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Ketogenic Diet in Patients with Dravet Syndrome

Roberto Horacio Caraballo, Ricardo Oscar Cersósimo, Diego Sakr, Araceli Cresta, Nidia Escobal, and Natalio Fejerman

**Servicio de Neurología, Hospital de Pediatría "Prof Dr Juan P Garrahan," Buenos Aires, Argentina*

Summary: *Purpose:* The ketogenic diet (KD) has been used as a therapeutic alternative to antiepileptic drugs (AEDs) for refractory epilepsy. Severe myoclonic epilepsy in infants or Dravet syndrome (DS) is one of the most malignant epileptic syndromes. In this retrospective study, we evaluated the efficacy and tolerability of the KD in patients with diagnostic criteria of DS.

Methods: Between March 1, 1990, and August 31, 2004, 52 patients who met diagnostic criteria for DS were enrolled in a study at our department. Twenty of them were placed on the KD with the Hopkins protocol and followed up for a minimum of 1 year.

Results: Three of the 20 original children stayed on the diet for 12 months, four children for 2 years, four children for 3 years, and two children for 4 years. One year after initiating the diet, 13 (65%) of the initial patients remained on the diet. Two (15%) patients were seizure free, eight (61.7%) children had a 75–99% decrease in seizures, and the remaining three (23%) children had a 50–74% decrease in seizures. Thus 1 year after starting the diet, 10 (77%) children had achieved a >75% decrease in their seizures. Four patients have been off the diet for >2 years; one of them is seizure free, two have sporadic seizures, and one, who abandoned the diet after 2 years of adhering to it, relapsed. No differences in seizure control when compared with age, sex, or seizure type were found.

Conclusions: Considering the severity and intractability of seizures in patients with DS, the fact that 10 of the 13 children who remained on the diet had a significant reduction in number of seizures shows that the KD is at present an interesting therapeutic alternative. Even in patients in whom seizure reduction was not dramatic, quality of life improved, and in all of them, the number of AEDs was reduced to one or two. We consider that children with DS should be offered the KD immediately after three adequate trials of AEDs have failed. **Key Words:** Dravet syndrome—Ketogenic diet—Refractory epilepsy—Seizures.

The ketogenic diet (KD) has been used as a therapeutic alternative to antiepileptic drugs (AEDs) for refractory epilepsy (1–3). The diet consists of an intake of 3 or 4 times as much fat as carbohydrates and protein combined (1–4).

Fasting has since long been believed to be a cure for epilepsy. Hippocrates used fasting as a specific treatment for patients with epilepsy in the 5th century BC, and in the Bible, Jesus suggested fasting after an epilepsy attack (New Testament: Saint Mark 9;14–29).

In 1921, Wilder (5) was the first to formulate the KD to induce the metabolic effects of fasting for the management of seizures. In spite of its effectiveness, the diet was replaced by the new AEDs. Phenobarbital (PB), the first AED, was introduced in 1912, and between 1935 and 1968, 16 additional AEDs became available. The KD was reserved for use in selected patients and at selected treatment centers. A variant of the classic diet using medium-chain triglycerides was introduced in the 1970s (6), but over the last decade, most of the centers have been adopting the classic diet in a 4:1 ratio of fat to combined proteins and carbohydrates. The group of Johns Hopkins Medical Institutions in Baltimore was the most enthusiastic in advising the KD, and they were able to reach public recognition through a movie and a very practical little book entitled, *The Epilepsy Diet Treatment* (1). Furthermore, the popularity of the Atkins diet as a weight-loss diet in the United States prompted the development of many food products that are "keto-compatible," increasing the tolerability of the KD (7).

No mechanism of action of the diet has been defined. Its efficacy has been ascribed to acidosis, cellular and extracellular dehydration, the direct action of aceto acetate or β-hydroxy-butyrate, and changes in the source or utilization of energy within the brain (8). Alternative mechanisms for the action of the KD are an increase in brain γ-aminobutyric acid, and the potential effects of changes in water and electrolytes have also been indicated as antiepileptic mediators (3,9).

