Experience With the Ketogenic Diet in Infants

Douglas R. Nordli, Jr, Maxine M. Kuroda, Joanne Carroll, Dorcas Y. Koenigsberger, Lawrence J. Hirsch, Harlan J. Bruner, William T. Seidel and Darryl C. De Vivo

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Experience With the Ketogenic Diet in Infants

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ABSTRACT. *Objective.* **To evaluate the effectiveness, tolerability, and adverse effects of the ketogenic diet in infants with refractory epilepsy.**

Methods. **A retrospective review of 32 infants who had been treated with the ketogenic diet at a large metropolitan institution.**

Results. **Most infants (71%) were able to maintain strong ketosis. The overall effectiveness of the diet in infants was similar to that reported in the literature for older children; 19.4% became seizure-free, and an additional 35.5% had >50% reduction in seizure frequency. The diet was particularly effective for patients with infantile spasms/myoclonic seizures. There were concomitant reductions in antiepileptic medications. The majority of parents reported improvements in seizure frequency and in their child's behavior and function, particularly with respect to attention/alertness, activity level, and socialization. The diet generally was well-tolerated, and 96.4% maintained appropriate growth parameters. Adverse events, all reversible and occurring in one patient each, included renal stone, gastritis, ulcerative colitis, alteration of mentation, and hyperlipidemia.**

Conclusion. **The ketogenic diet should be considered safe and effective treatment for infants with intractable seizures.** ***Pediatrics*** **2001;108:129–133;** ***ketogenic diet, effectiveness, safety, adverse effects, intractable seizures, infants.***

ABBREVIATION. RCF, Ross carbohydrate-free (formula).

The incidence of seizures is higher during the first 2 years of life than during any other period of childhood.[1] Outcome with regard to seizure control and development is poor.[2–6] Several severe catastrophic epilepsies present in infancy, including early myoclonic epilepsy, early infantile epileptogenic encephalopathy, West syndrome, and severe infantile myoclonic epilepsy. Seizures in these disorders may be difficult to control—sometimes only at the expense of multiple and toxic levels of antiepileptic medications. When these medications fail, alternative treatments are required. The ketogenic diet is a time-tested, effective treatment for older patients with refractory epilepsy.[7] There is, however, a striking lack of data regarding its efficacy and adverse effects in infants.

The diet is the primary therapy for infants with pyruvate dehydrogenase deficiency and glucose transporter protein deficiency.[8,9] We also believe that the diet is indicated in the treatment of generalized or multifocal infantile epilepsies, including infantile spasms, when multiple antiepileptic drugs fail or produce unacceptable side effects. Accordingly, the diet has been a treatment option at Columbia-Presbyterian Medical Center for >40 years. We used this experience to perform a retrospective review of all infants who had been treated with the ketogenic diet to determine its effectiveness, tolerability, and adverse event profile in this young population.

METHODS

Information regarding seizure types, seizure frequency, epilepsy syndrome, etiology, weight change, and ketosis was abstracted from the medical records of all infants (age <2 years) who had been treated with the ketogenic diet from October 1, 1983, through June 30, 1997. Criteria for treatment included intractable epilepsy, pyruvate dehydrogenase deficiency, and glucose transporter protein deficiency. Seizure frequency was recorded by Engel classification and then grouped into 3 categories: seizure-free (Engel I), worthwhile improvement (Engel II and III), or no significant change (Engel IV). Cause was divided into idiopathic/cryptogenic and symptomatic categories. Seizure types were recorded by International League Against Epilepsy criteria and also by a special semiologically based classification scheme tailored to infants.[10,11] Ketosis, measured by urine dipstick, was recorded as either none, variable, or consistently moderate to large.

Patients' families were contacted by telephone, and caregivers who were most familiar with the child's behavior at home were questioned. The respondent was almost always the patient's mother (the single exception was a patient's father). The parents were asked to rate the effects of the diet on seizure frequency, seizure intensity, speech/communication, comprehension/understanding, self-care, social interactions (eg, interest in others, playing), attention span/alertness, activity level, sleeping, motor skills, endurance, and behavior. These characteristics were rated on a Likert scale ranging from much worse (1), somewhat worse (2), same (3), somewhat better (4), or much better (5). These ratings have been used previously to assess the effects of the diet in older children.[12] The interview included questions on changes in antiepileptic medications while on the diet, the caregiver's impression of the overall benefit of the diet, and a reappraisal of the decision to try the diet.

