



Journal of the Selva Andina Research Society

ISSN: 2072-9294

ISSN: 2072-9308

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Selva Andina Research Society

Bolivia

Rodríguez-Hernández, Adán Israel; Pelayo-González, Mónica Elizabeth
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Journal of the Selva Andina Research Society, vol. 11, no. 2, 2020, pp. 142-152
Selva Andina Research Society
Bolivia

DOI: <https://doi.org/10.36610/j.jsars.2020.110200142x>

Available in: <https://www.redalyc.org/articulo.oa?id=361364361015>

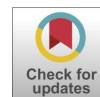
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Experiencia y hallazgos en el manejo de la dieta cetogénica en niños con epilepsia refractaria, estudio de 10 casos

Description and evaluation of the effects of the cetogenic diet in children with refractory epilepsy

Rodríguez-Hernández Adán Israel ^{*}, Pelayo-González Mónica Elizabeth

Data of the Article

Autonomous University of Aguascalientes.
Department of Nutrition and Physical Culture.
Av. Universidad # 940.
University City.
C.P. 20131, Aguascalientes.
México.
Tel: +52 4499107400. Ext 410.

* Contact address:

Autonomous University of Aguascalientes.
Department of Nutrition and Physical Culture.
Av. Universidad # 940.
University City.
C. P. 20131, Aguascalientes.
México.
Tel: (066)312510-(066)312230
Mobile: 966881161

Adán Israel Rodríguez-Hernández

E-mail address: israel.rodriguez@edu.uaa.mx
adan_israel1@yahoo.com.mx

Palabras clave:

Dieta cetogénica,
epilepsia refractaria,
crisis convulsiva.

J. Selva Andina Res. Soc.
2020; 11(2):142-152.

The ID of article: 134/JSARS/2019

Record from the article.

Received November 2019.
Returned February 2020.
Accepted April 2020.
Available online, August 2020.

Edited by:
**Selva Andina
Research Society**

Keywords:

Ketogenic diet,
refractory epilepsy,
convulsive crisis.

Resumen

La epilepsia refractaria se debió como aquella epilepsia farmacorresistente en la que no hay mejoría tras la aplicación de varios fármacos antiepilépticos (FAE). El Centro de Rehabilitación Infantil Teletón atiende a una gran población de niños con algún tipo de epilepsia. Recientemente la aplicación del protocolo de intervención domiciliario de la dieta cetogénica (DC) ha incrementado. Hace algunos años, la DC solo se atendía con extrema vigilancia en un centro hospitalario bajo esquemas rígidos. Con este antecedente, el objetivo de este estudio fue describir la experiencia y hallazgos de una serie de 10 casos de niños con EF tratados con este protocolo de DC a lo largo de al menos 1 año. Se revisaron por medio de expediente clínico electrónico todos los casos de niños (n=10) atendidos en el CRIT, Aguascalientes, México que fueron tratados con dieta cetogénica entre las fechas de febrero 2010 y junio 2015. Los niños cubrían los criterios para epilepsia refractaria, así como la vigilancia por neurología pediátrica y nutrición. El protocolo de intervención domiciliario de la DC se estableció bajo los criterios de Lambruschini-Nilo & Gutiérrez-Sánchez, donde se inició con una DC tipo clásica con relación 2:1 durante la primera semana de adaptación para después pasar a la relación 3:1 o 4:1 correspondiente según la tolerancia del paciente. Se procedió a medir la reducción del número de crisis a los 3 meses y al año de su intervención. Se aplicó un modelo lineal general ANOVA de un factor con medidas repetidas para medir la eficacia a los 3 meses y al año de tratamiento encontrando significancia estadística al comparar las medias de resultados del número de eventos epilépticos previo a la dieta ($p = <0.006$). El tipo de epilepsia más frecuente fue el Síndrome de West en 4 pacientes, el Síndrome de Lennox Gastaut en 3 pacientes, la Epilepsia Mioclónica Severa de la Infancia y otros tipos de epilepsia, 3 pacientes. Los efectos secundarios más comunes fueron el estreñimiento en el 60% de la población, y los menos comunes la dislipidemia tipo hipoalipoproteinemia en un 30%, el reflujo en el 20% y la litiasis renal en el 10%.

