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# The ketogenic diet in children 3 years of age or younger: a 10-year single-center experience

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The ketogenic diet (KD) is an effective treatment option for intractable epilepsy. Here, we reviewed the last 10 years of our experience with the KD and characterized its use in patients under 3 years of age. Medical records of all patients under the age of 3 years who were treated with the ketogenic diet from April 2004 to June 2014 were retrospectively reviewed. One hundred and nine patients with drug-resistant epilepsy were included. The mean age at the initiation of the KD was $1.4 \pm 0.8$ years old. The youngest patient was 3 weeks old. After 3 months, 39% (42/109) of patients responded to the KD and experienced more than 50% seizure reduction. Of those 42 patients, 20 (18%) achieved complete seizure control. Patients with a genetic etiology showed a better response to the KD in seizure reduction than the other patients ($p = 0.03$). Age at initiation of the KD was not related to eventual seizure outcome ($p = 0.6$). The KD continues to be an effective, safe, and well tolerated treatment option for infants with intractable epilepsy.

The ketogenic diet (KD) is a high fat, low carbohydrate, and protein restricted diet that is rigorously medically supervised and widely recognized as an effective treatment option for intractable epilepsy. It's use in the United States dates to the 1920s, when Woodyatt and Wilder independently described the production of beta-hydroxybutyric acid or ketonemia via dietary manipulation other than fasting[1,2].

In a randomized controlled trial analyzing 103 children of varying ages, seizure types, and epilepsy syndromes, 38% of children treated with the KD after 3 months had greater than 50% seizure reduction compared with 6% of controls using heterogeneous anticonvulsant therapies. 7% in the diet group had greater than 90% seizure reduction compared with none of the controls[3]. Overall, while the KD's use as a therapy for infantile spasms (IS) is perhaps the best known and investigated[4–7], its effectiveness, safety, and tolerability for infantile onset intractable epilepsy regardless of seizure type has started to be elaborated[7–9]. A recent survey of health care professionals on the use of the ketogenic diet updated the long held notion that it was a therapy of "last resort." Within sub-types of infantile onset epilepsy, it was considered the first or second treatment for glucose transporter protein 1 deficiency (GLUT1) (86%) and third or fourth for Dravet (63%) and West (71%) syndromes[10]. Despite this, various aspects of implementation and utility of the KD in infants remain less completely understood, including: predictors of favorable response, the combined use of extracted breast milk, potential adverse events, reasons for early withdrawal, as well as the diet's efficacy in management of specific epilepsy syndromes and etiologies. How advances in medical genomics and the burgeoning identification of causative gene mutations in epilepsy might eventually apply to the ketogenic diet is of considerable interest.

The ketogenic diet has been in continued use at Children's Memorial Hospital (renamed Ann & Robert H. Lurie Children's Hospital of Chicago) since 1963[11]. In this study, we retrospectively reviewed the last 10 years of our experience with the KD and characterized its use in patients under 3 years of age. Our goals were to (1) identify predictors of favorable outcome, (2) investigate reasons for early withdrawal with relation to age, diet formulation, or adverse events, and (3) to evaluate efficacy with specific regard to epilepsy syndrome or etiology, utilizing genetic diagnoses if available.

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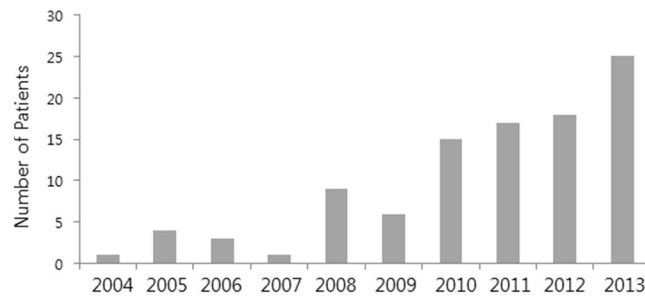
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**Figure 1.** Chart showing the use of the KD in patients under 3 years old in each year (From April 2004 to June 2014). (N. of patients in each year).

