ORIGINAL ARTICLE

The Efficacy of the Ketogenic Diet in Improving Seizures and EEG Findings in Patients with Refractory Infantile Spasms

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Abstract

Objectives

Infantile spasm is an epileptic disorder of early childhood and infancy and is characterized by cluster epileptic spasms and abnormal EEG findings. Developmental delay is prevalent. Some studies have indicated the significant effect of the Ketogenic Diet (KD) on intractable spasms in children who are unresponsive to first-line treatments. It has been used successfully as a first-line treatment with fewer side effects than ACTH.

Materials & Methods

This was an interventional study in which the effectiveness of KD over a six-month period was evaluated in patients with infantile spasms. Those who fulfilled the inclusion criteria and were willing to use the diet received free cans of the 4:1 ketogenic formula. The diet was prescribed based on the Johns Hopkins protocol in the outpatient setting. All patients used a full formula diet for one month. After a month, the patients were examined by a neurologist and a dietitian, and an EEG was obtained to compare pre- and post-KD findings. In order to compare pre- and post-KD seizures, the maximum number of seizures was multiplied by the longest duration of seizures.

Results

Ten patients were assessed for one month. Using the KD led to significant changes in seizures/clusters and EEG findings. Nine parents reported improvement in their children's social interactions after using the KD.

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Conclusion

Based on the findings of this study, the KD can control seizures in patients suffering from infantile spasms by reducing seizure frequency & duration and improving EEG findings.

Keywords: infantile spasm; ketogenic diet; refractory seizure
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Introduction

Infantile spasm is an epileptic disorder of early childhood and infancy. It is characterized by cluster epileptic spasms and abnormal EEG findings. Neurodevelopmental delay is prevalent. Seizures can range from a massive contraction of muscles to a brief head nod (1). Brain imaging, along with metabolic and genetic studies, is commonly used to diagnose the underlying etiology (2). The first-line treatment for this disorder is to administer ACTH and Vigabatrin (1, 3, 4).

The ketogenic diet (KD) is a high-fat, low-carbohydrate diet (5). Some studies have indicated significant effects of the KD on intractable spasms in children who are unresponsive to first-line treatments (6-13). Also, KD has been successfully used as a first-line treatment with fewer side effects than ACTH (14). In Iran, the ketogenic formula is not covered by insurance. Thus, clinicians and patients prefer to use multiple antiepileptic drugs rather than an expensive ketogenic formula. In this study, we aimed to explore the benefits of administering an outpatient ketogenic diet in children with refractory infantile spasms.

Materials & Methods

This was an interventional case series study in which all patients with infantile spasms referred to Children's Medical Center (CMC) from March 2018 to August 2019 were evaluated for the indication of using KD. Based on a neurologist's opinion, eligible candidates were referred to a dietitian's clinic, where inclusion and exclusion criteria for starting KD were assessed. This study was approved by CMC's Deputy of Research and Ethics committee.

Inclusion criteria were: age below two years old, being non-responsive to antiepileptic drugs, no past history of KD use, and the lack of metabolic disorders, renal disease, hyperlipidemia, thyroid disease, and heart disorders. The baseline EEG was performed before the start of using the KD. Once a patient fulfilled inclusion criteria, a session would be arranged with the parents to take the following measures.

1. Conducting an interview and gathering basic information, including:

- Demographic data: The child's age, sex, weight, and height, the presence or absence of parental consanguinity.
- Birth history: Gestational age at birth, any trauma, NICU admission.
- Seizure history: Age at onset, age of starting antiepileptic drugs, the types, duration, and frequency of seizures, family history of seizures in first- and second-degree relatives.
- Review of health documents, including laboratory tests' data, MRI, EEG, genetic studies, summa-

ries of hospital admissions, renal ultrasonography report, echocardiography report, consultations with nephrologists and cardiologists, and primary health care neurodevelopmental assessment (based on parents' reports regarding the ASQ result).

2. Proving information about the ketogenic diet, its probable mechanisms of action, how to use the formula, its benefits and complications, how to recognize red flags, how to control mild complications, and how to use the dipstick test.
3. Giving advice on how to report the data and communicate with the project's executive researcher and how to determine and document seizure frequency and its duration in a calendar. Parents were asked to record the duration and frequency of seizures every day before and during the month of using the KD. They were also requested to report the maximum frequency and duration of seizures.

The parents who were willing to use the KD for their children received free cans of 4:1 ketogenic formula (KetoVOLVE). The diet was prescribed based on John Hopkins' protocol (5, 15) in the outpatient setting. Calories increased over three days; all patients received multivitamins, calcium supplements, and Polycitra. Ketone examinations were performed daily until the 3+ result was achieved, and thereon, it was periodically monitored. All the patients, including >6-month-old children, used a full formula diet for at least one month (16).