Recent reports of series of patients after 1 year on the diet show an overall efficacy ranging from 15% to 50% in

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Address correspondence and reprint requests to Dr. R.H. Caraballo at Neurología, Hospital de Pediatría "Prof Dr Juan P Garrahan," Combate de los Pozos 1881, C.P. 1245, Buenos Aires, Argentina. E-mail: rcaraballo@janssen.com.ar

terms of patients becoming seizure free or having a 50–90% reduction in seizures (2–4,10–18). Use of the KD is generally advised for children between ages 2 and 7 years, but it is also well tolerated and efficacious in adolescents and adults with intractable epilepsy (19–21).

Severe myoclonic epilepsy in infants or Dravet syndrome (DS) is one of the most malignant epileptic syndromes and was first described and characterized by Dravet et al. (22,23). Since then, DS has been recognized as an independent epileptic syndrome with characteristic features in many countries. However, diagnosis of DS in the early stage is rather difficult because of the current diagnostic criteria, which place more importance on the clinical course than on the specific electroclinical features. DS is characterized by an onset of febrile hemiclonic or generalized status epilepticus in the first year of life, typically around age 6 months. Febrile seizures recur, followed by the evolution of afebrile seizures including myoclonic, absence, atonic, and partial seizures between ages 1 and 4 years. The EEGs in the early stage usually do not show paroxysmal discharges, but later generalized spike–waves and polyspikes–waves and focal abnormalities appear. Photosensitivity may appear early (22,23). Developmental progress is initially normal but slows in the second year, and thereafter the intellectual prognosis is usually poor (22,23).

In this retrospective study, we evaluate the efficacy and tolerability of the KD in patients who met diagnostic criteria of DS.

MATERIALS AND METHODS

Between March 1, 1990, and August 31, 2004, 52 patients that met diagnostic criteria of DS were enrolled in a study at our department. Twenty of them were placed on the KD with the Hopkins protocol (1) and followed up for a minimum period of 1 year. We saw ~11,500 children with epilepsy in our center during the same time period. The 32 remaining patients were not offered the KD, as they came from at-risk families, families of low socioeconomic level, were adolescents, or some combination of these. At-risk families were those not considered to be prepared to follow the diet strictly for different reasons, such as very numerous families or those with psychological problems. As Argentina is a developing country, a large percentage of the population lives in poverty and is not able to meet daily food requirements. All patients except two were refractory to AEDs. None of these patients had head-drops or drop attacks secondary to myoclonic–astatic seizures.

Frequency of the seizures was registered on the basis of daily seizure calendars kept by the parents. Electroencephalograms during wakefulness and sleep were performed ≥6 months before starting, while on, and after discontinuing the KD. All patients underwent intermittent photic stimulation (IPS). Baseline blood tests and lipid profiles were also obtained.

Children started fasting in the hospital for 36–48 h and were then gradually initiated on the classic KD (Johns Hopkins protocol). Children were begun on a 4:1 ratio (fat: protein plus carbohydrate) and stayed in the hospital for another 4 days for close monitoring. During this period, parents were taught about the diet. They were asked to keep the child on the diet for ≥2 months to regulate the diet for optimal tolerance and seizure control. The ratio of the diet was modified as needed to maintain 80 to 160 m*M* urinary ketosis and to avoid both weight gain and weight loss. Adverse events and reasons for diet discontinuation were recorded, as were changes in medication.

RESULTS

Fifty-two children with the diagnosis of DS were followed for 2 to 12 years. Of these children, 20 (12 boys and eight girls) were placed on the KD as add-on to the use of one to three AEDs. Ages at initiation of the KD were between 3 and 9.5 years (mean, 6 years).