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Abstract

Refractory epilepsy is due to that drug-resistant epilepsy in which there is no improvement after the application of various antiepileptic drugs (AEDs). The Telethon Children's Rehabilitation Center cares for a large population of children with some type of epilepsy. Recently, the application of the home intervention protocol for the ketogenic diet (DC) has increased. A few years ago, DC was only attended with extreme surveillance in a hospital center under rigid schemes. With this background, the objective of this study was to describe the experience and findings of a series of 10 cases of children with RE treated with this DC protocol over the course of at least 1 year. All the cases of children (n = 10) attended at the TCRC, Aguascalientes, Mexico, who were treated with the ketogenic diet between the dates of February 2010 and June 2015, were reviewed by means of an electronic clinical record criteria for refractory epilepsy, as well as surveillance for pediatric neurology and nutrition. The DC home intervention protocol was established under the criteria of Lambruschini-Nilo & Gutiérrez-Sánchez, where it started with a classic type DC with a 2: 1 ratio during the first week of adaptation and then went on to the 3: 1 or 4 ratio: 1 corresponding according to patient tolerance. The reduction in the number of crises was measured at 3 months and one year after surgery. A one-way ANOVA general linear model with repeated measures was applied to measure the efficacy at 3 months and one year of treatment, finding statistical significance when comparing the results means of

the number of epileptic events before the diet ($p = <0.006$). The most frequent type of epilepsy was West Syndrome in 4 patients, Lennox Gastaut Syndrome in 3 patients, Severe Myoclonic Epilepsy of Childhood and other types of epilepsy, 3 patients. The most common side effects were constipation in 60% of the population, and the least common were hypoalphalipoproteinemia-like dyslipidemia in 30%, reflux in 20%, and kidney stones in 10%.

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Introduction

The ILAE (International League Against Epilepsy) defines refractory epilepsy as: “Drug-resistant epilepsy (DRE) in which failure occurs in the treatment after the use of two antiepileptic drugs (AEDs), chosen and used inadequate (monotherapy or combination), either tolerated, who do not achieve a crisis-free state maintained¹.

According to ILAE and the World Health Organization (WHO) epilepsy is defined as a chronic and recurring condition of events triggered by abnormal electric shocks that have varied clinical manifestations, of multifactorial origin, that are associated with para-clinical disorders (abnormalities in electroencephalogram) (EEG) and that are presented in an unprovoked way^{1,2}.

On the other hand, the ILAE defined the concept of refractory epilepsy (RE) as a situation of lack of response to AEDs without reaching a crisis-free period that is three times longer than the longest inter-critical period presented before treatment¹. According to the ILAE and the WHO, many patients around the world, particularly in the United States and Europe are being treated in specialized centers with a ketogenic diet (KD) as the AED treatment and even neurological surgery. In Latin America, only the existence of centers where KD is used for RD management in Argentina, Brazil, Colombia, and Uruguay³. KD consists of a high-fat diet and low in carbohydrates and proteins, whose main characteristic is

the liver production of ketone bodies as an alternative substrate to glucose for energy use, and as an

essential part for the biosynthesis of cell membranes and lipids in a developing brain⁴.

Different types of KD are used according to eating habits and nutritional requirements of patients based on the experience of the hospital center where it is administered⁵. There are variations in the relationships between lipids and carbohydrates more proteins (4 to 1 or 3 to 1), as well as the lipid source (long or medium-chain triglycerides) of the KD, without finding differences in its effectiveness, although there are some in its tolerance^{3,6}.

