Ketogenic Diet for the Treatment of Refractory Epilepsy in Children: A Systematic Review of Efficacy

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ABSTRACT. *Objectives.* **To systematically review and synthesize the available evidence on the efficacy of the ketogenic diet in reducing seizure frequency for children with refractory epilepsy.**

Data Sources. **Medline searches were performed using the keywords epilepsy/therapy, dietary therapy, and epilepsy, and the text word ketogenic diet. The Cochrane Library of clinical trials was searched using the term ketogenic diet. Bibliographies of recent review articles and relevant primary research reports, as well as *Current Contents* were reviewed for additional relevant citations.**

Study Selection. **Studies were selected for inclusion in the review that reported the reduction of seizure frequency following treatment with the ketogenic diet in children with refractory epilepsy. The outcome measures used were the percentage of patients with: 1) complete elimination of seizures, 2) >90% reduction in seizures, and 3) >50% reduction in seizures.**

Results. **The evidence consists entirely of uncontrolled studies. Of 11 studies identified for this review, 9 are retrospective series of patients from a single institution. Two studies are prospective, 1 of which is a multicenter trial. The results of these studies are consistent in showing that some children benefit from the ketogenic diet, demonstrated by a significant reduction in seizure frequency. Estimates of the rates of improvement by combined analysis (confidence profile method) are complete cessation of all seizures in 16% of children (95% confidence interval [CI]: 11.0–21.7); a greater than 90% reduction in seizures in 32% (95% CI: 25.3–39.8); and a greater than 50% reduction in seizures in 56% (95% CI: 41.2–69.7). It is unlikely that this degree of benefit can result from a placebo response and/or spontaneous remission.**

Conclusions. **Although controlled trials are lacking, the evidence is sufficient to determine that the ketogenic diet is efficacious in reducing seizure frequency in children with refractory epilepsy.** *Pediatrics* **2000;105(4). URL: http://www.pediatrics.org/cgi/content/full/105/4/e46; *ketogenic diet, refractory epilepsy, children.***

ABBREVIATIONS. AED, antiepileptic drug; CI, confidence interval.

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Received for publication Nov 18, 1999; accepted Nov 18, 1999.

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Intractable or refractory epilepsy is defined by inadequate control of seizures despite optimal treatment with conventional medications. Of the 2.5 million patients with epilepsy in the United States, 25% to 30% can be considered to have intractable epilepsy.[1,2] Poorly controlled epilepsy has been associated with higher rates of mortality, unemployment, and cognitive impairments.[3]

A number of new antiepileptic drugs (AEDs) have been approved for use in refractory epilepsy (eg, felbamate, lamotrigine, gabapentin, and vigabatrin)and numerous trials of these agents as add-on therapy for refractory seizures in adult patients have demonstrated a modest benefit. A recent meta-analysis included an analysis of 10 placebo-controlled trials of gabapentin and 11 placebo-controlled trials of lamotrigine.[4] Response rates, defined as the percentage of patients with a greater than 50% reduction in seizures, were 20% for gabapentin versus 9.3% for placebo, and 21% for lamotrigine versus 8.9% for placebo. Although primarily labeled for adults, these agents are being used frequently by clinicians for children with refractory seizures.[5]

A second option for patients with refractory epilepsy is surgery. A resurgence of interest in surgical treatments for refractory seizures has occurred over the last decade. Definite indications for surgery include the presence of a epileptiform focus that is amenable to surgical resection. Approximately 10% of patients with refractory epilepsy meet these criteria.[2] In such patients, the success rate of surgery in eliminating or substantially improving seizures is up to 80%,[3,6] and this improvement seems to be stable for at least 4 years.[7] Controversy exists in the literature concerning indications for other types of antiepileptiform surgery (temporal lobectomy, callosotomy, and hemispherectomy).[7] The morbidity of neurosurgery for intractable seizures is not well-reported, with small retrospective series reporting on results from 1 type of surgery.[3,8–10] Serious complications have been reported, such as postoperative motor deficits, recurrent central nervous system bleeding, hydrocephalus, and wound infections. Unfortunately, the rates at which these complications occur remain ill defined.