All patients had more than one type of seizure before starting the diet: five patients had two types, 13 had three types, and two had more than three types of seizures. Patients with myoclonic seizures averaged 92 events per month; those with generalized tonic–clonic, clonic, or atonic seizures averaged 43 events per month; those with motor focal seizures averaged 39 events per month; those with absence or atypical absence seizures averaged 35 events per month, and those with secondarily generalized tonic–clonic seizures averaged 21 seizures per month.

The children had previously been exposed to a mean of 6.4 different AEDs and were taking a mean of 2.2 AEDs when the diet was begun. All patients had an IQ of <69.

Table 1 shows the electroclinical features of the patients before starting the KD, and the clinical and EEG features of our series of patients while on the diet are described.

Duration on the diet

Three of the 20 original children stayed on the diet for 12 months; four children remained on the diet for 2 years; four children remained on the diet for 3 years; and two children, for 4 years.

Efficacy of the diet

One year after initiating the diet, 13 (65%) of the initial patients remained on the diet. Two (15%) patients were seizure free; eight (61.7%) children had a 75–99% decrease in seizures; and the remaining three (23%) children had a 50–74% decrease in seizures. Thus 1 year after starting the diet, 10 (77%) children had achieved a >75% decrease in their seizures. Four patients have been off the diet for >2 years: one of them is seizure free, two have

TABLE 1. *Electroclinical features of the patients before starting the KD and while on the diet*

Before the diet							
Patients Patients	Age at onset (months)	Seizure type	Seizure frequency	Status epilepticus	EEG abnormalities	AEDs	Mental retardation
1	6	Myoclonia absences	Daily		GSW	VPA-CLB	Mild
2	3	[a]GTCS SPS	Weekly	Yes	GPSW IPS+	VPA-CLB-PHT	Moderate
3	8	Myoclonia absences GTCS	Monthly		MS	CLB-TPM	Severe
4	4	[a]Myoclonia absences CPS	Daily	Yes	MS IPS+	CLB-TPM-PB	Severe
5	5.5	Myoclonia SPS GTCS	Weekly		GSW-PSW	VPA-TPM	Moderate
6	4.5	Myoclonia [a]absences GTCS	Weekly		GSW-PSW	LTG-CLB-PHT	Moderate
7	11	Myoclonia SPS-CPS	Daily	Yes	GSW-FS	VPA-TPM- LTG	Moderate
8	9	Myoclonia absences [a]GTCS	Weekly		GSW-MS	VPA-ESM	Mild
9	9.5	[a]Absences SPS-CPS	Daily		GPSW-FS	CBZ-PB	Mild
10	5	Myoclonia SPS	Daily	Yes	GPSW IPS+	VPA-LTG	Moderate
11	6	Absences SPS-CPS [a]GTCS	Daily		GSW	TPM-CLB	Moderate
12	6.5	[a]Absences GTCS	Weekly		GPSW	CLB-ESM	Severe
13	7	[a]Myoclonia GTCS	Monthly	Yes	GSW-PSW	TPM-CLB	Moderate
14	7.5	Myoclonia absences SPS-GTCS	Monthly		GPSW	VPA-PHT	Moderate
15	10	Myoclonia absences GTCS	Weekly		GPSW IPS+	VPA-PHT	Mild
16	3.5	[a]Myoclonia SPS-GTCS	Daily	Yes	GSW-FS	TPM-PB	Moderate
17	8.5	[a]Myoclonia absences [a]GTCS	Daily		GSW-GPSW	VPA-LTG	Severe
18	6.5	Myoclonia CPS-GTCS	Daily		GSW	VPA-CLB	Moderate
19	6	Myoclonia [a]absences [a]GTCS	Weekly	Yes	GSW-FS	VPA-PHT-TPM	Moderate
20	10.5	Myoclonia [a]SPS-CPS	Monthly		GSW-MS	LTG-CLB-PHT	Moderate