Zupiec-Kania et al.⁷ state that the fat content in terms of a classic diet varies from 87% when you have a ratio of 3 g of fat to 1 g of lipids (3: 1), while the fat percentage increase up to 90% when it is establishing a relationship KD 4:1. For diets with medium-chain triglycerides (MCT), the percentage of ordinary fats is 11% adding 60% of MCT's single source. Moreover, they are combined fat diets, where the source of ordinary fat is 30% plus 40% TCM, for last, the percentages of these models vary from 9% and up to 12% protein⁷.

Consequently, the high-fat content, low contribution of carbohydrates and proteins in KD present various short and long-term side effects, most of which are gastrointestinal discomforts or complications such as vomiting, hypoglycemia, dehydration, kidney stones, constipation, acid/base imbalance, osteopenia, cardi-

omyopathy, recurrent infections, and hypercholesterolemia. However, these effects do not prevent the monitoring of the diet because they are effects of very low magnitude and transients that can be corrected with small dietary modifications⁸⁻¹². Vitamin deficiencies do not occur if there are specific nutrients supplementation in conjunction with KD^{8,13-15}. Accordingly, the complications of this diet, which can even contribute to growth arrest and bone demineralization, can be reduced¹⁶, regarding the anthropometric parameters, weight is generally maintained with a minimum drop of patients, and the size presents a slight deceleration staying within the normal range for children in this type of pathological situations⁸. From the above, it has also been described that these patients can maintain the relationship weight and height with the body mass index indicator (BMI) in normal ranges¹⁷.

How long the diet must be maintained is not clear. Some maintained it for two years and obtained a better response, with no relapse, which suggests that the diet has a permanent effect or that the pathophysiology of seizures has changed⁸.

There are some recommendations for the use of KD as a treatment in RD, which according to Kossoff et al.⁸, in the disease of the transporter deficit brain glucose (GLUT-1) is the first treatment of choice, in the background, it is mentioned that the KD is a useful treatment in Doose, Rett, Dravet, Lennox Gastaut syndromes, in spasms childhood and tuberous sclerosis. The effectiveness in other epileptic disorders is still under study.

KD is a safe and effective alternative for the treatment of ER in patients who do not have a need for epilepsy surgery. In several publications on treatment protocols for poor ER states, there is increasing mention of KD as a valid treatment^{3,6,8,18-25} and even also effective at parenteral nutrition pathway²⁶. Hence, the objective was to describe the experience

and findings from a series of 10 cases of children with refractory epilepsy treated with this protocol KD for at least 1 year.

Materials and methods

An observational, descriptive, retrospective and analytical study was carried out.

Procedures: 1) The study reviewed the physical and electronic records of patients, boys, or girls between 2 and 10 years old who had used KD for at less a year as an aid in the treatment of RDE and who had had between 4 to 8 AEDs without a favorable answer. The children (n=13) were cared for at the CRIT Aguascalientes, Mexico in the areas of nutrition and pediatric neurology between the dates of February 2010 and June 2015. Three patients dropped out of KD prior to one year of treatment. 2) Data sought to evaluate the effectiveness and side effects of KD used in all cases (KD Classic). This diet was monitored under the home protocol (Lambruschini-Ferri & Gutierrez-Sanchez)⁵, which requested tests such as I) general urine examination (for monitoring ketonuria), II) profile of lipids and liver, III) a diary of crisis. 3) The percentage reduction of epileptic events was evaluated at one month, three months, and one year after following KD in the 10 cases. 4) Nutritional management and anthropometric evaluation were described. The anthropometric indices references were based on Day et al.²⁷ growth curves (The Gross Motor Functional Classification System (GMFCS)) and based on Krick curves et al.²⁸ according to the type of disability. 5) Neurological management was described regarding the neurological diagnosis, epilepsy type and crisis, findings in electroencephalogram, structural brain injury, and the characteristics of pharmacological treatment.

