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J Child Neurol published online 20 July 2010
DOI: 10.1177/0883073810376443

Original Article

Journal of Child Neurology
000(00) 1-6

DOI: 10.1177/0883073810376443
http://jcn.sagepub.com

Do Patients With Absence Epilepsy Respond to Ketogenic Diets?

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Abstract

Dietary therapies are established as beneficial for symptomatic generalized epilepsies such as Lennox-Gastaut syndrome; however, the outcome for idiopathic generalized epilepsy has never been specifically reported. The efficacy of the ketogenic and modified Atkins diet for childhood and juvenile absence epilepsy was evaluated from both historical literature review and patients treated at Johns Hopkins Hospital. Upon review of 17 published studies in which absence epilepsy was included as a patient subpopulation, approximately 69% of 133 with clear outcomes patients who received the ketogenic diet had a >50% seizure reduction, and 34% of these patients became seizure free. At Johns Hopkins Hospital, the ketogenic diet (n = 8) and modified Atkins diet (n = 13) led to similar outcomes, with 18 (82%) having a >50% seizure reduction, of which 10 (48%) had a >90% seizure reduction and 4 (19%) were seizure free. Neither age at diet onset, number of anticonvulsants used previously, particular diet used, nor gender correlated with success.

Keywords

absence, ketogenic, diet, epilepsy, children, petit mal

Received May 23, 2010. Received revised May 29, 2010. Accepted for publication May 30, 2010.

The ketogenic diet was first created in 1921 and typically involves an initial brief fasting period, followed by slowly starting a high-fat, adequate-protein, and low-carbohydrate diet,[1] along with calorie and fluid restriction.[2,3] The modified Atkins diet was created at Johns Hopkins Hospital in 2002, to create a less restrictive option.[4] The modified Atkins diet induces ketosis without restricting calories, fluids, or protein and has become increasingly used for adolescents and adults not typically offered the traditional ketogenic diet.[4]

Studies have shown that the ketogenic diet is highly effective for children with intractable epilepsy due to infantile spasms, Dravet syndrome, and Lennox-Gastaut syndrome.[3] Most of these and other epilepsy syndromes typically treated with the ketogenic diet are symptomatic generalized epilepsies. In these circumstances, the ketogenic diet could be more effective than adjunctive anticonvulsants, with a 50% to 60% response rate after 6 months of treatment.[3]

Childhood absence epilepsy is an idiopathic, age-related epilepsy syndrome notable for multiple daily staring spells and occasional generalized tonic-clonic seizures.[5] Childhood absence epilepsy is initially treated with anticonvulsants, most commonly ethosuximide, valproate, and lamotrigine.[5] Juvenile absence epilepsy begins in early adolescence and is more likely to be associated with generalized tonic-clonic seizures.[6] Treatments for juvenile absence epilepsy are also usually anticonvulsants, often valproate, lamotrigine, and topiramate.[6] Most children with either form of absence epilepsy respond to anticonvulsants quickly.

However, there are some children with childhood and juvenile absence epilepsy who are medically refractory. For cases of symptomatic generalized epilepsy that are intractable, child neurologists often consider nonpharmacologic treatments such as vagus nerve stimulation and dietary treatments. To our knowledge, there are no publications addressing the effectiveness of dietary treatments for idiopathic generalized epilepsies and absence epilepsy specifically. The purpose of this study was to determine the efficacy of the ketogenic diet and modified Atkins diet for children with absence epilepsy, both from published literature as well as ongoing prospective studies of the ketogenic and modified Atkins diets at Johns Hopkins Hospital.

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Table 1. Epilepsy Treated With the Ketogenic Diet, 1922-2008