Statistical Analyses

Patients were grouped into the 3 categories of the Engel classification described previously. Differences in proportions were evaluated by χ^2; $P < .05$ was considered to be statistically significant. Multiple logistic regression evaluated the risk of infantile spasms to seizure improvement versus no improvement on the

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ketogenic diet while controlling for the effects of potential confounders. All analyses were conducted with the use of the Statistical Package for the Social Sciences for Windows (version 5.02; SPSS, Inc, Chicago, IL).

Ketogenic Diet

Patients were admitted to the pediatric neurology service for initiation of the diet and typically began fasting after dinner on the evening of admission. Noncaloric fluids and sugar-free gelatins were offered during the fast, and blood glucose was monitored periodically. During the fast, baseline blood tests (complete blood count, electrolytes, glucose, liver enzymes, total protein, albumin, blood urea nitrogen, creatinine, calcium, phosphorous, carnitine, and fasting lipid profile) were obtained. From 1995 onward, urine was tested for calcium, phosphorous, and creatinine.

The diet was started once ketones were present consistently in the urine, usually 12–38 hours after the start of the fast. During the fast, a nutrition assessment determined the child's caloric and protein requirements. Estimated caloric needs were as follows: younger than 1 year, 90 to 100 kcal/kg; 1 to 2 years of age, 80 to 90 kcal/kg. Protein needs were prescribed at 80% to 100% of the recommended daily allowances. The diet history was reviewed, and the child's preferences were incorporated into the new diet whenever possible. A 3:1 or 4:1 (fat:nonfat) ketogenic meal plan was designed. The intake of food and/or formula was started slowly. The ratio of the diet was adjusted as needed to produce moderate to strong ketosis. Meals or formula or both were divided into equal parts and offered at approximately the same time each day. Fluids were not restricted.

Standard Meals

For standard meals, 25% to 50% of the designed meal plan was offered initially. The meals were increased to 100% over the next 3 to 4 meals, depending on the child's tolerance.

Ketogenic Formula

Infants who received formula were given half-strength 3:1 formula for the first 24 hours, then increased to full-strength during the next 24 to 36 hours. For infants who were bottle or tube fed, the ingredients for the ketogenic formula were readily available and simple to prepare. Ross carbohydrate-free ([RCF], Ross Laboratories, Columbus, OH), Polycose powder (Ross Laboratories, Columbus, OH), and Microlipid (Mead Johnson, Evansville, IN) were used.

After the ratio, calories, and protein for the ketogenic diet were established, the amount of RCF concentrate needed to provide the protein requirements was calculated. This was mixed with an equivalent amount of water. The fat present in RCF was subtracted from the total fat, and Microlipid was added to supply the difference. Finally, Polycose was added to supply the necessary amount of carbohydrate. The minimum amount of Polycose was 2 g/batch. This formula sometimes was given in conjunction with solid foods. Multivitamins with iron, in the form of sugar-free drops, were used for vitamin and mineral supplements. Calcium and folic acid were given when indicated.

RESULTS

Thirty-four infants (19 boys and 15 girls) were placed on the ketogenic diet. Three were placed on the diet because of metabolic disorders (1 with glucose transporter protein syndrome, and 2 with pyruvate dehydrogenase deficiency); 2 of these infants (the patient with glucose transporter protein syndrome and 1 of the 2 patients with pyruvate dehydrogenase deficiency) did not have intractable seizures and were excluded from this study. Of the remaining 32 patients with epilepsy, 4 had progressive disorders (a multisystem progressive disorder, poliodystrophy, pyruvate dehydrogenase deficiency, and Tay-Sachs).

All patients were able to develop ketonuria. The majority (71.0%) had consistently moderate to large ketones on urine dipsticks and tended to have better seizure control than patients whose ketosis was variable (Table 1). However, the association between level of ketonuria and level of seizure control was not statistically significant.

Six patients (19.4%) with intractable epilepsy became seizure-free, 11 (35.5%) had worthwhile improvement, and 14 (45.2%) had no worthwhile improvement on the diet. Two of the patients with progressive disorders had worthwhile improvement, and 2 had no worthwhile improvement; thus, favorable seizure control (seizure-free and worthwhile improvement) was not affected by the removal of the 4 patients with progressive disorders. Seizure control did not differ by gender or by developmental delay (Table 1). As compared with patients with symptomatic epilepsy, fewer patients with idiopathic/cryptogenic epilepsy had favorable control; however, this difference did not reach statistical significance (Table 1).