Statistical analysis. A linear model was applied in general, a one-way ANOVA with repeated measures to compare the means of results, the statistically significant values were considered with $p = <0.05$ using the statistical package SPSS version 20.0²⁹.

Letters of informed consent were signed by parents. The study was approved by the Bioethics Committee of the center itself.

Results

Table 1 Percentage reduction of epileptic seizures

Case	Crisis/day No. before diet	% Reduction at 1 month	% Reduction at 3 months	% Reduction at 1 year
1	40	100	100	100
2	7	0	71	71
3	1	0	0	53
4	10	20	30	90
5	60	50	66	66
6	5	71	80	80
7	25	40	60	54
8	45	66	77	80
9	7	57	57	85
10	40	50	62	100
Average 29/day		Average 44.6%	Average 58.2%	Average 77.9%

Table 2 Neurological characteristics of cases at the onset of the ketogenic diet

Case	Neurological diagnosis	Type epilepsy	Type of crisis	EEG	Brain structural injury	Total Seizures before KD
1	Callous body hypoplasia and colpocephaly (brain dysgenesis)	West Syndrome	Spasms in saving	Hypsarrhythmia	Callous body hypoplasia and colpocephaly	40
2	Cerebral Palsy for Severe Asphyxia and Epilepsy	West Syndrome	Tonic spasms and crises	Hypsarrhythmia	Microcephaly	7
3	Severe Childhood Myoclonic Epilepsy (Dravet Syndrome)	Severe Childhood Myoclonic Epilepsy (Dravet Syndrome)	Myoclonic and tonic-clonics	Polipoints	No injury	1
4	Cerebral Palsy for Severe Asphyxia and Epilepsy	West Syndrome	Spasms	Hypsarrhythmia	Atrophic cortico-subcortical y Periventricular leukomalacia	10
5	Cerebral Palsy and Generalized Epilepsy	Tonic spasms and crises	Tonic spasms and crises	Hypsarrhythmia	Cortico-subcortical atrophy	60
6	Cerebral Palsy for Severe Asphyxia and Epilepsy	West Syndrome	Tonic spasms and crises	Hypsarrhythmia	Microcephaly	5
7	Adams Oliver syndrome	Secondary-widespread partial	Generalized motor and tonic partials	Multiple spotlights	Focal cortical dysplasia, callous leather hypoplasia and microcephaly	25
8	Idiopathic Lennox Gastaut syndrome	Lennox Gastaut Idiopathic Syndrome	Tonics, generalized tonics and myoclonic	2.5Hz polypoints and slow-point-wave	No injury	45
9	Cerebral palsy for viral encephalitis and hydrocephalus	Lennox Gastaut Symptomatic Syndrome	Tonics, atonics	slow wave tip 2.5Hz	Cortico-subcortical atrophy, compensated hydrocephalus	7
10	Cerebral Palsy for Severe Asphyxia and Epilepsy	Lennox Gastaut syndrome	Tonics, atonics, atypical absences	slow wave tip 2.5Hz	Microcephaly	40

EEG Electroencephalogram, KD ketogenic diet

The average age of the population at the beginning of the diet was ± 3.4 years, 50% were girls and 50% boys. 100% of patients were diagnosed with ER according to the latest classification of the ILAE1; all with polytherapy. The number of previously used drugs were from 4 to 8 in each case, and the most common drugs were valproic acid (VPA) and Topiramate (TPM) in all cases; Vigabatrin (VGB) and Clobazam (CLB) in 7 cases. In table 1, we can see that the percentage of reduction in each case was

significant from 3 months and improving by the year of treatment, this was evidenced by One-way ANOVA analysis with repeated measures both as in the inter-subject effects test where $p=0.006$ when comparing the number of crises prior to the KD vs. KD's number of crises a year. As there was significance when comparing the number of crisis prior to KD vs the number of crisis at 3 months, $p=0.05$.