Author	Year of Publication	Total Patients	Patients With Absence	Age Range, y	Seizure Description	Seizure Frequency (per Day)	>50% Seizure Reduction (%)	Seizure Free (%)	Total Diet Duration, mo
Goldbloom[7]	1922	2	1	10	Petit mal	60-100	1 (100)	0 (0)	[a]
Peterman[8]	1924	86	5	8-12	Petit mal	3-250	4 (80)	2 (40)	[a]
Peterman[9]	1925	37	16	3-14	Petit mal	1-500	14 (88)	7(44)	1.5-48
Talbot et al[10]	1926	12	3	7-13	Petit mal	6-50	3 (100)	2 (67)	2-3
Barborka[11]	1928	49	6	30-34	Petit mal	10-15	5 (84)	0 (0)	7-24
Lennox[12]	1928	2	1	13	Petit mal	1-8	1 (100)	1 (100)	[a]
Barborka[13]	1928	100	11	17-35	Petit mal	1-300	7 (64)	0 (0)	3-32
Wilkins[14]	1937	30	3	6-10	Petit mal	2-13	3 (100)	2 (67)	17-19
Helmholz and Goldstein[15]	1938	501	63	[a]	Petit mal	1-100	40 (63)	25 (40)	[a]
Keith[16]	1942	611	2	9	Absence	12-15	2 (100)	2 (100)	9-36
Dekaban[21]	1966	11	1	5	Absence	20-40	1 (100)	0 (0)	9
Sills et al[22]	1986	50	6	5-11	Absence	[a]	5 (83)	2 (33)	[a]
Vining et al[23]	1998	51	8	1-8	Absence	[a]	[a]	[a]	[a]
Vaisleib et al[24]	2004	69	8	5-10	Absence	[a]	3 (37.5)	1 (12.5)	[a]
Mackay et al[25]	2005	26	2	[a]	Absence	[a]	1 (50)	0 (0)	[a]
Bergqvist et al[26]	2005	48	3	6-12	Absence	[a]	2 (67)	1 (33)	1-48
Neal et al[27]	2008	145	2	[a]	Absence	[a]	0 (0)	0 (0)	[a]
Total	1922-2008	1830	141	1-35		1-500	92/133 (69)	45/133 (34)	1-48

[a] Not described or available for review.

Methods

To determine the presence of reported absence epilepsy cases in the literature, all ketogenic diet publications to date were reviewed. In publications reviewed prior to 1942, the term *absence epilepsy* was not specifically used, but rather *petit mal* was described.[7-16] Occasionally, studies detailed individual cases in which age, clinical semiology, and electroencephalography (EEG) made the diagnosis highly likely.[17-20] Most of these illustrative cases reported good outcomes. If patients were described as having seizures in infancy or adulthood, had multiple seizure types (not just staring spells or petit mal), or details of clinical semiology were not provided, they were not included in this analysis as having likely absence epilepsy. Limited information was available regarding the time of outcome assessment or ketogenic diet duration in most of these publications.

More recent articles since the 1960s often did describe children as having absence epilepsy, although these cases were all included within larger ketogenic diet cohorts.[21-28] Others either did not have clearly reported cases with absence epilepsy or did not describe their outcomes. In fact, one of the largest reports by Dr Samuel Livingston of 975 children stated that "the ketogenic diet is ineffective in controlling true petit mal spells" but failed to provide further information.[29] For several of the larger prospective studies,[17,18,24,26,27] authors were contacted via e-mail to confirm more detailed information regarding patients with absence epilepsy, including studies in which no children with absence epilepsy were included.

Children seen at Johns Hopkins Hospital since 1993 for either the ketogenic or modified Atkins diet were also reviewed. For those treated with the ketogenic diet, information was maintained in a database with demographic, outcome, and EEG data included. The Johns Hopkins Hospital Institutional Review Board approved the informational examination required for this study. Statistical analysis was performed with the Fisher exact test and Wilcoxon test. The significance level for all tests was $P < .05$.

Results

Historical Review

Seventeen previous ketogenic diet studies published from 1922 to 2009 were identified as having included subjects with childhood or juvenile absence epilepsy. In total, the publications included 141 children and adults with absence epilepsy who were treated with the ketogenic diet (Table 1). The age range at ketogenic diet onset was 1 to 35 years, with all but 2 publications solely treating children.[11,13] Of the 54 patients for whom gender was described, 27 (50%) were male. The few studies that described prior attempted (and failed) anticonvulsant medications before the ketogenic diet included succinimides, primidone, acetazolamide, barbiturates, trimethadione, mephobarbital, and phenytoin.[14,16]

Two large reviews listed many retrospective and prospective studies involving the ketogenic diet over the period 1970 to 2009.[3,30] Any studies listed that were not previously reviewed were examined as well for potential cases of childhood or juvenile absence epilepsy. In most of these studies, either enough detail confirmed a lack of childhood or juvenile absence epilepsy patients or contact was made with authors verifying that no children with absence epilepsy were present in their studies.[19,20,28,31-35] One study reported patients with absence epilepsy, but specific outcomes were not described for this subpopulation of 8 children, nor did the authors still have the data to review.[23]

In total, 133 children with absence epilepsy and clear documented outcomes were available for review. Ninety-two of 133 (69%) patients were reported as having a >50% seizure reduction, and 45 (34%) became seizure free for some period of time. Additional information regarding seizure severity or EEG changes was not often reported, nor were recurrence rates in those who became seizure free. The time to ketogenic diet response ranged from 3 days to 3 months, and the ketogenic diet was continued for 9 weeks to 3 years.