Mean start age was nearly 14 months (13.8 ± 5.7 months). Seizure control experienced by patients who began the diet at age 1 year or younger was at least as favorable (seizure-free and worthwhile improvement) as that experienced by patients who began the diet at older ages. Patients with favorable seizure control were maintained on the diet for longer intervals of time (Table 1). Twelve patients were on the diet as of July 1, 1997, 11 of whom had already been on the diet for at least 6 months.

The majority of patients had multiple seizure types. Having >1 seizure type did not predict poorer response to the diet. There was no difference in seizure control when seizure types were categorized as generalized versus partial. Patients with infantile spasms responded more favorably to the diet than did patients with other specific seizure types ($P < .05$; Table 1). In a logistic model that controlled for epilepsy cause, degree of ketosis, and age at start of diet, favorable seizure control was increased sixfold in infants with infantile spasms (odds ratio: 5.9; 95% confidence interval: 1.1, 32.3).

All but 1 of the 28 patients who had been on the diet for at least 3 months grew appropriately. Weight/height continued within appropriate percentiles with upward trend. The single exception was a patient with cerebral palsy and dysphasia.

Questionnaires regarding the diet's effect on seizure frequency/intensity and behavior were completed for 31 patients (Table 2). The family of 1 patient moved out of the United States and could not be reached for interview. The questionnaires revealed that 75% of parents believed that the frequency of their child's seizures decreased. There were no reports of increased seizure frequency. When asked about seizure intensity, 35.7% of the parents believed that the severity of their child's seizures lessened. The majority of parents reported improvements in their child's attention/alertness, activity level, and social interactions. Very few patients were rated as being worse in any behavioral or functional area. Half of the parents believed that their child benefited from the diet overall, and the majority indicated that if they had to decide again,

TABLE 1. Possible Predictors of Seizure Control (n = 31 Infants With Intractable Seizures*)

Parameter	Total (n [%])	Seizure-Free† (n [%])	Worthwhile Improvement‡ (n [%])	No Worthwhile Improvement§ (n [%])	P Value
Ketonuria					
Moderate to large	22 (71.0)	5 (22.7)	8 (36.4)	9 (40.9)	NS
Variable	9 (29.0)	1 (11.1)	3 (33.3)	5 (55.6)	
Gender					
Male	18 (58.1)	5 (27.8)	5 (27.8)	8 (44.4)	NS
Female	13 (41.9)	1 (7.7)	6 (46.2)	6 (46.2)	
Developmental delay					
Yes	24 (77.4)	5 (20.8)	9 (37.5)	10 (41.7)	NS
No	7 (22.6)	1 (14.3)	2 (28.6)	4 (57.1)	
Epilepsy etiology					
Idiopathic	12 (38.7)	1 (8.3)	4 (33.3)	7 (58.3)	NS
Symptomatic	19 (61.3)	5 (26.3)	7 (36.8)	7 (36.8)	
Age begun on diet					
≤12 mo	14 (45.2)	2 (14.3)	7 (50.0)	5 (35.7)	NS
>12 mo	17 (54.8)	4 (23.5)	4 (23.5)	9 (52.9)	
Duration on diet					
<3 mo	3 (9.7)	0	0	3 (100.0)	<0.05
3–5 mo	7 (22.6)	0	4 (57.1)	3 (42.9)	
≥6 mo	21 (67.7)	6 (28.6)	7 (33.3)	8 (38.1)	
Seizure type					
Generalized	10 (32.3)	2 (20.0)	2 (20.0)	6 (60.0)	NS
Partial unifocal	1 (3.2)	0	1 (100.0)	0	
Partial multifocal	5 (16.1)	0	2 (40.0)	3 (60.0)	
Generalized and partial	15 (48.4)	4 (26.7)	6 (40.0)	5 (33.3)	
Number of seizure types					
1	8 (25.8)	2 (25.0)	3 (37.5)	3 (37.5)	NS
2	11 (35.5)	1 (9.1)	3 (27.3)	7 (63.6)	
≥3	12 (38.7)	3 (25.0)	5 (41.7)	4 (33.3)	
Infantile spasms					
Yes	17 (54.8)	6 (35.3)	6 (35.3)	5 (29.4)	<0.05
No	14 (45.2)	0	5 (35.7)	9 (64.3)	

* One female patient with developmental delay and one seizure type (unifocal partial seizures of symptomatic known etiology) was started on the diet at age 11 months and developed moderate to large ketones. The diet was discontinued after 8 days because of adverse effects.
† Engel I (seizure-free).
‡ Engel II and III (worthwhile improvement, ie, >50% decrease in seizure frequency).
§ Engel IV (no worthwhile improvement).