Over the last decade, the ketogenic diet has gained popularity as another treatment option for this group of patients. Dietary measures have been described for the treatment of epilepsy since ancient times. Anecdotal reports documenting the success of fasting or starvation in the treatment of seizures exist as

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far back as the 5th century B.C.[11] Interest in this form of therapy was rekindled in the early 20th century after reports by physicians of dramatic improvements in seizure frequency after a period of fasting.

In the 1920s, pediatricians at Johns Hopkins University postulated that the antiepileptic effect of starvation resulted from ketosis, ie, the presence of ketone bodies in the circulation. These physicians demonstrated that it was possible to maintain a state of ketosis without prolonged starvation, by severely limiting the intake of carbohydrates and proteins, and thereby forcing the body to use ketone bodies as the predominant fuel source. The classic ketogenic diet, developed at Johns Hopkins, contains fats in a 4:1 ratio to carbohydrates. The amount of protein is regulated also so that ~90% of calories are derived from fat. This diet was used as a treatment for epilepsy fairly commonly in the 1920s and 1930s. In the late 1930s and 1940s, as effective antiepileptic drugs, such as phenytoin and phenobarbital, were introduced into clinical practice, the ketogenic diet was largely replaced by drug therapy.[12]

The mechanism of effect of ketosis on seizures is not understood. Various theories[11] have postulated that: 1) there is a direct stabilizing effect of ketone bodies on the central nervous system; 2) resulting acidosis accompanying ketosis modifies the seizure threshold; 3) changes in fluid and electrolyte balance result in reduced seizures; and 4) change in lipid concentration induced by the diet has an antiseizure effect.

Despite the lack of a well-defined mechanism of action, numerous reports have appeared in the literature that have suggested benefit of this diet in reducing the frequency of seizures. The objective of this present study is to systematically review and synthesize the literature evidence reporting on the efficacy of the ketogenic diet in reducing seizure frequency in children with refractory epilepsy.

METHODS

Search Methods

Medline searches were performed using the keywords epilepsy/therapy cross-referenced with the textwords ketogenic diet, and then using the keywords dietary therapy crossreferenced with the keyword epilepsy.

A World Wide Web Search was performed using the term ketogenic diet on the Alta Vista search engine. The Cochrane Library of clinical trials was searched using the term ketogenic diet. Bibliographies of recent review articles and relevant primary research reports, as well as *Current Contents* were reviewed for additional relevant citations.

Study Selection

Review of bibliographies revealed references dating back to the 1920s and 1930s. Because of the uncertainty of comparing studies of that era to more current research, article retrieval and review was limited to studies published in 1970 or later.

Studies were selected for inclusion in the review that met the following inclusion criteria: 1) reported relevant health outcomes after treatment with the ketogenic diet in children with refractory epilepsy (refractory was defined as suboptimal control of seizures despite multiple medication trials or intolerance to any effective medications); and 2) treatment given was either the classic ketogenic diet or a modification of this diet (eg, medium chain triglyceride diet).

The main outcome measure evaluated is a reduction in seizure frequency. The optimal outcome is complete elimination of seizures. A 50% or greater reduction in seizures is considered clinically significant. Many studies also reported the percentage of patients achieving near complete elimination of seizures, usually as a percent reduction of 90% or more. These 3 outcome measures (complete elimination of seizure, >90% reduction in seizures, and >50% reduction in seizures) are the outcomes that are reported in this review. Studies were excluded if they contained only subjective outcomes (eg, subjectively improved or not improved). A single study was excluded for this reason.[13]

Analysis

Combined analysis of the percentage of patients achieving the relevant outcome measure was performed using the confidence profile method (Fastpro software, Academic Press, Inc, New York, NY). For each outcome measure, a test of homogeneity was first run among the included studies with the following results: complete elimination of seizures ($\chi^2 = 15.5$; $P = .05$); 90% reduction ($\chi^2 = 10.3$; $P = .07$); and 50% reduction ($\chi^2 = 42.8$; $P < .001$). Because each of these tests of homogeneity reached or approached statistical significance, a random effects combined model was used.