Johns Hopkins Hospital Patients

The ketogenic diet has been used at Johns Hopkins Hospital for several decades, but an institutional review board–approved database of patients started prospectively has been used since September 1993. Since that time, 8 patients with classic childhood absence epilepsy have tried the ketogenic diet (Table 2). Although these patients were treated from June 1996 to July 2009, 5 of 8 (62.5%) were treated prior to 2002, largely reflecting a recent neurologist shift toward the modified Atkins diet for this seizure type. Since September 2002, 13 children have started the modified Atkins diet at our institution for the treatment of intractable childhood and juvenile absence epilepsy (Table 2). These children have been previously included in 1 retrospective[36] and 3 prospective[37-39] open-label studies. There was no significant difference in any of the baseline patient demographics (age, gender, seizure frequency, number of anticonvulsants tried) between children receiving the ketogenic or modified Atkins diet. Similarly, the 1- and 3-month outcomes also were not significantly different between those treated with the ketogenic and modified Atkins diet; therefore, any further analysis of these patients was combined (n = 21).

The median age of seizure onset was 4.5 years (range, 1-9 years), and the median age of diet onset was 6 years (range, 4-20 years). Only 3 children had a history of generalized tonic-clonic seizures, 2 of whom no longer had them actively at the time of starting the diet. The median number of anticonvulsants tried was 4 (range, 2-10); the median number of anticonvulsants used at the time of diet onset was 1 (range, 0-3). One patient was receiving vagus nerve stimulation at diet onset. The classic EEG findings of 3 per second spike and wave discharges were seen in 18 (86%), with slightly asymmetric polyspike and wave activity in 3 (14%). Seizures induced by hyperventilation occurred in 14 (67%).

At 1 month of dietary treatment, 16 (76%) reported >50% seizure reduction, of which 8 (38%) had >90% seizure reduction and 4 (19%) were seizure free. At 3 months, 18 (82%) reported >50% seizure reduction, of which 10 (48%) had >90% seizure reduction and 4 (19%) were seizure free. Baseline demographics were examined to identify factors predicting >90% seizure reduction at 1 month, but no correlating factor was found (Table 3).

Comparison of EEG results before and during dietary treatment was documented for 3 patients, all of whom continued to show epileptiform discharges. Only 1 patient with ongoing generalized tonic-clonic seizures was started on dietary treatment (patient 20), beginning the modified Atkins diet at the age of 20 years. She continued to have 1 generalized tonic-clonic seizure per month despite a 50% to 90% improvement in absence seizures, and remained on the modified Atkins diet for 22 months.

The outcomes from the literature (1922-2008) were then compared to the 3-month seizure reduction of patients at Johns Hopkins Hospital. There was a slightly higher rate in our subjects of a >50% seizure reduction (82% vs 69%, $P = .07$). Interestingly, there was a similar but negative trend regarding likelihood of seizure freedom (19% vs 34%, $P = .09$).

Discussion

These results demonstrate that dietary therapies can be effective for the treatment of absence epilepsy, similar to results published for symptomatic generalized epilepsy. Our center's experience appears to be similar to those published for the past 87 years, even acknowledging that some of the patients reported in the literature might not have had classic childhood or juvenile absence epilepsy. Overall, 71% (110/154) of patients who received dietary therapy had a >50% seizure reduction, which is similar to the overall response to dietary treatments for all children with epilepsy no matter the seizure type.[3]

There were no patient demographics that predicted who was more likely to respond to dietary treatment. Larger prospective studies with documented prediet EEG and, perhaps, larger sample sizes for those treated with particular concurrent anticonvulsants could demonstrate predictive factors. There appears to be a recent trend at our center toward starting children referred for diet for absence epilepsy with the modified Atkins diet. This could be due to various factors, including its attractiveness as an option to adolescents not typically offered the ketogenic diet, its outpatient initiation, and the possibility that absence epilepsy could be viewed by parents and child neurologists as a less severe and typically outgrown epilepsy that does not warrant the more restrictive ketogenic diet.

There are several limitations to this retrospective study. There was very little evidence of electrographic improvement, and it might be common for children to appear better clinically to parents yet continue to have significant EEG abnormalities.[40] Also, in our cases and those in the literature, only short-term outcomes (eg, 6-12 months) were usually available. Lastly, it is a possibility that some subjects with absence epilepsy published in ketogenic diet studies from more than 50 years ago could have been improperly described or incorrectly classified and might have had partial epilepsy without secondary generalization as the etiology for their petit mal seizures. In 4 studies, the only clear patients with absence epilepsy were those included as illustrative, brief case descriptions[7,8,12,15]; therefore, there might be a bias in these case series toward reporting only those with good outcomes as well. Future studies could benefit from EEG analysis, long-term outcomes, or possibly even using diets as a first-line therapy compared to anticonvulsants. In addition, evaluating the ketogenic diet in an animal