TABLE 2. Changes Reported by Parents on Domains Queried by the Questionnaire (n = 31)

Domain of Interest	n*	Worse (n [%])	Same (n [%])	Better (n [%])
Seizure frequency	28	0	7 (25.0)	21 (75.0)
Seizure severity	28	3 (10.7)	15 (53.6)	10 (35.7)
Speech/communication	28	1 (3.6)	14 (50.0)	13 (46.4)
Comprehension/understanding	26	0	16 (61.5)	10 (38.5)
Self-care (eg, dressing, feeding)	26	1 (3.8)	19 (73.1)	6 (23.1)
Social (eg, interest in others, playing)	27	1 (3.7)	11 (40.7)	15 (55.6)
Attention span/alertness	28	1 (3.6)	10 (35.7)	17 (60.7)
Activity level (eg, over- or underactive)	27	1 (3.7)	10 (37.0)	16 (59.3)
Sleeping	28	2 (7.1)	21 (75.0)	5 (17.9)
Motor skills (eg, strength, speed)	26	2 (7.7)	14 (53.8)	10 (38.5)
Endurance (eg, tiredness)	27	2 (7.4)	14 (51.9)	11 (40.7)
Behavior (eg, compliance)	28	2 (7.1)	17 (60.7)	9 (32.1)

* n < 31 because parents were not able to respond to every question.

they would put their child on the diet (Table 3); the reason given most often was that they would be willing to try anything that may be helpful for their child.

Six of the 32 infants (18.8%) developed complications possibly related to the diet (Table 4). One had severe vomiting, 1 developed renal stones with hematuria, 1 had gastrointestinal bleeding from erosive esophagitis believed to be attributable to a chronic nasogastric tube, 1 developed type I hyperlipidemia with triglycerides over 9000 mg/dL that resolved after switching to the medium-chain triglyceride diet, and 1 developed ulcerative colitis. All of the complications were reversible and occurred in patients who were begun on the diet after 12 months of age. The majority of patients with treatment-emergent adverse events had been on the diet for >1 year, and 2 were on the diet as of July 1, 1997. In addition to these events, 1 patient became comatose with hypoglycemia and acidosis after initiation of the diet.

TABLE 3. Parental Assessment of Overall Benefit to Child (n = 31)

Question	Yes (n [%])	No (n [%])	Unsure (n [%])
Overall, did your child benefit from the diet?	14 (50.0)	13 (46.4)	4 (3.6)
If you had to decide again, would you put your child on the diet?	21 (75.0)	6 (21.4)	4 (3.6)

TABLE 4. Treatment-Emergent Adverse Events

Gender	Start Age (Month)	Time on Diet (Month)	Event
M	14	7	Severe vomiting
M	16	17	Renal stones
F	17	18	Gastrointestinal bleeding
M	18	23	Type I hyperlipidemia
M	21	26	Ulcerative colitis
F*	11	8 days	Coma

* Excluded from analyses of seizure frequency/severity and behavior because of short time on diet.

This patient had been on the diet for only 8 days, and the effects fully resolved after cessation of the diet.

Three patients died, 2 while on the diet. One had a severe multisystem disease with nephrotic syndrome, small bowel malrotation, blindness, deafness, hypertension, autonomic crises, and multiple pulmonary infections. She was on the diet from 17 months until her death at 35 months of age. She died at home as a result of another pulmonary infection. One infant had congenital heart disease that required 2 surgical procedures, a hypoplastic lung, a paralyzed hemidiaphragm and vocal cord with stridor, and severe cerebral anoxic injury related to the second cardiac surgery. He was on the diet from 20 months of age until his death from respiratory failure at 25 months, probably as a result of aspiration. The third patient had pyruvate dehydrogenase deficiency, was on the diet from 4 months to 10 months of age, and died 2 months later (off the diet) from complications related to her underlying metabolic disorder.

