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Ketogenic diet in patients with myoclonic-astatic epilepsy

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ABSTRACT – For more than 80 years, the ketogenic diet has been used as an alternative to antiepileptic drugs for patients with refractory epilepsy. Myoclonic-astatic epilepsy in early childhood is one of the malignant epilepsy syndromes that often proves refractory to antiepileptic drugs treatment. *Objective.* In this prospective study we assess the efficacy and tolerability of the ketogenic diet in patients with myoclonic-astatic epilepsy. *Material and methods.* Between March 1, 1990 and August 31, 2004, 30 patients who met diagnostic criteria of myoclonic-astatic epilepsy were seen at our department. Eleven of them were placed on the ketogenic diet using the Hopkins protocol and were followed for a minimum of 18 months. *Results.* The children had previously received a mean of 5.2 different antiepileptic drugs and were on a mean of 2.2 antiepileptic drugs when the diet was started. Eighteen months after initiating the diet, six of the patients (54.5%) remained on the diet. Two patients (18%) were seizure-free, two (18%) had a 75-99% decrease in seizures, and the remaining two children (18%) had a 50% to 74% decrease in seizures. The first two patients were tapered off the diet after remaining seizure-free, without antiepileptic drugs for several years. In the two patients who had sporadic seizures, antiepileptic drugs were reduced to one, and in the last two the seizure frequency was significantly reduced. No differences in seizure control were found when compared for age, sex, or seizure type. Five of our patients discontinued the ketogenic diet in less than 3 months (four because of lack of effectiveness and one because of persistent vomiting). *Conclusion.* The ketogenic diet is a promising therapy for patients with myoclonic-astatic epilepsy, with over half the children showing a > 50% reduction in seizures, and seizure-freedom in 18%. In drug resistant cases of myoclonic-astatic epilepsy, the diet should be considered early in the course of this syndrome and not as a last resort.

Key words: ketogenic diet, myoclonic-astatic seizures, refractory epilepsy, seizures, Doose's syndrome

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The ketogenic diet (KD) has been used as a therapeutic alternative to antiepileptic drugs (AEDs) for the treatment of refractory epilepsy (Freeman and Kelly 1994, Phelps *et al*. 1998, Lefevre and Aronson 2000). The diet consists of an intake of three or four times as much fat as carbohydrates and protein combined (Freeman and Kelly 1994, Phelps *et al*. 1998, Lefevre and Aronson 2000, Di Mario and Holland 2002).

To date, no mechanism of action of the diet has been defined. Its efficacy has

been ascribed to acidosis, cellular and extra-cellular dehydration, the direct action of aceto acetate or β-hydroxybutyrate, and changes in the source or utilization of energy within the brain. Alternative mechanisms for the action of the KD are an increase in brain gamma-aminobutyric acid and the potential effects of changes in water and electrolytes have also been indicated as antiepileptic mediators (Freeman and Kelly 1994, Phelps *et al*. 1998, Lefevre and Aronson 2000).

Recent reports of series of patients after one year on the diet show an overall efficacy ranging from 15 to 50% of patients having a >50% reduction in seizures (Caraballo *et al*. 1998, Freeman *et al*. 1998, Phelps *et al*. 1998, Vining *et al*. 1998, Lefevre and Aronson 2000, Nordli *et al*. 2001, Di Mario and Holland 2002).

Myoclonic-astatic epilepsy is a generalized epilepsy syndrome with multiple seizure types, including myoclonic-astatic, absence, tonic-clonic and eventually tonic seizures, appearing in a previously healthy child between 18 and 60 months of age, with a peak around the age of three years. The course of the disorder has variable severity (Kaminska *et al*. 1999, Oguni *et al*. 2001). Background EEG activity can be normal at seizure onset, although characteristic 4-7 Hz monomorphic theta activity with diffuse distribution but prominent in centro-parietal areas is often observed. Interictal abnormalities consist of bursts of 2-3 Hz generalized polyspike-and-wave discharges. Sleep is accompanied by an increase in generalized discharges (Kaminska *et al*. 1999, Oguni *et al*. 2001).

In this prospective study, we evaluate the efficacy and tolerability of the KD in patients who met the diagnostic criteria for MAE.

Material and methods

Between March 1, 1990 and August 31, 2004, 30 patients who met the diagnostic criteria for MAE were seen at our center. Eleven of these 30 patients were placed on the KD using the Hopkins protocol (Freeman and Kelly 1994) and were followed for a minimum period of one year. Nine patients with refractory seizures were not offered the KD as they came from families who were considered not to be prepared to follow the diet, from families with a low socioeconomic level and/or were adolescents. Ten patients with MAE responded well to AEDs.