While on the diet							
Patients	Age at initiation of KD (years)	Seizure frequency	EEG abnormalities	AEDs	Side-effects	Duration of KD	Follow-up after KD ends	Results
1	7.5	Daily	GPSW	VPA-CLB		1 month		No response
2	3	Monthly	Isolated PSW IPS+	VPA		12 months		75–99%
3	9.5	Monthly	MS	CLB-TPM	Vomiting	2 months		Discont. Adv. Effects
4	4	Seizure-free	Normal	TPM		12 months		Seizure-free
5	6	Sporadic	Isolated GSW IPS+	VPA-TPM		2 years	3 years sporadic seizures	75–99%
6	6	Monthly	Isolated GSW	CLB-PHT		2 years		50–74%

(*Continued.*)

TABLE 1. *Continued.*

			While on the diet					
Patients	Age at initiation of KD (years)	Seizure frequency	EEG abnormalities	AEDs	Side-effects	Duration of KD	Follow-up after KD ends	Results
7	7	Daily	GSW-FS	VPA-TPM-LTG		2 months		No response
8	5	Sporadic	Normal	VPA-TPM		2 years	2.5 sporadic seizures	75–99%
9	4	Monthly	GPSW	CBZ-PB		3 years		75–99%
10	8	Daily	GPSW-IPS+	VPA-LTG		5 months		No response
11	6.5	Monthly	GPSW	TPM-CBZ		4 years		75–99%
12	5.5	Monthly	GPSW-FS	VPA		4 years		50–74%
13	4	Seizure-free	GSW	TPM		3 years	3 years seizure-free	Seizure-free
14	7.5	Monthly	GPSW-FS	VPA-ESM		6 months		No response
15	6.5	Weekly	GPSW-IPS+	VPA-PHT	Vomiting	1 month		Discont.adv. effects
16	6.5	Weekly	GSW-FS	TPM-PB		12 months		75–99%
17	4.5	Sporadic	GPSW	VPA-LTG		3 years	2.4 years seizure recurrent	75–99%
18	7	Daily	GPSW	VPA-CLB		3 months		No response
19	7	Monthly	GSW	TPM-VPA		2 years		50–74%
20	4	Sporadic	MS	LTG-CLB		3 years		75–99%

GTCS, generalized tonic–clonic seizure; SPS, simple partial seizure; CPS, complex partial seizure; GSW, generalized spike–wave; GPSW, generalized polyspikes–wave; MS, multifocal spike; FS, focal spike.
[a]Most-frequent seizure type.

sporadic seizures, and one relapsed and abandoned the diet after 2 years of adhering to it.

No differences in seizure control were found when comparing age and sex. Neither were any differences found when comparing the effect of the diet on seizure types. Four of five patients with status epilepticus responded well to the diet and did not repeat the event.

The number of children on the diet and the varying levels of seizure control they achieved are shown in Table 2.

Reasons for discontinuation of the diet, tolerability, and adverse events

Seven (35%) of the 20 children who initiated the diet discontinued within the first year. In five, the reason given for discontinuing the diet was lack of effectiveness. Four of these children discontinued between 1 and 3 months and one discontinued between 3 and 6 months after starting the diet.

Persistent and severe vomiting was the reason for discontinuing the diet in two children. The 13 patients who remained on the diet for >1 year did not develop complications.

Electroencephalographic changes

In the 13 patients who followed the KD with good response, the EEG recordings of ≥3 months before starting KD showed generalized, symmetric or asymmetric polyspikes and polyspikes–waves in nine patients and multifocal spikes and spike–waves in four.

One year after initiating the diet, the EEG abnormalities had improved in all 13 patients. In the two patients who became seizure free, the EEG recording was normal in one and showed isolated generalized polyspikes–waves in the other. In the eight patients who achieved a 75–99% decrease in their seizures, the EEG recording showed occasional and isolated generalized polyspikes–waves or spikes in seven, and in the remaining patient, the EEG recording had become normal. In the three patients who achieved a >50% decrease in their seizures, the EEG abnormalities during sleep improved between 60% and 80%. The changes of abnormalities on the sleep EEG were determined according to the quantity of paroxysmal discharges on the EEG recording. In two patients, we did not find any changes with IPS while on the diet.