DISCUSSION

We found the effectiveness of the diet in infants to be similar to the rates reported in the literature for older children.[13] This is noteworthy given the propensity for intractability in this age group. The effectiveness of the diet was independent of the cause of the epilepsy and seizure type, with the exception that children with infantile spasms/myoclonic seizures responded better than other children. This perhaps is comparable to the experience described by Livingston et al [14], who reported that 80% of children with myoclonic seizures showed improvement with the ketogenic diet.

Most children maintained strong ketosis. Important factors in this regard may be the high ratios of fat to nonfat (often above 4:1) and calories to body weight (often above 90 kcal/kg) used in our patients. We speculated that these infants required relatively large amounts of ketone bodies to supply the necessary substrates for cerebral metabolic functions. This is in keeping with the scientific observations showing a greater ability of the brain to extract ketone bodies in infancy.[15–17]

The dietary prescriptions were designed specifically to provide adequate calories and protein to sustain infants along their weight-height percentiles, and therefore it is not surprising that the infants maintained good growth and height gain.

Consistent with the observations of the usefulness of the diet in older children, parents of infants often cited improvements in behavior and function. In fact, the 2 domains most frequently noted as improved (activity level and alertness) were the same domains identified previously with the use of the same questionnaire in a survey of parents with older children.[12] This effect is consistent with basic scientific observations that the diet is not sedative and, in fact, increases brain energy reserves[18] and quantity of brain adenosine 5′-triphosphate.[19] Although it was not possible to determine whether behavioral and functional improvements were related to seizure control, decrease in anticonvulsant medication, or other factors (eg, maturational), most parents seemed to note changes within 6 months, suggesting that the ketogenic diet may have played some role in improving the child's behavior in these areas. The previous survey of older children reported that changes in these domains were evident within 4 weeks of starting the diet.[12] Time to improvement in the current study seemed to be longer, possibly because changes may be more easily ascertained in older children.

Of the noted adverse events, we believe that 5 may have been associated with the use of the diet, including severe vomiting, renal stones, hyperlipidemia, ulcerative colitis, and coma. Ballaban-Gil et al[20] reviewed complications of the diet in older children and noted similar adverse events. Alteration of mentation may occur in patients with inborn errors of metabolism, particularly pyruvate carboxylase deficiency,[21] but our patient did not have any abnormalities on detailed metabolic testing before initiation of the diet.

We believe that the deaths were related to the underlying disease processes and not to the use of the diet itself. Nevertheless, because infants with intractable epilepsy may experience a variety of occult etiologies, strong caution is advised to exclude inborn errors of metabolism, such as pyruvate carboxylase deficiency and organic acidurias, before starting the diet.

CONCLUSION

We believe that the ketogenic diet is an effective, well-tolerated, and beneficial treatment for appropriate conditions in infants. The current study was retrospective, and efficacy rates from retrospective studies may differ from that of prospective studies[13,22]; thus, data from prospective studies of infants who are on the ketogenic diet also are needed to establish the diet's efficacy in this age group. We found that complications may be observed and appropriate candidates must be selected carefully. Treatment and meticulous follow-up by personnel who are familiar with the use of the diet in this age

group are suggested. Parents should be committed to compliance and have the support of a well-informed, experienced team at a major medical center.

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MODERN PARENTING

If you walk through the parenting section of your local bookstore, you'll find such titles as *Building Healthy Minds, Baby Minds: Brain-Building Games Your Baby Will Love, and Right From Birth: Building Your Child's Foundation for Life*. If you go to an upscale toy store, in addition to innocent playthings you will find sophisticated development tools designed for fetus and infant cultivation. Even parents who didn't buy *WombSong Serenades*, a musical collection designed to stimulate babies' fetal brain activity, can probably still raise a perfect child if they fill the first weeks of his or her life with full doses of Mozart. My local Buy Buy Baby, the infant-oriented megastore, offers at least half a dozen selections, including *Mozart for Babies' Minds* (featuring the Violin Concerto No. 3), *Mozart Playtime* (with the Minuet in F Major), the *Parents Magazine Classical Music for Baby Mozart* collection (Serenade No. 13 in G Major), and *Mozart for Toddlers* (Symphony No. 35). Parents just have to choose which one will produce the best synaptic responses in their child's cerebral cortex.

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