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Long-term follow-up of the ketogenic diet for refractory epilepsy: Multicenter Argentinean experience in 216 pediatric patients

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ABSTRACT

Purpose: In this Argentinean retrospective, collaborative, multicenter study, we examine the efficacy and tolerability of the ketogenic diet (KD) for different epilepsy syndromes.
Materials and methods: we evaluated the clinical records of 216 patients started on the KD between March 1, 1990 and December 31, 2010.
Results: One hundred forty of the initial patients (65%) remained on the diet at the end of the study period. Twenty-nine patients (20.5%) became seizure free and 50 children (36%) had a 75–99% decrease in seizures. Thus, 56.5% of the patients had a seizure control of more than 75%. The best results were found in patients with epilepsy with myoclonic-astatic seizures, Lennox–Gastaut syndrome, and West syndrome. Good results were also found in patients with Dravet syndrome, in those with symptomatic focal epilepsy secondary to malformations of cortical development, and in patients with tuberous sclerosis. Seizures were significantly reduced in four patients with fever-induced refractory epileptic encephalopathy in school-age children and in two patients with epileptic encephalopathy with continuous spikes and waves during slow sleep. The median period of follow-up after discontinuation of the diet was 6 years. Twenty patients who had become seizure free discontinued the diet, but seizures recurred in five (25%). Of 40 patients with a seizure reduction of more than 50% who discontinued the diet, 10 presented with recurrent seizures.
Conclusion: The ketogenic diet is a good option in the treatment of refractory epilepsy. After discontinuing the diet, seizures recurrence occurred in few patients.

1. Introduction

The ketogenic diet (KD) is a high-fat, low-carbohydrate, adequate-protein diet. It is an established, effective, non-pharmacologic treatment that has been used as an alternative in the management of refractory epilepsy.[1–9] The KD is now considered a safe and effective optional therapy not only for children but also for adults with intractable epilepsy.[10,11]

Recently, modifications of the original KD, such as the Atkins diet and a low-glycemic-index diet, have been developed as alternatives for the treatment of refractory epilepsy.[10–13] However, these diets may not be as effective as the KD.

Although a large number of patient series has been reported, only a small number of controlled studies have been undertaken.[1,14–16] A recent randomized controlled trial supports its use in children with refractory epilepsy.[8] In this trial, 28 of the diet group had a greater than 50% seizure reduction compared with four controls (6%), and five children (7%) in the diet group had a greater than 90% seizure reduction compared with none of the controls.[8] A randomized trial of classic and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy has revealed that both diets are comparable in efficacy and tolerability; both ways of implementing the diet proved useful in the treatment of childhood epilepsy.[8]

Eighty-one percent of the members of a recent international consensus group on the KD believed that the classic diet should be offered to a child after two anticonvulsants have been used unsuccessfully, excluding surgically remediable epileptic syndromes.[9]

Several investigators have suggested that the diet might be beneficial for seizure control in specific epileptic syndromes, and

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metabolic diseases.[2,11,17–29] The KD is contraindicated in several specific disorders.[11,30]

A wide range of hypotheses has been suggested to explain the efficacy of the KD.[31,32] It is clear that fasting and the KD share a common mechanism in controlling seizures. The brain is an obligate user of glucose as its energy source. When carbohydrates are restricted, as in the KD or fasting, the brain no longer uses only glucose and starts to oxidize ketone bodies derived from fats instead of carbohydrates as the primary fuel source.[31]

In this Argentinean retrospective, collaborative, multicenter study, we examine the efficacy and tolerability of the KD in different epilepsy syndromes.

2. Materials and methods

We evaluated the clinical records of 216 patients started on the KD between March 1, 1990 and December 31, 2010.