Table 2. Demographics and Outcomes of Patients With Absence Epilepsy Treated With Dietary Therapy at Johns Hopkins Hospital, 1993-2009

Patient	Diet	Ketogenic Ratio	Gender	Age at Seizure Onset, y	Age at Diet Onset, y	Seizure Frequency (per Day)	Anticonvulsants at Diet Onset	Seizure Response (1 mo)	Seizure Response (3 mo)
1	Ketogenic	4:1	Male	1	6	1	Valproate	Seizure free	Seizure free
2	Ketogenic	3:1	Male	5	8	25	Lamotrigine	Seizure free	Seizure free
3	Ketogenic	3:1	Female	3	7	80	Lamotrigine	0%	0%
4	Ketogenic	4:1	Female	6	9	240	Ethosuximide	1%-50%	1%-50%
5	Ketogenic	3:1	Female	5	14	150	Valproate	50%-90%	50%-90%
6	Ketogenic	4:1	Female	1	4	50	Zonisamide, levetiracetam	90%-99%	90%-99%
7	Ketogenic	4:1	Female	6	9	50	Levetiracetam, valproate	50%-90%	50%-90%
8	Ketogenic	3:1	Female	4	14	25	Valproate, ethosuximide	Seizure free	90%-99%
9	Modified Atkins		Male	3	9	15	None	90%-99%	Seizure free
10	Modified Atkins		Male	6	8	30	Lamotrigine	50%-90%	90%-99%
11	Modified Atkins		Male	2	4	30	Levetiracetam	50%-90%	90%-99%
12	Modified Atkins		Male	6	7	75	Ethosuximide	90%-99%	90%-99%
13	Modified Atkins		Female	5	9	150	Topiramate	50%-90%	90%-99%
14	Modified Atkins		Female	9	11	10	Levetiracetam	Seizure free	Seizure free
15	Modified Atkins		Female	2	6	50	Lamotrigine	90%-99%	50%-90%
16	Modified Atkins		Female	3	7	15	Lamotrigine	1%-50%	50%-90%
17	Modified Atkins		Female	4	6	4	Valproate, lamotrigine	50%-90%	50%-90%
18	Modified Atkins		Female	3	5	25	Ethosuximide, lamotrigine	1%-50%	50%-90%
19	Modified Atkins		Female	4	9	10	Ethosuximide, lamotrigine	50%-90%	50%-90%
20	Modified Atkins		Female	6	20	1	Levetiracetam, zonisamide	50%-90%	50%-90%
21	Modified Atkins		Female	4	16	25	Levetiracetam, clobazam, oxcarbazepine	0%	0%

Table 3. Comparison of Demographics for Johns Hopkins Hospital Patients With a Likelihood of a >90% Seizure Reduction at 1 Month

	<90% Seizure Reduction (n = 13)	>90% Seizure Reduction (n = 8)	*P* Value
Age at seizure onset, y	4.5	3.5	.40
Age at diet onset, y	8.5	7.5	.61
Seizures per day	30	25	.51
Number of prior anticonvulsants	5	4	.28
Number of current anticonvulsants	1	1	.28
Receiving the modified Atkins diet (%)	9 (69)	4 (50)	.25
Gender, male (%)	2 (15)	4 (50)	.10

model of absence epilepsy could prove helpful, although there has been a single study of the genetic absence epilepsy rat of Strasbourg with no reported improvement in spike-wave discharges.[41]

In summary, both the ketogenic and modified Atkins diets appear to be effective treatments for intractable absence epilepsy. Not only were a significant majority of patients improved, but many had periods of seizure freedom. Further prospective studies of diets for absence epilepsy are warranted.

Author Contributions

LBG was the primary investigator and wrote the first draft of the manuscript. PLP was the research coordinator. ZT and JLD were study dietitians for patients enrolled at Johns Hopkins Hospital. VHG retrieved all historical manuscripts for review. EHK was a coinvestigator and helped with the writing of this manuscript.

Declaration of Conflicting Interests

The authors declared a potential conflict of interest (e.g. a financial relationship with the commercial organizations or products discussed in this article) as follows: Dr. Kossoff has received grant support from Nutricia, Inc., and consultant fees from Nutricia and Atkins Nutritionals, Inc. not related to this study. The other authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors financial support for the research and/or authorship of this article: Ms. Groomes received salary support for this study from the Carson Harris Foundation. Some patients enrolled in studies at Johns Hopkins Hospital were supported by the Dr. Robert C. Atkins Foundation, Nutricia, Inc., and Johns Hopkins University School of Medicine General Clinical Research, Grant # M01-RR00052, from the National Center for Research Resources/NIH.

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