In the five patients in whom the diet proved to be ineffective and in the two cases in whom the diet was not tolerated, the EEG abnormalities did not change.

Decreasing and discontinuing medications

Medications were decreased and discontinued nonsystemically with the aim of having the patient medication free. The different types of AEDs of the children on the diet are shown in Table 3.

TABLE 2. *Ketogenic diet in 20 patients with Dravet syndrome*

Number of patients	Discontinued because of adverse effects	No response	Seizure free	Decrease in seizures 75–99%	Decrease in seizures 50–74%	Later discontinued because of decrease in efficacy	Patients off the diet with good control
20	2	5	2	8	3	2	3

TABLE 3. *AEDs in patients on the ketogenic diet*

AEDs	No.	%
Topiramate	9	45
Clobazam	5	25
Lorazepam	3	15
Phenytoin	2	10
Lamotrigine	3	15
Valproic acid	2	10
Ethosuximide	1	5
Phenobarbital	2	10

DISCUSSION

Our experience with the KD in 20 children with DS shows an overall good response in terms of seizure frequency and quality of life.

To our knowledge, this is the first study of treatment with the KD related to DS, regardless of the seizure type. In this study, no differences were found in the effect of the diet on the seizure types. Previous reports have been published on children with refractory seizures, including infantile spasms, who were placed on the KD (16). We also described children with DS and myoclonic epilepsies treated with the KD in earlier reports (24,25). Our results support the general assumption that the KD is effective in patients with myoclonic seizures and other types of epileptic seizures. We believe that more precise definitions of epileptic syndromes may lead to the possibility of giving a clear prognosis in each particular case and that this concept should be applied to all therapeutic trials in epilepsy. For example, considering idiopathic and symptomatic focal seizures in the same trial to evaluate efficacy of a specific medication may lead to false results, as most children with benign focal epilepsies respond well to AEDs. The length of follow-up in trials should also be considered. Results at 3 or 6 months are of no real value to evaluate AEDs, the KD, or even surgical treatments.

A clear decrease in seizure control after a time on the KD has been reported (17,19). Incidentally, the significant decrease in efficacy after 9–12 months on the KD in patients with refractory symptomatic and cryptogenic partial or generalized epilepsies found in one study may have been due to the inclusion of all etiologies (19).

Selection of families that will be able to make the effort that treatments such as the KD require in children has to be very strict to reduce the number of failures.

It is interesting to note that seven patients who responded well to the diet received topiramate (TPM). In children with refractory epilepsy, co-treatment with TPM and KD may be considered, but special attention should be paid to the combined risk for metabolic acidosis and nephrolithiasis (26). However, we have not yet observed these complications. According to Takeoka et al. (26), seizure reduction did not appear to correlate with the reduction in HCO_3/reduction levels. The reasons that co-treatment with TPM and KD is effective are unknown. Considering the difficulty of controlling seizures in the studied population with medically refractory epilepsy, we believe the observed response to be significant.

Some authors have suggested that stiripentol and bromides are effective in DS (27,28). However, in Argentina, these drugs are not available.

Considering the severity and intractability of seizures in patients with DS, the fact that 13 of the 20 children who stayed on the diet had a significant decrease in their number of seizures shows that the KD is at present an interesting therapeutic alternative. Even in patients in whom the reduction in seizures was not dramatic, an improvement in quality of life was seen, and in all of them, the number of AEDs was reduced to one or two. One of these patients did not show any further mental deterioration.

The youngest child on the KD in our series of patients with DS was 3 years old. That is partly due to the difficulties we had in the past to define the diagnosis clearly and for the necessary time to elapse while trying an AED.

We consider that children with DS should be offered the KD immediately after three adequate trials of AEDs have failed. The present data strongly suggest the need for prospective comparative trials including the early use of the KD in one treatment arm.

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