÜ; draft manuscript preparation: SE, ÜY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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