Patients with benign myoclonic epilepsy in infancy, Dravet syndrome and Lennox-Gastaut syndrome were excluded.

Frequency of the seizures was registered on the basis of daily seizure calendars kept by the parents. Electroencephalograms during wakefulness and sleep were performed at least six months before starting, during and after discontinuing the KD. All patients underwent intermittent photic stimulation (IPS). Baseline blood tests and lipid profiles were also obtained. Serum bicarbonate levels were measured in all patients.

Children started fasting in the hospital for 36-48 hours and were then gradually started on the classic KD (Johns Hopkins protocol). Children were begun on a 4: 1 ratio (fat: protein plus carbohydrate) and remained in the hospital for another four days for close monitoring. During this period parents were taught about the diet. They were asked to keep the child on the diet for at least two months in order to regulate the diet for optimal tolerance and seizure control. The ratio of the diet was progressively modified as needed in order to maintain 80 to 160 mg/dL urinary ketosis, and to avoid weight loss. Adverse events and reasons for diet discontinuation were recorded, as were changes in medication.

Results

Thirty children with a diagnosis of MAE were followed for two to 13 years. Of these children, 11 (7 boys and 4 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 4 and 9 years (mean 5 years).

All patients had more than one type of seizure before starting the diet: two patients had two types, seven had three types and two had more than three types of seizure. Patients with myoclonic and myoclonic-atonic seizures experienced an average of 93 episodes a month, those with generalized tonic-clonic, clonic or atonic seizures, an average of 45, and those with absence seizures had an average of 32 episodes a month.

The children had previously received a mean of 5.2 different AEDs and were on a mean of 2.2 AEDs when the diet was begun.

Table 1 shows the electroclinical features, treatment and evolution of the patients before starting and while on the KD.

Duration of the diet

One of the 11 original children stayed on the diet for 18 months, two children remained on the diet for two years; two children remained on the diet for three years and one child for four years.

Efficacy of the diet

Eighteen months after initiating the diet, six of the initial patients (54.5%) remained on the diet. Two patients (18.2%) were seizure-free, two children (18.2%) had a 75 to 99% decrease in seizures and the remaining two children (18.2%) had a 50% to 74% decrease in seizures. Thus, 18 months after starting the diet, four children (66.6%) had achieved a more than 75% decrease in their seizures. Two patients have been off the diet for several years, are seizure-free, and do not receive any AEDs.

Table 1. The electroclinical features and treatment of the patients before starting and while on the KD and their progression.

Before the KD

Patients	Age at onset (months)	Seizure type	Seizure frequency	Status epilepticus	EEG abnormalities	AEDs	MR
1	18	*Myoclonic-atonic. Absences	Weekly	-	Symmetric GPWD	VPA-CLB	Mild
2	20	*Myoclonic-atonic.*GTCS. Absences	Weekly	Myoclonic Status	Symmetric GPWD	VPA-CLB-LTG	Moderate
3	37	Myoclonic-atonic. GTCS.*Myoclonia	Daily	-	Symmetric GPWD	CLB-TPM	Severe
4	24	*Myoclonic-atonic.Myoclonia. Absences	Daily	-	Symmetric GPWD	CLB-LTG-VPA	Normal
5	35	*Myoclonia *Myoclonic-atonic GTCS.	Daily	-	Symmetric GPWD	VPA-CLB	Moderate
6	25	*Myoclonic-atonic *CTCG. Myoclonia	Weekly	-	Symmetric GPWD	LTG-CLB	Moderate
7	19	Myoclonia. *Myoclonic-atonic *Absences	Daily	-	Symmetric GPWD	VPA-TPM LTG	Moderate
8	29	*Myoclonic-atonic Atonic-GTCS	Weekly	-	Symmetric GPWD	VPA-ESM	Normal
9	39	*Myoclonic-atonic. Atonic. *Absences	Weekly	-	Asymmetric GPWD	TPM-LTG	Mild
10	21	Myoclonia-*Myoclonic-atonic. Absences.* GTCS.	Daily	Myoclonic Status	Symmetric GPWD	VPA-LTG	Severe
11	40	*Atonic.*GTCS Myoclonic-atonic. Absences	Daily	-	Symmetric GPWD	LTG-CLB	Moderate