## Methods

Information regarding patient demographics, seizure types, seizure frequency, epilepsy syndrome, etiology, MRI findings and electroencephalogram findings was retrospectively abstracted from the medical records of all patients under the age of 3 years who were treated with the ketogenic diet from April 2004 to June 2014 at the Lurie Children's (formerly Children's Memorial Hospital). All patients had medically intractable epilepsy, defined as persistent seizures despite the use of two or more appropriate anticonvulsants at therapeutic doses.

Early withdrawal and early discontinuation were defined as cessation of the KD before 3 months of treatment had elapsed. In our analysis, we considered early withdrawal, early discontinuation, and non-adherence in aggregate. Patients were then categorized into two groups: (1) an early withdrawal group and (2) an adherent group (Fig. 1). To determine the reasons for early withdrawal, three clinical features were reviewed: very short-term efficacy of the KD, adverse events, and the implementation and practice of the KD. The number of patients who withdrew from the diet early because of ineffectiveness was calculated.

Further, the patients who completed 3 months on the KD were categorized into four groups based on the percentage of seizure reduction at 3 months: (1) complete seizure control, (2) >90% improvement, (3) 50–90% improvement, and (4) <50% improvement. Responders were defined as those who experienced >50% seizure reduction. Non-responders were defined as those who had <50% seizure reduction. Seizure frequency was reported by the parents as well as by EEGs when available. We defined adverse events broadly, including both new clinical symptomatology and lab abnormalities that started while using the KD. Events that prompted early withdrawal were also specified. To evaluate the practice details of KD implementation and maintenance, we assessed the ratio (grams of fat to grams of carbohydrate + protein) used, the method of food consumption, and the type of food that was consumed. Finally, in order to elucidate any age-dependent outcomes, patients were further categorized into three groups based on their age at the KD initiation and evaluated as follows: (1) patients <1 year old, (2) 1–2 years old, and (3) >2 years old. The study was approved by the Lurie Children's Hospital Institutional Review Board. All research was performed in accordance with relevant guidelines/regulations and a waiver of informed consent was granted for this retrospective study.

**The KD protocol.**   Before initiation of the KD, a multidisciplinary evaluation was performed by two registered dietitians, advanced practice nurses, and by a licensed clinical social worker. During the visit, a review of the medical history was obtained, diet protocols and lifestyle implications were discussed, and a neurologic examination was completed. After this preliminary visit, one of the following combinations of food consumption mechanism and food type were selected: oral liquid, tube-fed liquid, oral solids, or a combination of oral liquid and solid foods. Liquid foods included: individually designed meals with oils as well as commercial formulas including KetoCal® (Nutricia Inc., Gaithersburg, MD, U.S.A.) and Ross Carbohydrate Free® Soy Formula Base With Iron (Abbott Nutrition, Columbus, OH, USA). Individual calorie and protein amounts were calculated by our dietitians based on age-dependent standard daily requirements, baseline weight and height, level of activity, and the pre-diet intake evaluation. Supplementation with vitamins and minerals was provided based on individual patients' needs and food types used. The KD was initiated at a ratio of 1:1 (fat grams: carbohydrate + protein grams) without a fast as an inpatient in the hospital. The keto ratio was increased daily, reaching up to 3:1 on day 3. On day 4, patients were discharged home at the ratio of 3:1 with full calories. Fluids were not restricted. Patients were then evaluated by our multidisciplinary KD team 1 month later and then every 3 months thereafter. Intermittent outpatient adjustments of diet ratio, number of calories, and amount of protein were made to maximize seizure control, minimize side effects, and maintain appropriate growth.