A pediatric resident was on-call 24 hours a day for close follow-up, to answer the caregivers' questions, and to explain the challenges they faced. A follow-up phone call was made on the 15th day of starting the KD to check for the occurrence of any complications. After a month, the patients were visited by a neurologist and a dietitian, and an EEG was conducted to compare the findings before and after using the KD. Based on the consensus of an expert panel, effective treatment for infantile spasms requires the stop of spasms and the disappearance of hypsarrythmias on EEG (1). Spasms may be underestimated when they are subtle or short-term. Thus, a standard EEG is an appropriate tool to evaluate the efficacy of the treatment. All EEGs were performed in the Children's Medical Center. Data on seizure history were obtained, and all parents were asked about any improvement in their children's social interactions. The data was entered in the infantile spasm database, which is a local and limited-access database in CMC's Neurology Department.

If no complication was found after one month, patients older than six months were advised to receive a mixed diet containing the formula plus solid. Patients older than two years started a fully solid diet after one month of starting the KD.

The maximum frequency and maximum duration of seizures and clusters were documented by parents in their own diaries. They recorded the maximum numbers occurring before and one month after starting the diet. In order to compare the seizures happening before and after using the KD, we multiplied the maximum number of seizures by the longest duration of seizures for each patient (i.e., the maximum number of seizures/clusters in one day during a month × maximum duration of seizures/clusters during a month).

Data were analyzed in SPSS 25. Given the small sample size, we used nonparametric tests to compare changes. The Wilcoxon test was used to compare seizures' properties before and one month after using the KD.

Data availability

The data of this study are available from the corresponding author upon reasonable request.

Results

Demographic and Basic Information

Thirteen patients' parents volunteered to begin the diet, but three of them withdrew before completing the one-month follow-up period. One of them expired as a result of aspiration pneumonia, and two others experienced status seizures and were admitted to the ICU even before ketone would appear in their urine. The remaining ten patients were followed for at least one month, five of whom were followed for more than one month (four patients for three months and one patient for six months). One of the remaining ten patients died of septic pneumonia.

The patients were 6 to 24 months old, of whom four were females, and six were males. The patients had experienced their first seizure from the first day up to the sixth month of life. In this study, the subjects were chosen among those who were unresponsive to medications, so the number of epileptic drugs (classes) taken to control seizures ranged from three to seven. Eight patients reported trauma at birth and prematurity, and seven of them had been admitted to the NICU. Two cases had a positive family history of seizures (in the first- and second-degree relatives), and parental consanguinity was seen in seven cases. Nine patients suffered from neurodevelopmental delay based on the ASQ test performed during primary health care assessments. In addition, the findings of EEG, which was performed in CMC and by a neurologist, were abnormal in nine cases.

Spasm Reduction and EEG Changes

Based on the Wilcoxon test, seizures/clusters significantly changed after administering the KD. Nine patients became seizure-free after starting KD, and two of them remained completely seizure-free during the one-month follow-up.

In nine cases who had abnormal EEGs before starting the diet, eight revealed improvements in EEG findings after one month of initiating KD, as confirmed by a neurologist. Nine parents reported improvement in their children's social interactions after starting KD.

Complications

One patient developed a renal stone after two months of using KD. This patient did not have access to Polycitra for up to a month as there was a shortage of the drug in the market. Based on the nephrologist's opinion, the size of the stone was small, so the diet could be continued, and the regular use of Polycitra was advised. Unfortunately, the patient died from aspiration pneumonia before the scheduled follow-up ultrasonography. One patient experienced constipation, which was managed with a maintenance dose of a laxative. Two patients experienced abdominal distention and bloating after starting the mixed ketogenic diet (formula + solid). One of them was managed by modifying the diet; the other could not tolerate the symptoms; thus, the diet was discontinued. In two patients, seizures worsened during the second month of treatment with KD, but based on the neurologist's opinion, these changes were considered normal given the refractory nature of the disease. Thus, new drugs were added to the therapeutic regimen, and the diet was continued. These two patients were excluded from the third month's assessments and analyses. One patient was completely unresponsive to the diet despite the presence of urine ketones. Although no complication was reported, EEG findings and

seizure history did not change, and thus, the diet was discontinued. None of the patients experienced ketoacidosis, but flu-like symptoms were seen in all of them in the first ten days of using the diet, which were controlled by supportive care at home.

MRI Findings

All the patients underwent one MRI. Two patients were reported to have myelination delay, and one had lissencephaly. Others had no significant abnormalities in brain imaging.

Genetic Findings

Five patients underwent genetic assessment performed by whole-exome sequencing. One of them had no abnormal findings, and the other four patients demonstrated abnormal gene variants.

One patient was homozygous for likely a pathogenic variant in exon 5 of the NECAP1 gene (c.384-1 G>C). The autosomal recessive inheritance of this variant has been reported to be associated with early infantile epileptic encephalopathy.

Another patient displayed heterozygosity for a mutation in exon 12 of the CDKL5 gene (c.865 G>T) on chromosome X. This variant has been classified as a likely pathogenic variant predisposing to epileptic encephalopathy.

Another patient was homozygous for a likely pathogenic variant in exon 2 of the TBC1D24 gene (c.866 C>T). Based on the geneticist's opinion and a number of genetic databases, this mutant allele could be classified as a variant of uncertain significance. In this patient, two additional heterozygous missense variants of uncertain significance were detected in the genes of KCNT2 and PPP3CA.