The epileptic syndromes were defined according to the ILAE classification (Engel, 2001, 2006). These patients were seen at the department of neurology in three Argentinean centers between February 1990 and December 2009. One hundred thirty-six were seen at the Garrahan Hospital of Buenos Aires, 46 patients were seen at the Italian Hospital of Buenos Aires, and 34 were seen at the Centro de Neurociencias del Litoral, Santa Fé. Some of these patients were included in previous publications.[4,20–23,33] We used the Johns Hopkins Hospital Protocol diet in all patients. During diet initiation, blood glucose, urine ketones, and vital signs were routinely checked. The efficacy and tolerability of the diet was controlled every three months in the first year, and every six months in the follow years. Seizure frequency was registered three months before starting the diet, and at subsequent control visits on the basis of daily seizure calendars kept by the parents.

We analyzed gender, age at onset of seizures, seizure semeiology, family and personal history, physical examination, clinical evolution, and treatment. Brain CT scan and MRI were performed in all patients. Neurometabolic tests were done in 89 patients, and karyotype studies were performed in 68 patients. In addition to a complete examination, including growth parameters such as weight and height, laboratory studies were performed. All patients had several awake and sleep EEGs studies, and background activity, topography, and morphology of the paroxysms were analyzed. The EEG electrodes were placed according to the international 10–20 system. Video-EEG studies were done in most of the patients. Neuropsychological tests (Bayley, Vineland, Terman-Merryl, or WISC) to evaluate IQ were systematically administered to all patients. We also evaluated the duration of the diet, the reason why the diet was discontinued, and outcome after discontinuation the diet.

We considered the following inclusion and exclusion criteria:

- Inclusion criteria
  1. Patients with refractory epilepsy after two or three anticonvulsants were used unsuccessfully.
  2. Age between 1 and 18 years were included.
- Exclusion criteria
  1. Patients with liver, kidney, heart, gastrointestinal, psychiatric diseases, and progressive encephalopathy with or without a known metabolic marker, except those metabolic diseases for which the KD is the specific treatment.
  2. Inability to maintain adequate nutrition, and parent or caregiver noncompliance.

Patients are reported as-seizure free in this study if they have remained free of seizures during all period of this study.

3. Results

3.1. General characteristics

Two hundred sixteen patients (119 males, 97 females) were followed for 1–20 years. Mean age at onset of the diet was 5 years (range, 1–18 years). Mean duration of the diet treatment was 3.5 (range, 1–12 years). The mean time of follow-up was 9 years (range, 1–20 years).

The children had previously received a mean of six different AEDs and were on a mean of 3.5 AEDs when the diet was begun.

Eighteen months after initiating the diet, 140 of the initial patients (65%) remained on the diet. Thirty-one patients (22%) were seizure free, 48 children (34.5%) had a 75–99% decrease in seizures, 14 children (10%) had a 50–74% decrease in seizures, and the remaining 47 patients (33.5%) had less than 50% decrease in seizures. Thus, 18 months after starting the diet, seventy-nine of the initial patients (56.5%) had achieved a more than 75% decrease in their seizures. There were no apparent differences in efficacy based on age or sex.

Seventy-six of the 216 children (35%) who initiated the diet discontinued within the first year. In 43, the reason given for discontinuing the diet was lack of effectiveness. Thirty of these children discontinued between 1 and 2 months and 13 discontinued 3 months after starting the diet. In 21 patients persistent and severe vomiting and hypoglycemia were the reason for discontinuing the diet one month after initiation. Twelve patients were not able to maintain the diet accordingly.

Fifty patients remained on the diet for more than three years, seventy patients for 2–3 years, and 20 patients for 1–2 years.

3.2. Electroencephalographic changes

In all 140 patients who followed the KD, the EEG recordings carried out at least 3 months before starting KD showed generalized and/or focal epileptiform discharges. Eighteen months after initiating the diet, the EEG abnormalities had improved in most of the patients who had achieved a more than 75% decrease in their seizures. The EEG recording became normal in 29 patients who had become seizure free. In two patients who had become seizure free and in 40 patients who achieved a 75–99% seizure reduction, the EEG abnormalities improved between 50% and 70%. In 14 patients who achieved a 50–74% decrease in their seizures, the EEG abnormalities improved between 25 and 50%. The EEG abnormalities remained unchanged in 47 patients in whom seizure control improved less than 50%.