**Statistical analysis.**   In order to determine the factors that were associated with the early withdrawal of the KD, we compared the clinical variables between the early withdrawal group and the continuing (adherent) group. We used the independent $t$-test or the Mann-Whitney $U$ test to analyze continuous variables including the age at KD initiation, age at seizure onset, seizure onset prior to the KD initiation, duration of the KD, and the number of prior antiepileptic drugs. For categorical data, Pearson's chi-square test for independence of rows and columns was used. $P$ values < 0.05 were regarded as statistically significant. Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Data are expressed as number (%), mean ± standard deviation, or median (interquartile range (IQR)).
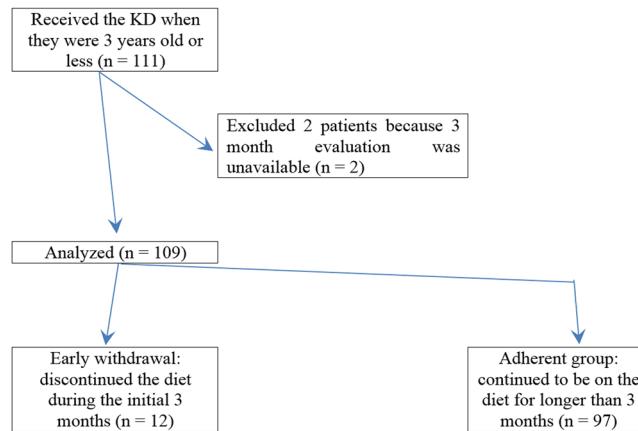
**Figure 2.** Flow diagram.

## Results

**Baseline characteristics.** One hundred and eleven patients under 3 years of age were started on the KD (Fig. 1). Two patients were excluded from the study: one underwent epilepsy surgery after one month of the treatment with the KD; the other, a patient with early myoclonic encephalopathy (EME), died due to respiratory failure 2 months into treatment with the KD. Ultimately, one hundred and nine patients with drug-resistant epilepsy were included for analysis (Fig. 2). Details of baseline patient characteristics are given in Table 1. The median age at seizure onset was 4 (IQR 1–6) months of age. The median number of previously attempted and/or concomitantly used medications at the time of the KD initiation was 4 (IQR 3–5). Approximately half (56%) of the patients had West syndrome. The EEG was abnormal in all patients at initiation of the diet.

The mean age at the initiation of the KD was $1.4 \pm 0.8$ years old. The youngest patient was 3 weeks old. Among 105 patients for whom information on the KD ratio was available, 20 were on a 3:1 ratio, 13 were on 3.5:1 and 59 were on 4:1. Overall, 12 were on a ratio higher than 4:1. The maximum ratio used was 4.75:1. Every child reached a fat to non-fat ratio of 3:1 or higher except one who was on a ratio of 2.75:1. The form of the food that was used included solid foods (33%, 35/104), liquid foods (32%, 34/104) and a combination of both (33%, 35/104). [Among 69 patients who received a liquid form of the KD, 96% (66/69) utilized the ketogenic formula while 4% (3/69) were put on an individually designed liquid. Eight patients used expressed breast milk. The median duration of the KD was 1.1 (IQR 0.5–2.2) years. All but one patient had positive urine ketosis at some point during the diet. In the one outlier, the level of serum $B$-hydroxybutyrate was 1.32 mmol/L and seizures did not respond (seizure reduction <50%) to the 3 months of the diet therapy.

**Efficacy.** After 3 months, 39% (42/109) of patients responded to the KD and experienced more than 50% seizure reduction. Of those 42 patients, 20 (18%) achieved complete seizure control and an additional 3 (3%) experienced >90% seizure reduction (Table 1). There was no significant difference between age at the seizure onset ($p = 0.2$) or age at initiation of the KD ($p = 0.5$) between responders and non-responders. The number of previously or currently used anticonvulsants was lower among responders ($p = 0.02$).

Possibly due to the small numbers of patients, no specific etiology was significantly related to a positive response to the KD (Table 2). Interestingly, however, patients with a confirmed genetic mutation or a chromosomal abnormality showed a better response to the KD in seizure reduction than the other patients ($p = 0.03$). Genetic abnormalities were identified in 29 patients and included mutations of the following genes: *BRAF*, *CDG 1p*, *CDKL5*, *SCN1A*, *SCN2A*, *SCN8A*, *KCNQ2*, *DCX*, *EEF1A2*, *GFAP*, *GRIN2A*, *MTO*, *POLG*, *RARS2*, *TSC2*, *SLC35A2* and *SLC6A8*. Trisomy 21 was found in 5 patients. Microdeletions of chromosome 1, 6 and 16 were found in 5 patients. The KD was similarly effective in patients with diverse early onset epilepsies and in patients with West syndrome.

