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Pediatric emergency department visit characteristics of the patients on the ketogenic diet

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ABSTRACT

Background: The ketogenic diet (KD) has been frequently used for the patients with drug-resistant epilepsy in recent years. The management of these patients in emergency departments (EDs) has some difficulties due to the special needs of KD. We aimed to determine the characteristics and the management of the patients on the KD in the pediatric ED setting.
Methods: Patients who were on the KD and admitted to the ED were included in the study. Demographic, clinical, and laboratory data of all patients were retrospectively reviewed and recorded.
Results: There were 105 emergency admissions of 27 patients. The median age of all patients was 55.0 (IQR: 29.0–91.0) months. The most common symptom was vomiting (43.8%). Four patients had upper gastrointestinal bleeding, and one patient had hyperammonemic acute hepatic failure while receiving KD. Of the patients, 41.9% had seizure-related ED admission. Infections were present in 41.9% of the ED visits. The frequency of status epilepticus was significantly lower in the patients who were on the KD for more than 6 months ($p < 0.01$). In 42.9% of all ED admissions, dextrose containing maintenance fluids was administered mistakenly; although ketosis rate was lower, no seizure was observed in this group.
Conclusion: The patients on the KD can be admitted to EDs with intercurrent illnesses or adverse effects of the KD. For accurate management, emergency physicians must be aware of the common reasons for ED admission of these patients and the effects of the KD.

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1. Introduction

Epilepsy is one of the most common neurologic disorder which influences an estimated 50 million people worldwide [1]. Although antiseizure drugs (ASD) are the mainstay treatment of childhood epilepsy, approximately 20–30% of the patients do not respond sufficiently to ASDs and are considered drug-resistant [2]. The ketogenic diet (KD) is a kind of low-carbohydrate, adequate protein, and high-fat diet; and it is one of the treatment options for drug-resistant epilepsy (DRE) [3]. It was created at the Mayo Clinic in the beginning of 1920s when only a few ASDs were available for the treatment of epilepsy. Although its popularity had declined with the invention of new ASDs, the use of KD has increased again worldwide after the 1990s, since a large number of new generation ASDs failed to reduce the rate of DRE [4].

The patients on the KD can be admitted to the EDs with acute intercurrent illnesses which are not related to the KD such as gastrointestinal disturbances, infections, and dehydration, or seizures related to epilepsy. Although acute intercurrent illnesses can be managed with usual treatment protocols, the patients on the KD can require special needs and close monitoring. There are many studies about the adverse effects of the KD, but severe side effects necessitating ED admissions are rare [3].

The aim of this study is to evaluate the reasons for the ED admissions of the patients on the KD therapy, including KD related and acute intercurrent illnesses.

2. Material and methods

All pediatric neurology consultations in a tertiary care pediatric ED center with more than 100.000 admissions each year were reviewed retrospectively over a period of 2 years. The keywords to discriminate the KD patients were selected as “ketogenic diet”, “ketogenic”, “diet”, “KD”, and “ketone”. All the patients included in this study were matched with medical records of the pediatric neurology department. Patients' medical records were reviewed for demographical and clinical data including age, sex, neurological diagnosis, and the number of ASDs

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received before and during KD. The initiation time, adverse effects, total duration, and the reason for cessation of the KD were recorded. The main reason for admission to the ED, length of hospital and/or intensive care unit stay, and maintaining fluid treatments administered were also recorded for every emergency visit. Laboratory findings included glucose, blood and/or urine ketone levels, uric acid, electrolytes, blood urea and creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) and white blood cell concentration. The ED visit frequencies were recorded as per month.

2.1. Statistical method

Statistical analyses were performed using SPSS Software 22.0 (IBM Corp., Armonk, NY, USA). If the numerical data fit the normal distribution, the mean ± standard deviation was calculated, while if the numerical data did not fit a normal distribution, median and the interquartile range (IQR) 25th–75th percentile were calculated. Chi-square test was used for the categorical variables. Statistical significance was accepted as $p < 0.05$ for all tests.