The other patient was homozygous for a variant of uncertain significance in the SLC25A12 gene.

Table 1. Patients' demographic, medical and seizure histories

Case number	Gender	Age at first visit (months)	Age at first seizure	Age antiepileptic drugs were begun	Number of antiepileptic drugs /classes	Trauma at birth	Born preterm	NICU admission	Neurodevelopmental delay	Family history of seizure disorder in first- and second degree relatives
#1	F	8	2m	2m	3	negative	negative	negative	positive	negative
#2	F	24	1 d	6m	7	positive	negative	positive	positive	negative
#3	M	18	20 d	20 d	5	negative	negative	negative	positive	negative
#4	M	9	2m	2m	3	negative	negative	negative	positive	negative
#5	F	18	6m	6m	7	negative	negative	negative	positive	negative
#6	M	20	3.5m	5.5m	3	negative	negative	negative	positive	positive
#7	M	13	3m	3m	4	positive	positive	positive	positive	negative
#8	F	22	5m	5m	3	negative	positive	negative	positive	negative
#9	M	14	1.5m	2m	4	negative	negative	negative	positive	negative
#10	M	6	1 d	1 d	4	negative	negative	positive	negative	positive

Parental consanguinity	Maximum seizures/clusters in one day before the ketogenic diet	Maximum duration of seizures/clusters before the ketogenic diet (seconds)	Maximum seizures/clusters in one day during the first month of using the ketogenic diet	Maximum duration of seizures/clusters during the first month of using the ketogenic diet (seconds)	P value Wilcoxon test-compared before and one month after using ketogenic diet	Maximum seizures/clusters in one day during the 2nd and 3rd months of using the ketogenic diet	Maximum duration of seizures/clusters during the 2nd and 3rd months of using the ketogenic diet (seconds)	Developmental improvement (social interaction)	EEG improvement
negative	20	2	10	2	.008	3	2	positive	positive
positive	60	15	20	15		1	120	positive	positive
positive	3	20	5	2				positive	positive
negative	3	60	3	30		3	30	positive	Positive
positive	4	120	1	60				positive	Positive
positive	8	180	2	2		2	2	positive	Positive
positive	6	60	0	0				positive	Positive
positive	4	300	5	15				positive	Positive
negative	200	1	0	0				positive	Positive
positive	3	3600	3	3600				negative	Negative

Discussion

The KD is available as a therapeutic option for treating infantile spasms (5, 6, 8-10, 12, 15). At times, it has even been successfully used as a first-line treatment (14). In this study, the participants referred by a neurologist had been under treatment with at least three classes of antiepileptic drugs. One of the most important reasons for preference for these medications over KD is the cost of the ketogenic formula in Iran, where it is not covered by insurance. In addition to the cost, access to the formula is also limited. In our study and based on the clinician's opinion, a number of parents were advised to continue the KD for their children even after the study. They had problems accessing the formula, which was available only in selected pharmacies and was further unavailable over a certain period of time. In a similar vein, sanctions affect access to the essential elements of the KD, like Polycitra and the dipstick test. Therefore, despite the remarkable number of patients suffering from infantile spasms, few of them are referred to use KD in a referral hospital like CMC. During a period of six months, only 13 patients fulfilled the inclusion criteria, and just 10 of them completed a one-month trial. Although the number of the cases was limited, and despite the fact that the patients were chosen among those with refractory infantile spasms, a significant change was observed in seizures within a month of using the ketogenic formula, as evidenced by a nonparametric statistical test. Also, EEG findings and social interactions notably improved after one month of starting the regimen. The limited number of samples hindered us from following up on an adequate number of patients for a longer period. Furthermore, some of the patients were excluded due to the need for using new medications or the occurrence of complications.

Earlier studies have indicated the key role of the KD in controlling seizures in children with refractory infantile spasms. Long-term follow-ups have shown that the KD could result in seizure-free survival in 23-62% of patients and partial seizure control in 27-77% of cases (6,9,10,13). In our study, nine out of 10 patients reported seizure-free episodes after starting the KD, and two out of 10 patients became completely seizure-free within a month.

In Hung et al.'s study (8), 18% of patients with infantile spasms (a total of 104 subjects) showed normal EEG findings after starting to use the KD, and improvements were reported in 62% of cases with developmental delay. In our study, nine of 10 patients had abnormal EEGs before starting the diet; eight of them achieved improvements in EEG findings after a month. Moreover, nine families reported improvements in their children's social interactions after initiating the use of KD.

An important limitation of this study was that the data were reported by parents, rising concerns over either underestimation, overestimation, or inaccurate reports. Moreover, the small sample size of the study limits the generalizability of the findings. Thus, studies with larger sample sizes or randomized controlled trials are recommended to confirm our findings.

In Conclusion

Based on the findings of this study, the KD can control seizures by reducing their frequency & duration and correct EEG findings in patients suffering from infantile spasms.

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Author's Contribution

Statistical analysis was conducted by Reza Shervin Badv and Melika Hanifiha MD MPH, Children's Medical Center

Conflict of interest

None

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