In general, there was no single EEG abnormality that was independently related to a favorable response to the KD. Among patients with focal slowing and spikes on the baseline EEG, the presence of electrodecrements was suggestive of a poor response, but failed to show a significant difference ($p = 0.09$).

**Early withdrawal and associated factors.** Only 12 of 109 patients (11%) withdrew from the diet before 3 months. The most common cause for withdrawal was parental unhappiness with the diet's rigidity (7/12). Only five patients stopped early either because of perceived ineffectiveness (3/12) or because of an adverse event (2/12) (Table 3). Young patients who were given ketogenic formula with or without solids were more likely to continue the diet ($p = 0.003$). A high KD ratio ($\geq$4:1), the use of feeding tube or the use of expressed breast milk was not related to early KD withdrawal. Young patients who were given ketogenic formula were more likely to continue the diet ($p = 0.003$). A high KD ratio ($\geq$4:1), the use of feeding tube or the use of expressed breast milk was not related to early KD withdrawal.

Young patients who were given ketogenic formula were more likely to continue the diet ($p = 0.003$). A high KD ratio ($\geq$4:1), the use of feeding tube or the use of expressed breast milk was not related to early KD withdrawal.

| | | Values |
|---|---|---|
| Males/Females, n | | 50/59 |
| Age at the seizure onset, median (IQR), y | | 0.3 (0.1–0.5) |
| Age at the initiation of the KD, mean ± SD, y | | 1.4 ± 0.8 |
| Duration of the KD, median (IQR), y | | 1.1 (0.5–2.2) |
| N of prior anticonvulsants, median (IQR) | | 4 (3–5) |
| Epilepsy syndrome, n(%) | West syndrome | 61 (56) |
| | Dravet syndrome | 9 (8) |
| | Localization related epilepsy | 7 (6) |
| | LIEE | 5 (5) |
| | EIEE/EME | 3 (3) |
| | Doose syndrome | 2 (2) |
| | Myoclonic epilepsy | 2 (2) |
| | MMPI | 1 (1) |
| | Unknown | 19 (18) |
| Etiology, n(%) | Structural | 24 (22) |
| | Perinatal events (HIE or IVH) | 20 (18) |
| | Genetic (chromosomal abnormalities or single gene defect) | 14 (13) |
| | Channelopathy | 13 (12) |
| | Metabolic disorder | 8 (7) |
| | Leukodystrophy | 4 (4) |
| | Trauma | 3 (3) |
| | Unknown | 23 (21) |
| EEG findings, n(%) | Diffuse slowing with Mf spikes + electrodecrements | 47 (43) |
| | Diffuse slowing with Mf spikes | 38 (35) |
| | Focal slowing and spikes + electrodecrements | 14 (13) |
| | Focal slowing and spikes | 9 (8) |
| | Generalized spike wave discharges with no slowing | 1 (1) |
| Outcome, n(%) | Seizure free | 20 (18) |
| | Reduction >90% | 3 (3) |
| | Reduction 50–90% | 19 (17) |
| | Reduction <50% | 55 (50) |
| | Withdrawal during the initial 3 months | 12 (11) |

**Table 1.** Patient characteristics (n = 109). KD, ketogenic diet; N, number; IQR, interquartile range; SD, standard deviation; LIEE, late infantile epileptic encephalopathy; EIEE, early infantile epileptic encephalopathy; EME, early myoclonic encephalopathy; MMFSI, malignant migrating focal seizures in infancy; HIE, hypoxic ischemic encephalopathy; IVH, intravenous hemorrhage; EEG, electroencephalogram.