Regarding the type of epilepsy, the most frequent was West Syndrome (WS) in 4 patients and Lennox Gastaut Syndrome (LGS) in 3 patients, Severe Myoclonic Epilepsy of Childhood, and other types of epilepsy, 3 patients. The type of crisis more common tonic crisis (7 patients) and spasms in saves (4 patients, seeing that some patients have more than

one type of crisis. The most common electrical pattern hypsarrhythmia (4 patients). Structural alterations were reported in the Central Nervous System (CNS) observed by tomography or MRI: in 9 patients, and without structural injury in 2 patients table 2.

Table 3 Nutritional characteristics of the population before and after the diet

Case	Age at the start of KD	Gender	KD Type	Initial Nutritional status	Final nutritional status	Food route	KD duration (years)
1	1	M	Ratio 2-1	Normal	Normal	Via Probe by Gastrostomy	1y and ongoing
2	2	F	Ratio 3-1	Obesity	Normal	Via Probe by Gastrostomy	2y and ongoing
3	5	F	Ratio 3-1	Normal	Normal	Orally	1y and ongoing
4	2	F	Ratio 3-1	Normal	Normal	Orally	1y
5	3	M	Ratio 3-1	Normal	Normal	Orally	3y and ongoing
6	2	M	Ratio 4-1	Normal	Overweight	Via Probe by Gastrostomy	5y and ongoing
7	4	F	Ratio 4-1	Normal	Overweight	Via Probe by Gastrostomy	3y and ongoing
8	5	F	Ratio 3-1	Normal	Normal	Orally	1 year
9	5	M	Ratio 3-1	Normal	Overweight	Via Probe by Gastrostomy	3y and ongoing
10	5	M	Ratio 3-1	Overweight	Obesity	Via Probe by Gastrostomy	2 years

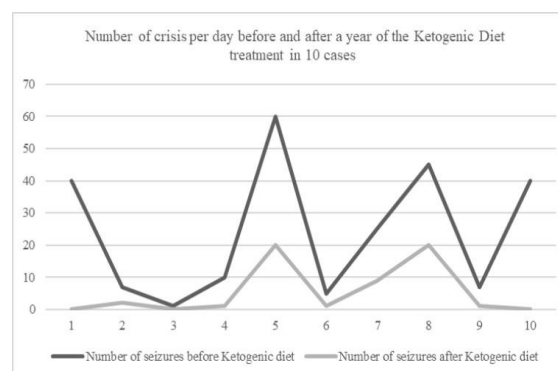
Table 3 describes the nutritional characteristics of the population that, in relation to their initial weight, 8 of the cases had normal weight while in the end, only 6 had kept it. On the one hand, the number of patients with some degree of overweight increased from 2 subjects to 4 subjects, 60% of the patients had a diet gastrostomy tube when starting KD and 60% had oral feeding. On the other hand, 60% of patients regularly tested positive for ketones in the urine.

Figure 1 shows in general, the total reduction of epileptic seizures per case. Regarding the duration of treatment with KD a minimum duration of 1 year was reported and as a maximum of 5 years. 7 Patients are currently maintaining the treatment.

In figure 2, the most common side effects of the KD were constipation (60%) and hypoalbuminemia-type dyslipidemia (50%). To a lesser extent gastroesophageal reflux, repetitive urinary tract

infections (UTIs), and kidney stones were other complications during the diet, and in 2 of the cases, there were no complications of treatment.

Figure 1 Reduction in the number of seizures per day after a year of the ketogenic diet



Discussion

Currently, the evidence seems to point to a greater benefit in certain types of epilepsy among which are

found the transporter deficiency of cerebral glucose, Doose syndrome, Dravet, Lennox Gastaut as well as infantile spasms^{8,16,15,30}. Doose syndrome, Dravet, Lennox Gastaut as well as infantile spasms^{8,16,15,30}.

