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Place of the Ketogenic Diet in Refractory Infantile Spasms

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ABSTRACT

Introduction: The ketogenic diet is an alternative nutritional regimen for refractory epilepsies, including infantile spasms. The objective of our study is the primary and secondary evaluation at 12 months of the effectiveness and tolerance of the ketogenic diet on seizure frequency, EEG (electroencephalogram) patterns, and side effects.

Patients and Methods: We evaluated the ketogenic diet as a second- or third-line treatment, following corticosteroid therapy and/or Vigabatrin. We assessed the effectiveness and tolerance of the ketogenic diet based on patients being seizure-free, experiencing a reduction in seizures of more than 50%, improvement in EEG background pattern (suppression of hypsarrhythmia), psychomotor development, side effects, and reduction in antiepileptic drugs during clinical, electrical, and neurocognitive follow-ups at 1, 3, and 12 months.

Results: Thirty-eight children, twentytwo boys, and sixteen girls, with a gender ratio of 1.37, presenting with infantile spasms visualized directly clinically or through videos and electric evaluation, with or without hypsarrhythmia on EEG, all symptomatic: genetic etiologies (14, 36.9%), structural in 18 patients (47.3%), and metabolic in six patients (15.8%). At 3 months, the number of patients who were seizure-free with a normal EEG was 22 patients (57.9%), and those with a reduction in seizures of more than 50%, 15 patients (39.5%).

At 12 months on the ketogenic diet, the number of patients who were seizure-free was 24 (63.2%), and those with a reduction in seizures of more than 50% 14 patients(36.8%). Good tolerance and efficiency of the diet were confirmed by treatment compliance, maintained high response rate, and a reduction in the number of antiepileptic drugs to 1.97. The children became more vigilant, attentive, and responsive to their parents.

Conclusion: Implementing the ketogenic diet within a short period of time, less than a year, would yield even better results in terms of seizure frequency and behavior in a developing infant brain.

KEYWORDS: infantile spasms, pharmacoresistant, ketogenic diet..

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INTRODUCTION

Infantile spasms is a rare and serious epilepsy. It is characterized by epileptic spasms occurring in bursts (clusters), a delay in neurodevelopment preceding or accompanying the spasms, and or a typical or atypical hypsarrhythmia[1,2]

According to the American Association of Pediatrics, the treatment of spasms is based on Adrenocoticotropin (ACTH) in the first line, and or Vigabatrin [3]. These have proven short-term efficacy in suppressing seizures and hypsarrhythmia. Relapse is the rule, linked either to the persistence of spasms or to significant side effects leading to heavy treatment. Other second- or third-line molecules or drugs: vitamin therapy, sodium valproate, Leveteracetam, Lamotrigine, Felbamate and Topiramate have been tested, but with limited efficacy[4,5].

The ketogenic diet represents a therapeutic alternative for this epilepsy, with efficacy proven by randomized controlled studies and multicenter studies with seizure suppression and hypsarrhythmia in 17 to 57% and a reduction in seizures of more than 50% in 50% of cases[3,6].

MATERIALS AND METHODS

We conducted a prospective, evaluative study,from October 1, 2020 to October 30, 2022, in a pediatric neurology consultation, at the pediatric department of the Constantine University Hospital. Diagnosis of infantile spasms was based on visual seizure counting by doctors and parents, by a critical video-EEG plus ENMG and or a one-hour intercritical EEG with a 20-minute wake-up call.

The protocol adopted is the implementation of the ketogenic diet on an outpatient basis, without prior fasting. The choice of ketogenic diet is based on a classic diet, with a ratio of 3:1 for patients under 12 months of age and 4:1 for others. A few patients switched to the modified Adkins or low glycemic index diet, which is less restrictive after 6 to 12 months of the diet. .

Weekly, monthly, and then quarterly follow-up has three objectives: a clinical follow-up based on seizure counting (Seizure Agenda), neuromotor assessment, psychomotor assessment failing that, children's behavior, an intercritical EEG follow-up of one hour plus waking up of 20 minutes. A biological and radiological assessment: renal, hepatic, blood ionogram, ultrasound, renal, hepatic, and cardiac.

The analysis of the data by the SPSS software, the statistical tests used for univariate analysis are the Pearson test and the exact Fischer test, and for the multivariate analysis are the logistic regression test: significant results for a p=0.05.

III. RESULTS

III. 1 Demographic and Pathological Characteristics

The ketogenic diet was applied to thirty-eight patients with a predominantly female sex-ratio of boys to girls They all presented with infantile spasms drug-resistant to 1st line treatment, and e 2nd line. Eleven patients with late-onset spasms. The mean age of onset of spasms is 9.13 ± 10.54. The average duration of epileptic activity from before the start of the ketogenic diet is 29.68 ± 20.5 months. The average number of bursts of spasms before the ketogenic diet is 4.82 ± 3.772, with a median of 4 and extremes ranging from 2 to 20.The average number of spasms before the ketogenic diet is 12.71 ± 14.275, with a median of 6 and extremes ranging from 2 to 60. The regimen was started in 55.3% of patients after 24 months and 21% between 12 and 24 months and only 23.7% less than 12 months.

The etiologies of spasms were dominated by acquired structural etiologies in 15 patients (39.5%), genetic genetic causes in 10 patients (26.3%), followed by metabolic etiologies in 6 patients (15.8%) and congenital structural etiologies in 3 patients (7.8%).