The two adverse events that caused early withdrawal were behavioral food refusal and persistent acidosis in the setting of poor food intake. No one specific adverse event occurred more frequently among the early withdrawals. Constipation was more likely to be reported in the adherent group who were on the diet for a longer period of time (p = 0.009). Further details of the adverse events are provided in Table 4.

**The effects of age.** Age at initiation of the KD was not related to eventual seizure outcome (p = 0.6). Likewise, age was not related to early withdrawal from the KD (p = 0.2). Interestingly, however, the age group most likely to withdraw from the KD early was group 2 (patients between 1 and 2 years old) (7/12, 58%). This group also showed a wider variety of food types used during the KD compared to the other two groups whose food options were more selective. As would be expected, formula was used more in younger patients (<1 year old), In older patients (>2 years old), solid foods were more predominantly used. In patients between 1 and 2 years old, no single predominant food type was found (p < 0.0001). Details are given in Table 5. The overall occurrence of an adverse event was not related to age (p = 0.6). Patients who started the KD earlier (before 2 years old), however, were more likely to report constipation (p = 0.005). Kidney stones were observed only in patients younger than 1, but the difference according to age was not statistically significant (p = 0.07). Patients who discontinued the KD early because of an adverse event were 1.9 and 2.6 years old at the time of the KD initiation.

## Discussion

Within a span of 10 years at our center, more than 100 patients were initiated on the KD before they turned 3 years old. Overall, 20% of patients became seizure free and many (39%) experienced a significant seizure reduction (>50%) after the initial 3-months of the KD therapy. This trend is similar to what other studies have reported for older children, in which 27–38% of children have a >50% seizure reduction after 3 months[3,12]. The results

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| | | Responder | Non-responder | p-value |
|---|---|---|---|---|
| n | | 42 | 67 | |
| Age at the seizure onset, median (IQR), y | | 3 (2–6) | 3 (1–3) | 0.2 |
| Age at the initiation of the KD, mean ± SD, y | | 1 ± 0.8 | 1 ± 0.8 | 0.5 |
| N of prior anticonvulsants, median (IQR) | | 3 ± 1.6 | 4 ± 1.9 | 0.02 |
| Risk factor | Positive MRI finding | 20 | 34 | 0.7 |
| | Genetic abnormality | 20 | 19 | 0.03 |
| | Metabolic abnormality | 3 | 7 | 0.6 |
| Etiology | Channelopathy | 5 | 7 | 0.9 |
| | HIE or IVH | 9 | 8 | 0.2 |
| | Leukodystrophy or Metabolic disorder | 4 | 7 | 0.9 |
| | MCD or TS | 6 | 17 | 0.2 |
| Epilepsy syndrome | West syndrome | 24 | 36 | 0.7 |
| | Non-West syndrome | 18 | 31 | |
| EEG findings, $n = 108$ | a. Diffuse slowing with Mf spikes | 16 | 22 | 0.4 |
| | b. Diffuse slowing with Mf spikes + electrodecrements | 18 | 29 | |
| | c. Focal slowing and spikes | 5 | 4 | |
| | d. Focal slowing and spikes + electrodecrements | 3 | 11 | |

**Table 2.** Differences between responders (seizure reduction >50%) and the non-responders (seizure reduction <50%) on the ketogenic diet. KD, ketogenic diet; IQR, interquartile range; SD, standard deviation; N, number; MRI, magnetic resonance image; HIE, hypoxic ischemic encephalopathy; IVH, intravenous hemorrhage; MCD, malformation of cortical development; TS, tuberous sclerosis; Mf, multifocal.

| Reason | N (%) |
|---|---|
| Parental unhappiness | 7 (6) |
| Ineffectiveness | 3 (3) |
| Adverse event | 2 (2) |

**Table 3.** Reasons for early withdrawal (n = 109).

were also comparable to the rates of seizure reduction reported for the infants with West syndrome, which ranged from 39% to 67%[4,6,13].