3. Results

Thirty-four patients on the KD were reviewed retrospectively. Of them, seven patients were excluded due to lack of data. Twenty-seven patients and 105 emergency visits were originally included in this study. Of the patients, 51.9% were male, and the median (IQR) age was 55.0 months (29.0–91.0). The median age at onset of KD was 42.0 (21.0–77.0) months. The median number of ASDs used before KD was 3.0 (2.0–4.0) whereas the median number of ASDs used during KD was 2.0 (1.0–3.0). The median admission rate to the ED was 0.17 (0.09–0.34) per month. Of the patients, 75.2% had urinary ketosis on initial admission to the ED. In the group with high urine ketone level, status epilepticus rate was significantly lower ($p = 0.01$); but there was no relationship between ketone level and the other reasons of the ED visits ($p > 0.05$). Intravenous fluid replacement treatment was administered in 73.3% of all ED visits. On 42.9% of these visits, high-carbohydrate fluids were administered to the patients mistakenly as initial fluid, and the rate of ketosis were significantly lower (64.3% vs 35.7%; $p = 0.03$), but no seizure was observed in any of these patients.

Clinical and laboratory findings are summarized in Table 1. The most common complaint for admission to the ED was vomiting. One patient had four ED visits with upper gastrointestinal hemorrhage, and proton pump inhibitor treatment was started after the first ED visit. On follow-up, Nissen fundoplication was performed for gastroesophageal reflux by pediatric surgery because of the resistance to medical treatment. Elevated liver enzymes were observed in two patients. One of them was admitted with hyperammonemic acute hepatic injury, and she was receiving carbamazepine and levetiracetam for epilepsy along with KD. Aspartate aminotransferase and ALT levels of the patient increased up to 19,374 IU/L and 17,114 IU/L, respectively, and turned to the normal levels in four days. Her blood ammonia level also increased up to 551 μg/dL. Two patients who were receiving valproic acid had thrombocytopenia.

Table 1
Clinical and laboratory abnormalities on the initial admission to the ED.

Reasons for ED visits	n (%)
Seizure-related admissions	
Status epilepticus	24 (22.9)
Seizure	20 (19.0)
Infection	
Upper respiratory infections	20 (19.0)
Lower respiratory infections	20 (19.0)
Acute gastroenteritis	3 (2.9)
Urinary infection	1 (1.0)
Gastrointestinal symptoms	
Vomiting	46 (43.8)
Isolated vomiting	20 (19.0)
Abdominal pain	14 (13.3)
Constipation	9 (8.6)
Upper gastrointestinal hemorrhage	4 (3.8)
Metabolic derangements	
Dehydration	11 (10.5)
Hypokalemia	5 (4.8)
Metabolic acidosis	5 (4.8)
Hypoglycemia	6 (5.7)
Hyperammonemia	1 (1.0)
Elevated liver enzymes	2 (1.9)
Fasting	3 (2.9)
Thrombocytopenia	2 (1.9)

ED: emergency department.

Table 2
Comparing of seizure-related admissions and the rest of the patients.

	Seizure-related admissions	Rest of the patients	*p*
Age (months)	57.5 (46.5–71.5)	63.0 (42.0–85.0)	0.50
Gender(male)	44 (41.9)	61 (58.1)	0.67
Duration of KD (months)	8.0 (4.1–18.7)	18.0 (9.0–29.5)	**0.03**
Length of hospital stay (day)	3.0 (1.0–6.0)	4.0 (1.5–10.0)	0.49
Length of PICU stay (day)	3.0 (2.0–5.0)	12.0 (6.0–12.0)	**0.03**

KD: ketogenic diet, PICU: Pediatric Intensive Care Unit.
Values are presented as median (IQR). Mann–Whitney *U* test was used to compare two groups.
Statistically significant p values are shown in bold.

Infection was observed 41.0% of all emergency visits, and hospitalization was required in 46.5% of them. Vomiting (55.0%) and seizure (40.0%) were the most common concomitant issues in these patients. The frequency of infection-related ED visits was higher in the patient group receiving KD for at least six months compared to the group receiving the KD for a shorter duration. The leucocyte counts between the groups showed no significant difference ($p = 0.55$).