During the KD

Patients	Age at initiation (years)	Seizure frequency	EEG abnormalities	AEDs	Side effects	Duration of KD	Follow-up after end of KD	Results
1	6	Daily	GPWD	VPA-CLB	-	3 months		No response
2	4.5	Monthly	GPWD	VPA	-	1 month		No response
3	5	Monthly	GPWD	CLB-TPM	Vomiting-diarrhea	1 month		Discont. Adv. Effects
4	4	Seizure-free	Normal	VPA	-	3 years	10 years seizure free	Seizure-free
5	6	Sporadic Myoclonia	Occasional GPDW	VPA-TPM	-	3 years		75-99%
6	4.5	Monthly	GPDW	CLB	-	2 months		No reponse
7	4	Weekly Myoclonia Absences	Occasional GPDW	VPA-LTG	-	4 years		50-74%
8	5	Seizure-free	Normal	VPA	-	2 years	2.5 years seizure-free	Seizure free
9	4.5	Sporadic Absences	Isolated GPWD	CLB	-	2 years		75-99%
10	6	Daily	GPWD	VPA-LTG	-	4 months		No response
11	5.5	Monthly GTCS	Occasional GPWD	LTG	-	18 months		50-74%

Two patients have sporadic seizures, but AEDs were reduced to one. Although the study population was limited, there were no apparent differences in efficacy based on age or sex.

Reasons for discontinuing the diet, tolerability and adverse events

Five of the 11 children (45.5%) who initiated the diet discontinued within the first year. In four, the reason given for discontinuing the diet was lack of effectiveness. Three of these children discontinued between one and two months, and one discontinued three months after starting the diet.
In one child, persistent and severe vomiting was the reason for discontinuing the diet one month after initiation. Six patients who remained on the diet for more than one year did not develop severe complications, such as high levels of uric acid, kidney stones, severe acidosis, lethargy, hypoglycemia, etc.

Electroencephalographic changes

In all six patients who followed the KD with good response, the EEG recordings performed at least three months before starting the KD showed generalized, symmetric or asymmetric polyspike-and-wave discharges. Eighteen months after initiating the diet, the EEG abnormalities had improved in all of them. The EEG recording was normal in both patients who became seizure-free. In the two patients who achieved a 75 to 99% seizure reduction, the EEG recording showed occasional generalized polyspikes and waves. In the two patients who achieved more than a 50% decrease in their seizures, the EEG abnormalities during sleep improved between 50 and 70%. The changes in the abnormalities on the sleep EEG were determined according to the quantity of paroxysmal discharges in the EEG recording.
The EEG abnormalities remained unchanged in the four patients in whom the diet proved to be ineffective and in one patient who did not tolerate the diet.

Decreasing and discontinuing medications

Medications were decreased and discontinued non-systematically with the aim of the patient becoming medication-free.

Discussion

Our experience with the KD in 11 children with MAE shows an overall good response in terms of seizure frequency.
As in our study on the treatment with KD of patients with Dravet syndrome (Caraballo et al. 2005), no differences were found in the effect of the diet on the seizure type. Other reports on children with refractory seizures including infantile spasms, who were placed on the KD, have been published (Caraballo *et al*. 1998, Freeman *et al*. 1998, Kaminska *et al*. 1999, Nordli *et al*. 2001, Oguni *et al*. 2001, Kossoff *et al*. 2002, Caraballo et al. 2005). We have also described children with Dravet syndrome and myoclonic epilepsies treated with the KD in earlier reports (Caraballo *et al*. 1999, Fejerman *et al*. 2004). Our results support the general assumption that the KD is effective in patients with mainly myoclonic-atonic seizures and other types of generalized 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.
Families that are able to make the effort that a treatment such as the KD requires have to be carefully selected so as to reduce the number of failures. Risk families are those in whom the parents are considered to be unable to follow strictly the diet for different reasons, such as having numerous children or having psychological problems. In developing countries, caregivers may not have the financial means to assume the extra cost imposed by the diet.
It has been previously suggested that the KD is the most effective therapy for patients with MAE (Sills *et al*. 1986, Oguni 2002, Laux *et al*. 2004).
The KD is a promising therapy for MAE, with over half of children showing a > 50% reduction in seizures, and 18% achieving seizure-freedom. It should be considered early in the course of the syndrome, and not as a last resort. The patients that responded well to the diet did not deteriorate mentally any further.
The youngest child on the KD in our series of patients with MAE was 4 years old. This is partly due to the fact that patients with MAE often respond well to AEDs and the KD is only tried later in the treatment.
The present data strongly suggest the need for prospective and comparative trials involving the early use of the KD in one treatment arm. □

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