Our previous study was the first to investigate the role of the KD in infants with epilepsies other than West syndrome/infantile spasms[7]. Fifteen years ago, we had only a limited ability to assess the efficacy of the KD with etiologic specificity. Since then, there have been smaller studies and case series or case reports looking at the diet's role in individual epilepsy syndromes or diseases that could include an infantile presentation, such as: GLUT-1 deficiency syndrome, pyruvate dehydrogenase deficiency (PDHD), severe myoclonic epilepsy of infancy (Dravet syndrome), Rett syndrome, and selected mitochondrial disorders[14–17]. None of these studies, however, focused exclusively on early introduction of the KD during the time period of 3 years of age and younger. It is would be of great benefit to determine which epilepsy syndromes, beyond West syndrome, and which etiologies are more responsive to the KD, so as to promote early referral and initiation of treatment. In the present study, there was no significant difference between the effectiveness of the KD for patients with West syndrome and other epilepsy syndromes, which suggests that the KD should be considered early in all infants with refractory epilepsy once contraindications are ruled out.

Moreover, in our experience, a confirmed genetic abnormality was predictive of a good response to the KD. Nearly half of the patients with a confirmed genetic abnormality enjoyed a reduction in seizure frequency of >50%. A similar finding was described in a retrospective chart review of 64 consecutive patients with refractory epilepsy, children and adults, who were started on the KD at a tertiary epilepsy center[18]. This finding implies that the KD could also be considered by providers earlier, perhaps even before a patient fails two previous anticonvulsant medications, if he or she receives a positive genetic diagnosis. Furthermore, early diet initiation not only capitalizes on age-related ease of use and tolerability, but could also appeal to parents concerned about potential anticonvulsant side effects, a finding shared in other studies[8,19].

In our experience with 109 children under 3 years of age, the KD was safely implemented and tolerated for the initial 3 months. Only about 10% of the children withdrew early. Among these, we found no critical adverse event related to use of the KD. The rate of early withdrawal was comparable to those reported in older children, which ranged from 12% to 16[3,12,20]. A much higher number of early withdrawals have been reported in a study with adults. Implementation and maintenance of the KD was easier in young children whose diet habits are still flexible, a finding supported by previous studies with smaller sample sizes which found similarly low rates of early withdrawal in of children in this age group (<2 years old)[4,5,7,13].

| | | Total | Adherent group | Early withdrawal group | p-value |
|---|---|---|---|---|---|
| N | | 109 | 97 | 12 | |
| Male/Female | | 50/59 | 44/53 | 6/6 | 0.8 |
| Age at the initiation of the KD, mean $\pm$ SD, $y$ | | 1.4 $\pm$ 0.8 | 1.4 $\pm$ 0.8 | 1.4 $\pm$ 0.8 | 1 |
| N of prior anticonvulsants, $n = 95$ | | 4 $\pm$ 1.9 | 4 $\pm$ 1.9 | 4 $\pm$ 1.8 | 0.7 |
| Improved cognition, $n = 95$ | | 47 | 47 | 0 | 0.007 |
| High KD ratio $\geq$ 4:1 | | 71 | 67 | 4 | 0.07 |
| Food type, $n = 104$ | Solid | 35 | 28 | 7 | 0.1 |
| | Liquid | 34 | 32 | 2 | |
| | Solid and liquid | 35 | 32 | 3 | |
| Feeding tube, $n = 105$ | 49 | 46 | 3 | 0.1 | |
| Use of a solid food | | 70 | 60 | 10 | 0.2 |
| Ketogenic formula | | 66 | 63 | 3 | 0.003 |
| Expressed breast milk | 8 | 7 | 1 | 0.9 | |
| AE or abnormal lab result | 69 | 65 | 4 | 0.01 | |
| | Constipation | 35 | 35 | 0 | 0.009 |
| | Decreased $HCO_3^-$ level* | 36 | 34 | 2 | 0.2 |
| | Vomiting, reflux | 22 | 11 | 11 | 0.7 |
| | Low free carnitine level# | 9 | 9 | 0 | 0.3 |
| | Feeding difficulty | 6 | 5 | 1 | 0.7 |
| | Kidney stone | 3 | 3 | 0 | 0.5 |
| | Transient hypoglycemia | 2 | 2 | 0 | 0.6 |
| | Others | 7 | 7 | 0 | 0.3 |
| AE which required a management | 63 | 59 | 4 | 0.1 | |