An overall assessment of study quality was not performed because of the uncertain validity of overall quality measures.[14] Rather, specific aspects of the study design that were believed to be most likely to contribute to variability in outcomes were abstracted. The first of these elements was prospective versus retrospective study design. A sensitivity analysis was performed using only the prospective studies. The second set of elements related to the patient population. Although the treatment given and the outcome measurements were relatively uniform, the patient populations and the degree to which these populations were described varied considerably. The following data elements were abstracted: mean age of patients, type of seizures, mean pretreatment seizure frequency, mean number of pretreatment AEDs, development stage/IQ, and completeness of reporting inclusion/exclusion criteria. For each of these factors, a score of 0 (no information on that parameter), 1 (incomplete information on that parameter), or 2 (complete information on that parameter) was given. Sensitivity analysis was performed on the studies that were rated the highest on these specific elements.

RESULTS

A total of 11 studies were identified that were published since 1970 and met the inclusion criteria for detailed review[15–24] (also J. M. Freeman et al, unpublished data, July 1998). This body of evidence consists of uncontrolled studies of children treated with the ketogenic diet. There are no controlled studies that directly compared the ketogenic diet to drug therapy or surgery. Patients treated in these studies were all refractory to treatment with AEDs, although the definition of refractory varied among studies. In general, all patients had failed or were intolerant of treatments with multiple drug regimens.

Data from the studies reporting efficacy of the ketogenic diet are summarized in Tables 1 and 2. Ten studies were full-length articles published in peer-reviewed journals.[15–24] The final study was an unpublished manuscript obtained with permission from the authors (J. M. Freeman et al, unpublished data). Nine of the 10 published studies were retrospective clinical series of patients treated with the ketogenic diet at a single institution.[15–23] Vining et al[24] is a prospective, multicenter, uncontrolled trial enrolling 51 patients from 7 clinical centers. Finally, Freeman et al (unpublished data) is a prospective study of 150 consecutive patients treated at 1 institution.

Nine studies reported the percentage of children who became seizure-free,[15–21,24] (also J. M. Freeman et

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TABLE 1. KD in the Treatment of Refractory Seizures—Study Characteristics