3.3. Decreasing and discontinuing medications

Medications were decreased and discontinued non-systematically with the aim of the patient becoming medication free. Medications were discontinued in 40 patients and significantly decreased in 53 patients.

3.4. Efficacy in different epilepsy syndromes

The types of epilepsy or epileptic syndrome and etiologies in 212 patients with refractory epilepsy treated with the KD are shown in Table 1.

The remaining patients included in our series of patients were: two patients with GLUT-1 deficiency, one of whom had epileptic encephalopathy and the other refractory epilepsy with typical absences, one patient with Rett syndrome associated with myoclonic status, and another with subacute sclerosing panencephalitis associated with epileptic spasms in clusters and focal seizures with or without secondary generalization.

Table 1
Types of epilepsy or epileptic syndrome found in 212 patients with refractory epilepsy treated with the KD.

Type of epilepsy and epileptic syndrome	Etiology	Number of patients
Symptomatic focal epilepsy	Cortical dysplasia	20
	Tuberous sclerosis	13
	Encephalitis	18
	Hypoxic–ischemic encephalopathy	11
	Porencephalic cyst	3
	Vascular malformations	4
Epilepsy with myoclonic-astatic seizures		38
Cryptogenic Lennox–Gastaut syndrome		7
Symptomatic Lennox–Gastaut syndrome	Encephalitis	6
	Cortical dysplasia	10
	Chromosomal abnormalities	4
	Neonatal hypoglycemia	3
	Hypoxic–ischemic encephalopathy	2
Cryptogenic West syndrome		8
Symptomatic West syndrome	Hypoxic–ischemic encephalopathy	4
	Porencephalic cyst	4
	Cortical dysplasia	5
	Aicardi syndrome	2
	Tuberous sclerosis complex	2
	Septo-optic dysplasia	1
	Meningitis	1
	Encephalitis	1
Dravet syndrome		32
Cryptogenic epileptic encephalopathy with CSWSS		3
Symptomatic epileptic encephalopathy with CSWSS	Unilateral polymicrogyria	2
Fever-induced refractory epileptic encephalopathy		5
Epilepsy with myoclonic absences		2
Migrating focal seizures in infancy		1

The efficacy of the KD in different epilepsy syndromes is shown in Table 2. Both patients with GLUT-1 deficiency became seizure free. One patient with Rett syndrome and myoclonic status and another patient with subacute sclerosing panencephalitis associated with epileptic spasms had a seizure reduction between 75% and 99%

3.5. Therapy

Different antiepileptic drugs treatment schemes were used associated with the KD. It is of interest that ten patients who became seizure free, fifteen patients with a 75–99% seizure reduction, and three patients with a 50–74% seizure reduction received topiramate.

3.6. Side-effects

Table 3 lists the adverse effects of the KD in 140 patients who remained on the diet. Side effects were well treatable. Three of six patients who developed kidney stones had received topiramate. The same table also shows the more severe adverse events provoked by discontinuation of the diet. Five patients died during the treatment with the KD. Cause of death was pneumonia in two, sepsis in one, status epilepticus in one, and was unknown in the remaining patient.

3.7. Evolution

The diet was discontinued for the following reasons: seizure freedom for more than 2 years in 20 (14%), seizure reduction of more than 50% for more than two years in 40 (28%), severe toxicities in seven (5%), inability to adhere to the diet in 14 (10%), lack of efficacy in 12 patients (8%), and patient or family request in 12 patients (8%).