Seizure-related admissions were observed in 41.9% of the patients, and in the 54.5% of them, convulsive status epilepticus was noted. Comparisons of the data between seizure-related and unrelated admissions are summarized in Table 2. Of the patients, 75.2% were receiving KD for a duration longer than six months. Frequency of status epilepticus was significantly lower in patients receiving KD for longer than six months compared with the patients receiving KD for less than six months (13.9% and 50% respectively, $p < 0.01$). One of the patients had recurrent admissions with status epilepticus both in the six months of KD and after. When that patient was excluded from the analysis, statistical significance was maintained ($p < 0.01$). Comparisons of the data between patients receiving KD for <6 months and ≥6 months are shown in Table 3.

4. Discussion

Drug-resistant epilepsy is still an important issue for the EDs, especially in the pediatric population. Since it has increasingly been used in patients with DRE, the emergency physicians more often face the patients who were on the KD. Although the KD has been accepted as a safe and tolerable nonpharmacologic treatment option and has a positive effect on seizure control in selected patients, it may cause numerous adverse effects that vary from mild to life-threatening serious events [5]. General evaluation and emergent treatment of the patients receiving KD are somewhat different from other epileptic children admitted to pediatric ED. In the current study, we aimed to define the common reasons for ED admissions and the management difficulties of the pediatric patients on the KD.

4.1. Gastrointestinal disturbances

The most common side effect of the KD is gastrointestinal disturbances such as vomiting, diarrhea, constipation, gastroesophageal reflux, and abdominal pain [6]. Following the initiation of the KD, high

Table 3
Comparing the frequent reasons for ED visits according to KD duration.

	KD < 6 months n = 26 (%100)	KD > 6 months n = 79 (%100)	P*
Seizure-related admissions	17 (65.4)	27 (34.2)	**0.05****
Seizure	4 (30.8)	16 (23.5)	0.57
Status epilepticus	13 (50.0)	11 (13.9)	<**0.01****
Infection	6 (23.1)	38 (48.1)	**0.03**
Vomiting	4 (15.4)	42 (53.2)	**0.01**
Isolated emesis	2 (7.7)	18 (22.8)	0.08
Total	26 (100.0)	79 (100.0)	

* Chi-square test was used to compare two groups.
** One of the patients had recurrent admissions with status epilepticus both in the six months of KD and after. When that patient was excluded from the analysis, statistical significance was maintained for seizure-related admissions and status epilepticus ($p = 0.03$ and $p < 0.01$, respectively).

ketone levels can cause susceptibility to nausea, vomiting, dehydration, and metabolic acidosis [7]. In our study, vomiting was the most common symptom for admission to the ED; however, 56% of these patients were secondary to other conditions such as infections including acute gastroenteritis. Vomiting was also significantly higher in the patients treated with KD for longer than six months, but there was no statistical relationship between ketosis and vomiting. We thought that these data were related to the patients with secondary vomiting who presented an important proportion. The KD is a predisposing factor for gastroesophageal reflux, which is often treated with proton pump inhibitors or H2 receptor blockers [3]. Jung et al. [8] also reported that prior multidrug usage is another predisposing factor. In our study, one patient with cerebral palsy had recurrent admissions with upper gastrointestinal bleeding, and Nissen fundoplication was performed for gastroesophageal reflux because of resistance to medical treatment at follow-up.

4.2. Metabolic derangements

Asymptomatic metabolic acidosis is an expected adverse effect in patients on the KD. However, preexisting metabolic acidosis may be increased by carbonic anhydrase inhibitors such as topiramate as well [5]. In the current study, five patients had mild metabolic acidosis, and one of them was using topiramate as ASD. However, bicarbonate therapy was not required for any of the patients. The rest of the patients had concurrent mild dehydration. The KD is also a predisposing factor for dehydration because of its diuretic effect. If the patient has an aggravating acute disease such as febrile illness or acute gastroenteritis; the physicians in ED should consider providing adequate intravenous fluid replacement [5]. In the emergency settings, drugs should be selected for patients on the KD. Usually, isotonic solutions with dextrose are used for maintenance fluid treatments in the pediatric EDs if the patients do not have hyperglycemia [9], but high-carbohydrate fluids can abruptly reduce ketosis and diminish the antiseizure effect of the KD [5]. One of the interesting results in this study was that dextrose containing fluids were started mistakenly in 42.9% of the patients admitted to the ED for intravenous hydration, and diminished ketosis was observed in the majority of them. Fortunately, no seizure was observed in any of the patients following high-carbohydrate fluid administration. The overcrowded EDs are an important issue worldwide, thus to discriminate the patients with special needs can be challenging. For a preventive method to obviate life-threatening situations, the patients on the KD should carry an identification card or a bracelet, and a notification in the medical record system to warn the healthcare workers for not to be exposed to high-carbohydrate containing treatments.