**Table 4.** Differences between the patients who continued to be on the KD and the patients who withdrew early before they completed the 3 months of the KD therapy. KD, ketogenic diet; SD, standard deviation; N, number; AE, adverse event; KD. *Decreased HCO3- level ($<18$ mEq/L). #Low free carnitine level ($<27$ μmol/L).

Considering that this study was performed at a tertiary pediatric epilepsy center with a specialized KD team, it was surprising to find that parental dissatisfaction with the diet was the most commonly reported cause for early withdrawal. This finding emphasizes the extensive amount of multidisciplinary support that parents need while using the diet, especially during the complicated period of solid food introduction.

Adverse events were a rare cause of early withdrawal in children (2%), although many children experienced at least one during their 3 months use of the KD (63%, 69/109). This finding is in partial agreement with previous reports which described that approximately 30% of the children experience an adverse event, but only 3–5% of children discontinue the diet due to adverse events[4,5]. We suspect that the reported rate of adverse events was higher in our study because our pre-determined threshold for adverse event reporting was intentionally set low. For instance, symptoms as mild as feeding difficulty or self-limited, small emesis were included as adverse events, which were in turn related to the fastidiousness of parental report or clinical judgement of the involved health care professional. Additionally, laboratory abnormalities such as decreased bicarbonate or glucose levels which were described in other studies but not reported as adverse events were counted as such in ours. We believe that the comprehensiveness of our reporting will be helpful in guiding physicians and caregivers when they plan to start the diet in infants and toddlers.

There was a significant relationship between early withdrawal from the diet and the food type that was used. While a few case-series and short studies have suggested improved tolerability of the liquid-based KD[4,21–23], its use has never been studied exclusively in infants, the group that not only makes most frequent use of this formulation, but who may also benefit most from it. Our study demonstrates that a liquid-based KD with ketogenic formula can be used safely and effectively in infants and that it may even enhance patient and parental maintenance of the diet. We also report here on eight children who successfully completed the diet with a combination of formula and expressed breast milk. The use of breast milk was neither related to early withdrawal, nor to poor outcome in terms of seizure control. This finding suggests that consideration of ketogenic diet therapy should not reflexively prompt early weaning from breast milk.

We did not find any age-related difference in regard to the outcome or the practice of the KD therapy in young children. Some studies have suggested a young age at the time of the KD to be a favorable factor while others did[7,20,24]. In our study, age was not related to the seizure outcome but to the methods of the KD and to the adverse events. Younger ones ($<$1 year old) were more likely to be fed with the liquid KD food while older ones ($>$2 years old) were fed with the solid foods. Younger ones were more likely to report constipation and low carnitine levels compared to the older ones. Additionally, although we failed to see a statistically significant difference, we also saw an age-related trend in relation to early withdrawal. Interestingly, it was not the older children ($>$2 years old) or the younger ones ($<$1 year old), but the children who started the KD between 1 and 2 years old, who tended to withdraw early from the diet more frequently than the other two groups (p = 0.15). We hypothesize that applying the KD may be more challenging to children when they are being introduced to the solid foods for the first time.