3.8. Outcome after discontinuation of the diet

The median period of follow-up after discontinuation of the diet was 6 years (range, 1–15 years). Seizures recurred in five (25%) of 20 patients in the seizure free group who discontinued the diet. Of 40 patients with a seizure reduction of more than 50% who discontinued the diet, seizure frequency remained the same in 30, seizures recurred in 10, and seizure frequency decreased in five. All patients in the seizure free group and those in the group with a seizure reduction of more than 50% in whom seizures recurred after diet discontinuation had brain lesions and EEG abnormalities.

Table 2
Efficacy of the ketogenic diet considering the epileptic syndromes in 136 patients.

Epileptic syndrome	Seizure freedom (*N* of patients)	75–99% seizure reduction (*N* of patients)	50–74% seizure reduction (*N* of patients)	Less than 50% seizure reduction (*N* of patients)
Symptomatic focal epilepsy	2	17	5	24
Epilepsy with myoclonic-astatic seizures	11	9	1	4
Dravet syndrome	2	10	4	4
West syndrome	5	2	2	3
Lennox–Gastaut syndrome	7	4	1	7
FIRES	1	2	1	1
CSWSS	1	1	–	2
Epilepsy with myoclonic absences	–	1	–	1
Migrating focal seizures in infancy	–	–	–	1

Table 3
Side effects of the ketogenic diet in 174 (80.5%) patients.

Adverse events	Number of patients	Diet discontinuation
Vomiting	15	No
Diarrhea	12	No
Anorexia	8	No
Constipation	18	No
Abdominal pain	13	No
Weight gain	5	No
Hypercholesterolemia	10	No
Hypertriglycerinemia	11	No
Hypocarnitinemia	8	No
Metabolic acidosis	6	No
Hypercalciuria	15	No
Kidney stones	6	No
Prolonged QT	4	No
Hypoglycemia	12	No
Dehydration	14	No
Anemia	5	No
Obtundation	5	No
Renal tubular acidosis	1	Yes
Optic neuropathy	1	Yes
Infectious disease	2	Yes
Leukopenia	2	Yes
Dehydration + metabolic acidosis + vomiting	1	Yes

Regarding adverse events after the diet was discontinued, we have not found any signs or received any reports of long-term health implications so far.

4. Discussion

In this collaborative study, 140 of the initial 216 patients (65%) remained on the diet. Thirty-one patients (22%) became seizure free and 48 children (34.5%) had a 75–99% decrease in seizures. Thus, 56.5% of the patients attained a seizure control of more than 75%. The best results were found in patients with epilepsy with myoclonic-astatic seizures, Lennox–Gastaut syndrome, and West syndrome, including the symptomatic cases. Good results were also found in patients with Dravet syndrome, one of the most severe epilepsy syndromes. Good seizures outcomes were also noted in patients with symptomatic focal epilepsy secondary to malformations of cortical development and tuberous sclerosis. Another important finding was that four patients with FIRES and two patients with epileptic encephalopathy with continuous spikes and waves during slow sleep (CSWSS) had a marked reduction in seizure frequency. Finally, seizure control was significantly improved in one patient with epilepsy with myoclonic absences, one with Rett syndrome, and another with subacute sclerosing panencephalitis.

Other studies confirm our findings. The KD has been successfully used in children with a variety of seizure types and epileptic syndromes, including Lennox–Gastaut syndrome,[2,20] infantile spasms,[17,18,24] myoclonic-astatic epilepsy,[20,23,25,34] Dravet syndrome,[21,23,26,35] Landau–Kleffner syndrome,[36] tuberous sclerosis,[37,38] Rett syndrome,[39–41] and – temporarily – subacute sclerosing panencephalitis.[42] Early diet intervention may lead to better outcomes in children with Dravet syndrome, myoclonic-astatic epilepsy, and Lennox–Gastaut syndrome.[20–23] Recently, the KD has proved to be effective in controlling status epilepticus in a group of patients with FIRES, a devastating condition initiated by prolonged Perisylvian refractory status epilepticus triggered by fever of unknown cause. The KD may also be proposed as an alternative treatment in other types of refractory status epilepticus in pediatric patients.[43] The efficacy of the KD in patients with focal seizures was similar to efficacy in patients with generalized seizures in uncontrolled trials.[44,45] However, the KD was not effective in patients with Lafora disease and did not stop disease progression in these patients.[46] Single reports mention the clinical benefits of the diet in metabolic diseases such as phosphofructokinase deficiency,[47] glycogenosis type V,[48] and mitochondrial respiratory chain complex disorders.[30]