Study/Year	Patients	Diet	Hospitalization	Study Design	Outcome Assessment	Compliance (Percentage of Patients Who Discontinue Diet)	Adverse Effects
Hopkins and Lynch/1970	34 children with seizures refractory to medications. Social environment conducive to KD	Classic KD. 3:1 fat/protein ratio	Length of hospital stay not specified	Clinical series. Retrospective analysis	Method NR. Response evaluated after at least 2 mo on diet	32% (11/34) 9 patients could not tolerate diet from outset, 2 patients discontinued despite improvement	Marked transient drowsiness—9% (3/34) Kidney stones—3% (1/34) Most patients showed moderate growth retardation
Huttenlocher et al/1971	12 children with seizures refractory to AEDs. Minimum of 4 seizures/wk for at least 4 mo	MCT diet	4–10 d	Clinical series. Retrospective analysis (?)	Method NR. Response assessed after at least 1 mo on diet	17% (2/12) 1 patient discontinued attributable to adverse effects, 1 attributable to intolerability	GI symptoms in 33% of patients (4/12), leading to discontinuation of diet in 1 patient
Janaki et al/1976	15 patients recalcitrant to various combinations of AEDs. 13/15 children	Classic KD. 4:1 fat/protein ratio	5–6 wk	Clinical series. Retrospective analysis	Method NR. Response evaluated after ≥12 wk	A few patients discontinued diet	NR
Huttenlocher/1976	18 children refractory to medications after "extensive trials. . .in various combinations"	MCT diet	NR	Clinical series. Retrospective analysis (?)	Method NR. Response evaluated after at least 3 mo on diet	NR	NR. No significant increase in serum lipids while on diet
Berman/1978	18 children refractory to medications in various combinations	MCT diet. 8/18 children had been treated with classic KD	NR	Clinical series. Retrospective analysis	Method NR. Variable length of time on diet	NR	NR
Trauner/1985	17 children with intractable seizures, despite numerous AEDs	MCT diet	NR	Clinical series. Retrospective assessment of outcomes (?)	Seizure activity log maintained by parents. Variable length of time on diet (6 mo–4 y)	29% (5/17) 17.6% (3/17) attributable to adverse effects. 11.8% (2/17) attributable to intolerability	3 patients (17.6%) with severe GI symptoms—diarrhea, vomiting, abdominal pain.
Sills et al/1986	50 children who had failed to respond to appropriate AEDs. Exclude severely retarded or developmentally delayed.	MCT diet	Average stay 18 d	Clinical series. Retrospective assessment of outcomes (?)	Hospital records and home logs by parents. 2 wk following stabilization of diet.	12% (6/50) at outset. 18% (9/50) later (time period not specified)	Mild diarrhea and abdominal pain—"common"
Schwartz et al/1989	59 patients who had failed to respond to adequate trials of conventional AEDs, or intolerable adverse effects. 55 children/4 adults	Classic KD—15 patients MCT diet—22 patients Modified MCT—13 patients Mixed—9 patients	Length of stay NR	Clinical series. Retrospective assessment of outcomes	Seizure activity log maintained by parents. Evaluated after 6 wk on diet	3.4% (2/59)	GI symptoms occurred in "approximately half" of patients. Transient drowsiness in 25% of patients upon starting diet
Kinsman et al/1992	58 consecutive patients treated with KD, all refractory to multiple AEDs and adequate home environment	Classic KD. 4:1 fat/protein ratio	3–4 d	Clinical series, consecutive patients. Retrospective analysis	Reports by parents and physicians. Variable length of treatment at time of assessment	5.2% (3/58) Estimated 80% of patients with >50% decrease in seizures remained on diet at 12 mo	Kidney stones—5% (3/58) Hypouricemia—3% (2/58) Acidosis—2% (1/58) Hypocalcemia—2% (1/58)
Vining et al/1998	51 children, 1–8 y old, >10 seizure/wk, failed at least 2 AEDs, adequate psychosocial situation, enrolled from 7 sites	Classic KD. 4:1 fat/protein ratio	4 d	Prospective, multicenter, uncontrolled clinical trial	Reports by parents. Outcomes assessed at 3-, 6-, 12-mo intervals	3 mo—12% (6/51) 6 mo—27% (14/51) 12 mo—45% (23/51)	Lethargy—4% (2/51) Acidosis—4% (2/51) Constipation—8% (4/51) Increased infections—4% (2/51) Vomiting—(2/51)
Freeman, unpublished data	150 consecutive children treated with ketogenic diet. Age 1–16 y, >2 seizure/wk, failed at least 2 AEDs	Classic KD. 4:1 fat/protein ratio. Some children <2 y old and adolescents put on 3:1 ratio	4 d	Prospective, uncontrolled clinical trial	Reports by parents. Outcomes assessed at 3-, 6-, 12-mo intervals	3 mo—17% (25/150) 6 mo—29% (44/150) 12 mo—45% (67/150)	Kidney stones—4% (?)

KD indicates ketogenic diet; MCT, medium chain triglyceride; NR, no report; GI, gastrointestinal.