Figure 2 Number of patients who presented side effects of the ketogenic diet

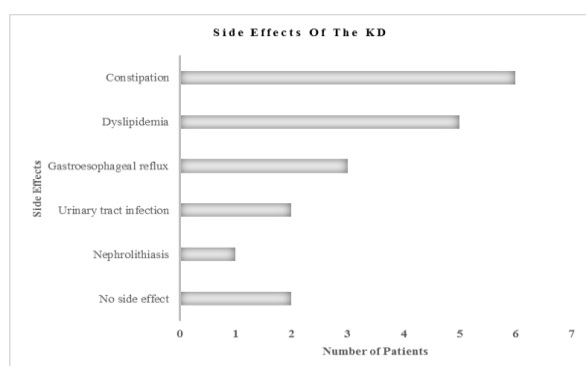
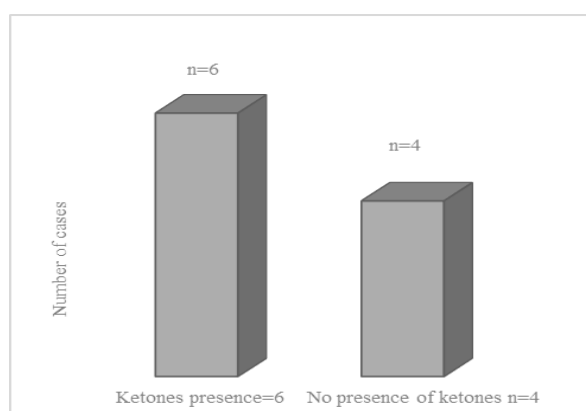


Figure 3 Presence of ketonuria of the patients



In these types of studies, a satisfactory response to KD management can be observed with a crisis reduction percentage greater than 70% in the patients with SW and LGS, mostly lesions by hypoxia. In contrast, the worst were observed in patients with genetic etiology epilepsy (Dravet and Adams Syndrome Oliver). Unlike other studies of the case, Ramírez et al.¹⁵ report some constant intervention pharmacological during treatment with KD. In this study, there were no modifications to antiepileptic treatment for at least the first year.

Shull et al.¹⁷ evidenced that KD is effective regardless of differences in weight, height, or BMI for the age, even in children with obesity. In this study, the ratio of weight for initial height to KD as the weight for the final height time, 2 of the subjects increased their BMI to a degree of obesity while the others maintained the initial nutritional status without affecting the efficacy of the diet. On the other hand, the findings described on weight gain and not having had variations in the weight/height of the subjects in this study are contrary to other types of KD like the case of KD of the Atkins type, used not only for epilepsy but also not as a strategy for loss in weight³¹, whereas the classic diet in this study had no such effect in any of the cases. However, the effectiveness of KD had not been correlated with any nutritional status without any distinction regarding the date since the year or started treatment^{19,21,32}. In turn, Groleau et al.¹¹, Bertoli et al.¹⁶ report a growth slowdown in the course of treatment with KD representing a height/age below the 25th percentile, in our study when using the Day's growth curves (Life Expectancy Project, Day et al.²⁷) based on Gross Motor Function System for patients with a disability of neuromusculoskeletal type this was not a reported effect because the curves respond to this status of children with these disabilities of neurological nature.

Zupec et al.⁷, Kossoff et al.⁸, The Subspecialty Group of Neurology, the Society of Pediatrics, Chinese Medical Association¹⁰, Wibisono et al.¹², Suo et al.¹⁸, Pablos et al.³⁰, Fung et al.³³, report problems to maintain the oral intake of this KD, including the desertion of the same, this due to the high-fat content, the situation with which coincides, since in this study 4 patients who started orally were excluded as they had difficulties in preparation, acceptance or KD's liking.

On the other hand, those fed by gastrostomy tube $n = 6$ (60%) had higher acceptance and attachment than orally fed patients. Although, Jung et al.²⁶ conclude that in the parenteral or enteral feeding is best for ketone control, despite having enteral feeding via a gastrostomy tube, of the patients $n = 6$, in this study only 4 reported ketonuria compared to the total of 6. The effectiveness in the rest of the patients without ketonuria also did not discriminate against the efficacy of KD, which opens lines for research.