| | | Total | <1 year old | 1–2 year old | >2 year old | P-value |
|---|---|---|---|---|---|---|
| N | | 109 | 44 | 38 | 27 | |
| Female | | 59 | 23 | 23 | 13 | 0.6 |
| West syndrome | | 60 | 28 | 24 | 8 | 0.0009 |
| Outcome at 3 months | Seizure free | 20 | 10 | 6 | 4 | 0.6 |
| | >90% reduction | 3 | 2 | 0 | 1 | |
| | 50–90% reduction | 19 | 8 | 4 | 7 | |
| | <50% reduction | 55 | 21 | 21 | 13 | |
| Discontinuation before 3mo | | 12 | 3 | 7 | 2 | 0.2 |
| Improved cognition per parent, $n = 95$ | | 47 | 23 | 14 | 10 | 0.4 |
| High KD ratio $\geq 4{:}1$ | | 71 | 37 | 18 | 16 | 0.001 |
| Tube-fed | | 49 | 23 | 17 | 9 | 0.4 |
| Expressed breast milk | | 8 | 8 | 0 | 0 | 0.002 |
| Food type, $n = 104$ | Solid | 35 | 4 | 17 | 14 | <0.0001 |
| | Liquid | 34 | 16 | 11 | 7 | |
| | Solid and liquid | 35 | 22 | 10 | 3 | |
| Ketogenic formula, $n = 104$ | | 66 | 37 | 20 | 9 | <0.0001 |
| AE or abnormal lab results | | 69 | 30 | 25 | 14 | 0.6 |
| | Constipation | 35 | 22 | 9 | 4 | 0.005 |
| Decreased $HCO_3^-$ level | | 36 | 18 | 9 | 9 | 0.2 |
| | Vomiting, reflux | 12 | 5 | 5 | 2 | 0.8 |
| Low free carnitine level | | 9 | 4 | 5 | 0 | 0.07 |
| | Feeding difficulty | 6 | 0 | 3 | 3 | 0.08 |
| | Kidney stone | 3 | 3 | 0 | 0 | 0.07 |
| Transient hypoglycemia | | 2 | 1 | 1 | 0 | 0.7 |
| | Others | 7 | 5 | 2 | 0 | 0.2 |
| AE which required a management | | 63 | 29 | 23 | 11 | 0.01 |

**Table 5.** Age-related differences. AE, adverse event; KD, ketogenic diet. *Decreased HCO3- level (<18 mEq/L). Low free carnitine level (<27 μmol/L).

Restricting the diet or measuring the amount can be more difficult for the parents during this period. Our data regarding the selected food options supports this finding in which a bigger variation was reported among children aged between 1 and 2 years old in comparison to the other two age groups in which one type of foods (solid vs. liquid) were predominantly used (p = 0.001).

Patient growth data were not included. Some studies have reported osteopenia, growth arrest and weight loss in children on the KD[25,26]. It would be beneficial to learn how to address these issues in a more focused manner in the infant period, however, they may be more properly addressed in a long-term evaluation in collaboration with an endocrinologist. At present, the role of ketosis during the diet remains unknown. In our study, potential relationships between ketosis and seizure frequency or withdrawal from the KD was not evaluated. Technical limitation: urine ketones positive for most of the patients. Additionally, because of the retrospective nature of the study, it was difficult to identify the temporal relationship between urine ketones and seizure reduction. A recent study demonstrated the inconsistent relationship between ketosis and good seizure control in infants[12,13]. The fidelity of this relationship could be addressed in a future study. Lastly, the context in which this study was completed - a comprehensive epilepsy center with two dietitians working exclusively on the KD – may have lowered the rate of early withdrawal. On the other hand, because of a high volume of referrals for intractable epilepsy, we may have selectively included children with the most severe forms of epilepsy. Despite these limitations, the study has clinical significance demonstrating a safe and variable use of KD in young children. These findings will facilitate the safe use of the diet therapy in this population.

## Conclusion

The KD continues to be an effective, safe, and well tolerated treatment option for infants with intractable epilepsy. Tolerability may be enhanced by using a liquid-based diet in this age group, the role of expressed breast milk in which should be further elaborated. The availability of new diagnostic studies such as genetic testing could promote early and effective use of the KD by identifying patients who might favorably respond to the KD. Future studies with larger patient sample sizes require multi-center collaboration and would further refine our understanding of which genetic abnormalities and epilepsy syndromes respond best to the ketogenic diet.

## Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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## Author Contributions

## Additional Information