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TABLE 2. KD in the Treatment of Refractory Seizures—Outcomes

Study/Year	*n*	Diet	Seizure Free (% of Total)	>90% Decrease (% of Total)	>50% Decrease (% of Total)	AED Use	Comments
Hopkins and Lynch/1970	34	Classic KD. 3:1 fat/protein ratio	8.8% (3/34)	NR	NR	NR	Other response categories: "much improvement (29%)," "moderate improvement (42%)"
Huttenlocher et al/1971	12	MCT diet	33% (4/12)	NR	NR	NR	GI symptoms in 33% of patients (4/12), leading to discontinuation of diet in one patient
Janaki et al/1976	15	Classic KD. 4:1 fat/protein ratio	20% (3/15)	NR	100% (15/15)		Study performed in India. Variation in diet as compared to United States
Huttenlocher/1976	18	MCT diet	22% (4/18)	56% (10/18)	89% (16/18)	NR	Correlation found between plasma level of ketone bodies and anticonvulsant effect
Berman/1978	18	MCT diet	MCT-5.6% (1/18) Classic-25% (2/8)	NR	33% (6/18) 50% (4/8)	NR	Concluded results superior with classic KD, no statistical tests performed
Trauner/1985	17	MCT diet	29% (5/17)	NR	29% (5/17)	NR	3 patients discontinued diet after 3–4 y and remained seizure-free. 29% of patients could not comply with diet
Sills et al/1986	50	MCT diet	16% (8/50)	24% (12/50)	44% (22/50)	4/8 patients 1 with complete control and required no further AEDs	4 children stopped diet after 2 or more y of treatment with no recurrence of seizures
Schwartz et al/1989	59	Classic KD: 15 patients MCT diet: 22 patients Modified MCT: 13 patients Mixed: 9 patients	NR	41% (26/63)*	81% (51/63)	NR	Results for 63 studies in 55 children. Trend toward lesser response in adults. No significant differences in effect by type of diet
Kinsman et al/1992	58	Classic KD. 4:1 fat/protein ratio	NR	29% (17/58)	38% (22/58)	For improved patients (n = 39): 10% discontinued all AEDs. 64% had reduction	3 patients with adverse effects severe enough to stop diet. Compliance ~90% at 6 months in patients who responded with >50% reduction
Vining et al	51	Classic KD. 4:1 fat/protein ratio	3 mo: 12% (6/51) 6 mo: 12% (6/51) 12 mo: 10% (5/51)	25% (13/51) 29% (15/51) 22% (11/51)	54% (28/51) 53% (27/51) 40% (20/51)	Details of AED use NR	Probability of remaining on diet closely related to efficacy in decreasing seizures
Freeman et al, unpublished data	150	Classic KD. 4:1 fat/protein ratio	3 mo: 3% (4/150) 6 mo: 3% (5/15) 12 mo: 7% (11/150)	33% (50/150) 32% (48/150) 27% (41/150)	60% (89/150) 51% (77/150) 50% (75/150)	Some patients had decrease in AED use. Details NR	Probability of remaining on diet closely related to efficacy in decreasing seizures

KD indicates ketogenic diet; MCT, medium chain triglyceride; GI, gastrointestinal; NR, no report.