Radcliffe and modified Atkins Liu & Wang¹⁹ diets have been compared. No differences have been reported more effective and suggesting in that study KD with medium-chain triglycerides (TCM) that could be an option to improve acceptability Edelstein & Chisholm³⁴.

In this study, we report that the use of the classic type of KD implies an effort for parents in the preparation or elaboration of it when used orally.

Regarding KD side effects, it is important to note that we agree with most of the authors who describe the same complications among the different types of KD Kossoff⁸ Dodson et al.⁹, Dressler et al.²², Felton & Cervenka²⁰, KD Study Group of the Subspecialty Group of Neurology¹⁰, Wibisono et al.¹², constipation or constipation or gastrointestinal disturbances (nausea, colic, bloating, etc.) being the most common, most of these authors conclude that most of these side effects have been reversed with nutritional supplementation, recommendations, and multidisciplinary interventions. The least common effects reported by the authors were lithiasis, hypoproteinemia, pneumonia, gastroesophageal reflux, and hyponatremia. Regarding the duration of KD.

Bertoli et al.¹⁶, indicate that management for more than 5 years can induce demineralization in GLUT-

1 deficiency syndrome, duration of the diet course that some of the subjects in this study already had. Regarding kidney stones, which is rare, Wibisono et al.¹² reported that prophylactic treatment to prevent hypercalciuria is potassium citrate. In our study, 10% ($n = 1$) developed nephrolithiasis reported in renal ultrasound in a hospital unit that did not have to be surgically intervened since it remitted with conservative management.

One of the most important related findings with side effects in our study was that 5 patients (50%) developed dyslipidemia of the type hypoalphalipoproteinaemia (low HDL high-density lipoproteins).

The different finding regarding another type of dyslipidemia, Felton & Cervenka²⁰ ensures that KD is the best option for treating the ER despite the fact that in their results they found high levels of LDL (low lipoproteins density), so it suggests paying attention to the balance of the type and quality of oils, fats and/or seeds to prevent cardiometabolic risk.

It is worth mentioning that adherence to indications in relationship with the quality and type of registered fats the records of the treated cases were not followed exactly as established since the families had vulnerable economic conditions and opted for different or low-cost oils in substitution.

Based on the results obtained we can conclude that KD is a good alternative in managing ER in children. we consider it important to maintain the patient without pharmacological interventions except for the first 6 months of KD in order to assess its benefit as well as initiate a gradual decrease in drugs since in where KD is started and drugs are added simultaneously, there is no way to ensure the effectiveness of the diet. We consider that it is im-

portant to create ambulatory KD protocols for oral and catheter administration. Gastrostomy for the Mexican pediatric population already that the adjustments in the type of food will allow a better acceptance and adherence to the treatment. The multidisciplinary treatment of KD side effects as well as the constant publication of the experience of managing KD in the world allows different professionals to have a reliable approach with the present protocols.

Funding Source

The authors report that the study was self-financed.

Conflicts of interest

It is declared that there are no potential conflicts of any interest or relationship with persons or associations that intervene with the results of this investigation.

Acknowledgment

Our sincere thanks to the Centro de Rehabilitación Infantil Teletón Aguascalientes by support research. To Dr. Mónica Bocard Meraz, Dr. Macri Colucci and Dr. Patricia Corrales.

Ethical aspects

The study was approved by the bioethics committee of the center itself. The research was in accordance with the provisions of the Universal Declaration of Human Rights of 1948, the ethical standards of the

Nuremberg Code in 1947 and the Helsinki Declaration of 1964.

Likewise, the local regulations regarding the federal law on the protection of personal data held by individuals, DOF Law 05-07-2010 and the General Law on the Rights of Girls, Boys and Adolescents DOF Law 06-20-2018.

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