It is interesting to note that a significant number of our patients who responded well to the KD additionally received topiramate. This association may increase the risk of kidney stones, but may also improve seizure control.[49]

Interictal epileptiform abnormalities improved in most of our patients who had a seizure reduction of more than 75%. Similar findings have been reported in the literature.[15,33,50,51]

The side effects of the KD are well described in the literature.[49,52–58] The actual incidence of side effects in patients treated with the KD is difficult to determine as few long-term prospective studies have been conducted.

Of 216 patients treated with KD, seven (3.2%) discontinued the diet due to adverse effects. Gastrointestinal manifestations were the most frequent adverse effect. One patient presented a severe copper deficit, however, symptoms disappeared with copper supplementation. The finding of copper deficiency in association with KD has been previously published.[52] The role of the KD in producing copper deficiency is still not well known, but the copper deficiency may be due to antioxidant deficiency in the bowel secondary to KD.

The timing and method of KD discontinuation are tailored to the patient's response to the diet. Although current practice is to continue with the diet for at least 3 months even if initially ineffective, recent data suggest that the KD works rapidly with 75% of children responding within 14 days.[11] If a family opts to remain on the KD for longer than 6 months even though the diet seems ineffective, this decision should be supported.

In children with a greater than 50% seizure reduction, the KD is typically discontinued after approximately 2 years, as the diet is difficult to maintain. This 2-year period is traditionally based on a similar time period used for anticonvulsant drugs, which are often discontinued after that time in children who become seizure free. However, in children in whom seizure control is nearly complete (a greater than 90% seizure reduction) and who have few side effects, the diet has been reported to be useful for as long as 6–12 years.[59] Children with GLUT-1 deficiency, pyruvate dehydrogenase deficiency, Dravet syndrome, symptomatic encephalopathies, cortical dysplasia, or tuberous sclerosis complex may require longer KD duration. The use of the KD was prolonged in patients with these epilepsy syndromes described in this report. An EEG recording should be obtained prior to discontinuing the KD, to identify risk factors for seizure recurrence. In five patients, seizure frequency improved after the diet was discontinued. These cases might suggest that the ketogenic diet may have not only an anticonvulsant, but also an antiepileptogenic effect.[60]

Previous research has indicated that the risk of recurrence is higher in patients with epileptiform EEGs, structural abnormalities on neuroimaging, and tuberous sclerosis complex.[61] The epilepsy syndrome may also be of importance. In most patients with Dravet syndrome who had a good response to KD seizures recurred after diet discontinuation. In patients who had become seizure free and in whom seizures recur after discontinuing the diet, seizure control may be achieved again with either KD or anticonvulsants.[61] A recent study assessing the long-term safety and efficacy of the KD after the diet has been discontinued has shown that the majority of patients were doing well both in terms of health and seizure control.[62]

Future controlled studies with a long-term follow-up would be necessary to better define the efficacy, tolerability, duration of the treatment, as well as the prognosis after discontinuing the diet taking into account the epileptic syndromes.

5. Conclusion

Our study corroborates that the KD is a good option in the treatment of refractory epilepsy in terms of tolerability and efficacy. After discontinuing the diet, seizure recurrence occurred in few patients. We have not observed any long-term health implications so far.

In certain epileptic syndromes, such as epilepsy with myoclonic astatic seizures, Dravet syndrome, cryptogenic Lennox–Gastaut and West syndrome, the KD should be considered early in the course of treatment.

Conflict of interest statement

None of the authors has any conflicts of interest.

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We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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