TABLE 3. Quality Scores for Included Studies

Study/Year	Mean Age	Seizure Type	Mean Seizure Frequency	Mean Number of Previous AEDs	Developmental Stage/IQ	Inclusion/ Exclusion Criteria	Total Score
Vining/1998	4.7 y (range: 1.3–8.6 y; total points = 2)	All types except partial seizures alone (total points = 2)	230/mo (range: 11–1880; total points = 2)	7.0 (total points = 2)	NR (total points = 0)	Inclusion: 1–8 y of age; >10 seizure/wk; at least 2 previous AED trials; electroencephalogram criteria Exclusion: partial seizure only; metabolic or degenerative disease; inadequate psychosocial situation (total points = 2)	10
Freeman, unpublished data	5.3 y (range: 4 mo–16 y; total points = 2)	All types (total points = 2)	410/mo (total points = 2)	6.2 (total previous AEDs) 1.97 (current AEDs) (total points = 2)	70% of patients with IQ <69 (total points = 1)	Inclusion: 1–16 y old; >2 seizure/wk; at least 2 previous appropriate AED trials (total points = 1)	10
Huttenlocher et al/1971	10.1 y (range: 2.5–16 y; total points = 2)	All types (total points = 2)	Range: 1–50 per d in 9/12 patients. Almost continuous in 3/12 (total points = 1)	All patients had trials of AEDs in various combinations (total points = 1)	NR (total points = 0)	Inclusion: at least 4 seizure/wk for a 2-mo period (total points = 1)	7
Kinsman et al/1992	5.5 y (total points = 2)	All types (total points = 2)	NR (total points = 0)	4.9 ± 1.7 (total points = 2)	NR (total points = 0)	Family and home situation sufficient to adhere to diet (total points = 1)	7
Hopkins and Lynch/1970	6.5 y (range: 1–13 y; total points = 2)	Majority of patients had minor motor epilepsy (total points = 1)	NR (total points = 0)	Most had received virtually every anticonvulsant commonly in use (total points = 1)	NR (total points = 0)	Inclusion: patient had good tolerance of fatty foods; parents and home climate conducive to maintaining diet; able to afford extra cost of diet (total points = 2)	6
Trauner/1985	Range: 1–13 y (total points = 1)	All types (total points = 2)	13/17 patients had multiple daily seizures; 4/17 had seizures at least every 2–3 wk (total points = 1)	All had been tried on numerous anticonvulsant medications (total points = 1)	NR (total points = 0)	NR (total points = 0)	5
Huttenlocher/1976	Range 18 mo to 8 y (total points = 1)	All types (total points = 2)	NR (total points = 0)	"Trials on anticonvulsant drugs in various combinations" (total points = 1)	NR (total points = 0)	NR (total points = 0)	4
Janaki et al/1976	33% 0–10 y 47% 10–20 y 20% 21–30 y (total points = 1)	All types (total points = 2)	Range 3/wk–29/d (total points = 1)	"Recalcitrant seizures despite medication" (total points = 0)	NR (total points = 0)	NR (total points = 0)	4
Berman/1978	Range: 2–17 y (total points = 1)	All types (total points = 2)	NR (total points = 0)	"Failed to respond to . . . various drugs or combinations of drugs." (total points = 1)	NR (total points = 0)	NR (total points = 0)	4
Sills et al/1986	NR (total points = 0)	Generalized tonic-clonic, myoclonic absence, or complex partial (total points = 2)	NR (total points = 0)	"Failed to respond to appropriate anticonvulsant given as a single agent" (total points = 1)	NR (total points = 0)	Inclusion: children considered to have a good chance of achieving reasonable function (total points = 1)	4
Schwartz et al/1989	34% 0–5 y 42% 5–10 y 15% 10–15 y 9% >15 y (total points = 1)	All types (total points = 2)	NR (total points = 0)	". . . failed to respond to adequate trials of conventional anti-epileptic therapy" (total points = 1)	NR (total points = 0)	NR (total points = 0)	4
Historical controls (Huttenlocher and Haphel/1990)	3.4 y old (age at onset)	All types	More than 1 seizure/mo	Uncontrolled seizure "despite . . . appropriate anticonvulsant agents at maximum tolerated blood levels"	61% of patients with mild/moderate mental retardation (IQ <70)	Age of onset <13 y; IQ >30; absence of cerebral mass lesion; presence of epileptiform discharges on electroencephalogram	

NR indicates no report.
Scoring key: 0 = no information on this parameter contained in report; 1 = some information contained in report, but of vague nature, or incompletely reported (eg, frequent seizures; previous use of multiple AEDs); and 2 = contained explicit information on parameter in report (eg, all patients had seizure frequency of greater than 1 week; patients had failed at least 2 trials of AEDs).