Pharmacodynamic interaction between ASDs and KD has not been studied up to now. Although there are some concerns about hepatotoxicity in the patients with KD therapy receiving valproic acid, current data support that the use of valproic acid is safe [10,11]. In our study, no patient receiving valproic acid along with KD had hepatotoxicity. Hyperammonemic acute hepatic injury was observed in one patient using carbamazepine and levetiracetam as ASDs. The recommendation of the international KD study group is that the KD therapy should be tapered slowly over 2–3 months and discontinued, except if there is an emergency situation [5]. Since we could not find any other possible cause for hepatotoxicity in this patient, KD was abruptly discontinued in the emergency settings.

4.3. Infections

Infections, especially respiratory tract infections, were one of the major reasons for ED admissions. Our data showed that if the patient receiving the KD has a concomitant problem such as seizure, vomiting or dehydration; the hospitalization was required. Because the KD predisposes to dehydration in the patients especially with high fever, the emergency physicians should consider intravenous low-carbohydrate fluid treatment. In children followed-up outpatiently, the emergency physicians should encourage oral hydration and measuring the urine gravity with urine dipstick to maintain adequate hydration status [5]. Counseling the families via telephone or email can also reduce the ED admissions.

There are limited data for the effect of KD on the immune system. Some authors defined that copper deficiency can be seen secondary to KD [12,13]. And also Rashidian et al. [14] were reported a girl on the KD with severe neutropenia and anemia due to copper deficiency but, in our patients, there were no clinical findings related to the copper deficiency. Schreck et al. [15] studied the impact of KD on leukocyte counts, and they found that there is a significant decrease in leucocyte counts in patients receiving KD. In our series, although the frequency of infections was significantly higher in the patient group receiving KD for at least six months, there was no difference for leucocyte counts between the groups. Additionally, we did not have comparative data about ED visit frequency of the patients before the initiation of the KD. So we did not find any relationship between infection and KD.

4.4. Seizure-related admissions

All patients with seizure were managed according to our local status epilepticus protocol and international guidelines [16,17]. In our study, 41.9% of all emergency visits was seizure-related as expected. When compared to the rest of the group, the duration of KD and length of PICU stay were significantly shorter in the patients with seizure-related admissions. This may be related to KD effectiveness established over time and easier seizure control achievement in patients receiving KD.

5. Limitations

Our study had some limitations due to its retrospective design. The patients on the KD therapy were reviewed in this study. However, there was no information about their previous ED visits before initiation of the KD, thus we could not compare the pre- and post-KD periods. Moreover, since we did not have healthy control group which were monitored during the same period, we could not evaluate the reasons and rates of ED admissions between these two groups.

6. Conclusion

In conclusion, the patients on the KD are usually admitted to EDs due to acute intercurrent illnesses or seizure rather than adverse effects of the KD. In our study, vomiting was the most common complaint for ED visits, followed by seizure-related admissions and infections. One of the striking results of this study is that dextrose containing fluids were administered to nearly half of the patients mistakenly, which might be life-threatening. For accurate management of the patients receiving KD, emergency physicians must be aware of the common reasons for ED admissions and the side effects of the KD.

Authorship

A.Ç., E.U., A. E., F.A., U.Y., A.Ü., and H.A. designed the report. A.Ç., S.S., M.Ö., S.E., and F.ÇÇ. collected the data. A.Ç., E.U., Ü.Y., and S.E. analyzed the data.

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Informed consent

Informed consent was not obtained because this is a retrospective study.

Ethical approval

This study was approved by the institutional ethical committee.

Human rights

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Declaration of Competing Interest

The authors confirm that the paper is original, is not under consideration by another journal, has not been previously published, and has been prepared according to the manuscript guidelines. The authors have no conflict of interest.

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