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TABLE 4. Sensitivity Analysis of Included Studies

Included Studies	Seizure-Free	>90% Reduction in Seizures	>50% Reduction in Seizures
All (n = 11)	15.8% (CI: 11.0–21.7)	32.2% (CI: 25.3–39.8)	55.8% (CI: 41.2–69.7)
Prospective (n = 2)	8.8% (CI: 3.9–15.1)	27.6% (CI: 19.9–36.5)	46.5% (CI: 33.4–60.1)
High quality (n = 5)	14.9% (CI: 7.0–24.8)	27.6% (CI: 19.9–36.5)	44.6% (CI: 33.8–55.9)

al, unpublished data) with a range of 7% to 33%. The percentage of patients with a greater than 90% reduction in seizures was reported in 6 studies[18,21–24] (also J. M. Freeman et al, unpublished data) and ranged from 22% to 56%. Nine studies reported the percentage of patients who had a greater than 50% reduction in seizures, ranging from 29% to 100%[17–24] (also J. M. Freeman et al, unpublished data).

Combined analysis of these outcome data were next performed. Three separate analyses were performed by the confidence profile method (FastPro) for the outcomes of percentage of patients with complete elimination of seizures, percentage of patients with a greater than 90% reduction in seizures, and the percentage of patients with a greater than 50% reduction in seizures. The combined point estimate for the outcome of percentage of patients who became seizure-free was 15.8% with a 95% confidence interval (CI) of 11.0 to 21.7. For the outcome of greater than 90% reduction in seizures, the point estimate was 32.2% with a 95% CI of 25.3 to 39.8. For the outcome of greater than 50% reduction in seizures, the point estimate was 55.8% with a 95% CI of 41.2 to 69.7 (Table 4).

Two sensitivity analyses were performed, the first limited to prospective studies (n = 2)[24] (also J. M. Freeman et al, unpublished data), and the second limited to studies with a quality score for the description of patient population of greater than 4 (n = 5)[15,16,20,24] (also J. M. Freeman et al, unpublished data). As shown in Table 4, there is a slight diminution of the treatment effect for each of the sensitivity analyses. However, the results are not substantially different from the percentages of responders using all the studies.

Compliance with the diet was inconsistently reported. The definition of compliance varied. Some studies restricted compliance to those patients who had clinical improvement and did not consider patients without improvement who stopped the diet to be noncompliant. The range of reported noncompliance was 3% to 32%.

Adverse effects were not consistently reported in the 9 clinical series reviewed. Mild gastrointestinal symptoms were common when reported,[16,21,22] occurring in one third to one half of treated children. Other adverse effects, such as kidney stones and metabolic abnormalities, occurred in <5% of children when reported.[15,23] Vining et al[24] systematically reported adverse events in 51 patients. Complications consisted of lethargy, acidosis, constipation, vomiting, and an increased number of infections. These adverse events occurred with a frequency of 4% to 8% (Table 1). One retrospective study,[25] which did not meet the inclusion criteria for this review, specifically examined the incidence of kidney stones in 120 patients treated with the ketogenic diet over a 10-year period. This study reported kidney stones in 5% of patients (6/120), as ascertained by review of patient records.

DISCUSSION

The results of this analysis suggest that approximately half of children with refractory epilepsy will have a clinically meaningful improvement after treatment with the ketogenic diet. Because these results are based on uncontrolled studies, it is possible that the results could be explained by the placebo effect, spontaneous remission, and/or random variation. However, it is unlikely that these factors could account for the degree of seizure reduction seen in these trials.

To estimate the magnitude of the placebo effect in the treatment of refractory epilepsy, the placebo response in recent add-on trials of newer AEDs for patients with refractory epilepsy was examined. These data are on treatment of adults, unfortunately corresponding data on children is lacking. A recent meta-analysis summarizes the relevant data.[4] This study analyzed 51 placebo-controlled trials of 6 newer antiepileptic agents (some not available in the United States). In all trials, response rates were defined by the percentage of patients with greater than 50% reduction in seizures. The percentage of patients receiving placebo who responded ranged between 6.2% and 13.8%. Combining results from all patients treated with placebo, 137 of 1396 patients or 9.8% responded to placebo. This is contrasted with the estimate of 55.8% (95% CI: 41.2–69.7) of patients who had a greater than 50% response to the ketogenic diet, making the placebo effect an extremely unlikely explanation for these findings.

Spontaneous remission occurs in pediatric epilepsy. For patients with intractable epilepsy, the natural history of the disorder is not well defined. A single retrospective study was identified that reported on spontaneous remission in patients with refractory epilepsy.[1] In this study, spontaneous remission was related to intelligence level and was observed to occur at a rate of 4% per year in patients with normal intelligence per year, and at 1.5% per year in patients with mental retardation. This rate of 1.5% to 4% per year is compared with the estimated 15.8% (95% CI: 11.0–21.7) of patients who became seizure-free on the diet, most within a much shorter time period than 1 year. The lower limit of this CI is more than twice as high as the upper limit of the incidence of spontaneous remission. Also, a comparison of the patient population in this study with the populations for the included studies (Table 4) reveals that the patients treated in the ketogenic diet studies have more severe epiliepsy. Thus, spontaneous remission might account for a small number of patients

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who improve on the ketogenic diet but is unlikely to explain the majority of the improvement.

This analysis is limited by several factors. The overall quality of this body of literature is not high. There are no controlled trials of the ketogenic diet compared with drugs or surgery, and the majority of the clinical series reported in the literature are retrospective in nature. However, sensitivity analysis by quality of the studies resulted in only a slight dimunition of the treatment effect. A second limitation is the lack of a biological explanation for the treatment effect. Although several theories on mechanism of action have been proposed, none are supported by empirical data.

There are only limited data on adverse effects of the ketogenic diet. Effects on growth and development over the intended course of the diet (2–3 years) are not known. Some authors commented that children may show growth retardation,[15] but this has not been systematically examined. It is expected that cholesterol levels and triglyceride levels will rise on the diet. Delgado et al[26] reported in abstract form that 5 of 17 children (29%) developed significant hypercholesterolemia (greater than 250 mg/dL) while on the diet, and 4 of 17 (24%) developed hypertriglyceridemia. The mean cholesterol for the 5 children with hypercholesterolemia was 367 mg/dL with a range of 253 to 512. The significance of this degree of hypercholesterolemia for a 2- to 3-year period is not known.

CONCLUSION

In summary, the ketogenic diet seems to be efficacious in reducing the frequency of seizures in children with refractory epilepsy. Some children will benefit, as demonstrated by a reduction in seizures that is unlikely to be attributable to a placebo effect or to spontaneous improvement. Compared with alternatives, this improvement is in the range or greater than that reported with the addition of newer AEDs. For a properly selected subset of patients, surgery may achieve as good or better seizure control but involves the potential for greater morbidity associated with neurosurgery. Therefore, treatment with the ketogenic diet should be considered a valid therapeutic option for children with refractory epilepsy.

ACKNOWLEDGMENTS

The work for this project was supported by the Blue Cross and Blue Shield Association Technology Evaluation Center.

We would like to acknowledge the input of the Blue Cross and Blue Shield Association Technology Evaluation Center Medical Advisory Panel for their assistance in the formulation, review, and revisions to the enclosed manuscript. The members of this panel are James Armitage, MD; Wade Aubry, MD; J. Lawrence Colley, ME; Helen Darling, MA; Richard D. Dent, ME; David Eddy, MD; PhD, Alan Garber, MD, PhD; Kathleen Goonan, MD; Michael Hattwick, MD; I. Craig Henderson, MD; Albert Jonsen, PhD; Peter Margolis, MD, PhD; Barbara McNeil, MD, PhD; Richard Roberts, MD, JD; Earl Steinberg, MD, MPP; Clifford Waldman, MD; Paul Wallace, MD; and Les Zendle, MD.

We would also like to thank Kathleen Zegler, PharmD, for her assistance with manuscript preparation and editing.

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