III.2. Evaluation of Response to the Ketogenic Diet

III.2.1 Effectiveness of the kd

At the end of kd: 24 patients (63.1%) are seizure-free and fourteen patients (36.8%) have a seizure frequency reduction of more than 50%.

At 1 month of kd: 4 patients (10.6%) are seizure-free and 18 patients (47.4%) have a reduction in seizure frequency of more than 50%.

At 3 months before kd: 22 patients (57.9%) are seizure-free and 15 patients (39.5%) have a reduction in seizure frequency of more than 50%.

III.2.2 Efficiency of the electrical response at 12 months of the kd

The intercritical EEG after diet was hypsarrhythmic in 16 patients (42.1 (it was hypsarrhythmic in 76.3% of patients before diet) of which 14 or 19.9% were atypical. Suppression of hypsarrhythmia after kd was noted in 34.2% of patients.

III.2.3. Efficacy of kd on neurodevelopment.

Patients with mild to moderate delay after ketogenic diet are at 28 patients or 73.6%. The delay of moderate to severe neurodevelopment is the same before and after diet: 10 cases (26.4%). There were 5 and 3 patients with delayed severe neurodevelopment respectively before and after CR, and 5 and 7 patients with moderately impaired development respectively before and after CR. Thus, two patients with severe delay switched to medium delay.

III.2.4 Tolerability and Side Effects

Side effects are noted in 63% of cases. They were dominated during the follow-up of the first days by digestive disorders: constipation in 38 patients (100%), vomiting in 11 patients (28.94%), Ketoacidosis was noted in 3 patients with drowsiness, vomiting, polypnea, with 4-cross ketosis in the urine chemistry.

These side effects were dominated during monthly follow-up by: Renal lithiasis in 2 patients on 12-month follow-up renal ultrasound, hypercholesterolemia in two patients on the 3 and 12 month follow-up assessment.

III.2.5 Reduction of antiepileptic drugs

Our study noted a reduction in the mean number of antiepileptic drugs after initiating the ketogenic diet from 2.66 before the ketogenic diet to 1.68 after dieting.

IV. PROGNOSTIC FACTORS

IV.1Influence of gender on response to KD

Our study found that girls were more responsive than boys at 12 months: 13 girls (81.2%) vs. 11 boys (50.0%) were seizure-free p=0.088 (not statistically significant)

IV.2 Influence of Etiology on Response to KD

The ketogenic diet is 100% effective in acquired genetic, metabolic, and structural spasms. This efficacy is reduced to 66.3% in spasms of congenital structural causes.

DISCUSSION

Infantile spasms are a form of epilepsy occurring in a maturing and developing brain where seizure frequency, intercritical activity (EEG hypsarrhythmia) and psychomotor regression can impact or worsen developmental encephalopathy and constitute a prognostic factor. [1] The electroclinical control of seizures and hypsarrhythmia leads

either to a restart of development or to its stabilization, thus avoiding multiple hospitalizations and therefore a lower cost of health care.[9]

Our study, like the other reports, demonstrated electro-clinical seizure control:

Indeed, the rate of patients free of seizures: is 10.6%, 57.9% and 63.3% respectively at 1.3 and 12 months. The rate with a reduction in seizures of more than 50% is 47.4%, 39.5% and 36.8% respectively at 1.3 and 12 months.

These results are comparable to those of those of the Pirez and Eun literature with the difference that the rate of seizure-free patients is higher in our study despite the severe phenotype of our epilepsy: by removing the causes of metabolic at 21% response, the seizure-free rate would be at 42.3%, We are in the interval of the multicenter study of Presacio with the rate of free seizures in 15 to 52.4% [11,12].

We note a delayed response compared to the other authors, related to the outpatient placement and without prior fasting, the reluctance of the parents and the adaptation of the new fatty acid energy substrate instead of carbohydrate and ADP instead of ATP.

Maintenance of response with recruitment of other patients free of seizures over time, also reported by Hong in 2010[10] .

Suppression of hypsarrhythmia was noted in 34% (hypsarrhythmic tracing 76% before the t-regimen and 42% after CR). The tracing was normal in 23% of cases before the diet and 55.2% after the diet, a difference of 32.2%. The addition of 23% of the non-hyspharrhythmic tracing with 32.2% of the normal tracing after diet, i.e. a total of 66% of the normal tracing concordant with the seizure-free patient rate of 63.2% [10,11].

It was found that the response to the ketogenic diet was better in spasms of metabolic etiologies followed by genetics without lesions on MRI followed by genetics with MRI lesions followed by acquired structural with 100%, 80%, 50% and 46.7% respectively with a significant p of 0.04.Our results are in agreement with the multicenter study and other studies demonstrating a positive correlation with etiology.

The other correlations studied concerning sex, age of onset of spasms, and initial neurodevelopmental delay did not show an impact on diet response with a non-significant p in agreement with single- and multicenter studies. [14]

For the Becoming of Spasms at 12 Months

Mortality

We have recorded two deaths, or 10.5% in the ketogenic group, which is lower than in previous studies where this rate is close to 30% Wong[2]. This is explained on the one hand by the improvement in the management of spasms, the rapid abandonment of corticosteroids due to their side effects in favor of the ketogenic diet, and on the other hand by the better management of inhalation pneumonia with resuscitation means.

Evolution of epilepsy at 12 months

We note a rate of seizure-free patients after a ketogenic diet of 63.1%, in the other cases the epilepsy persisted and progressed to generalized epilepsy such as Lennox Gastaut syndrome in 18.4%, it relapsed in 21% of cases and the drug-resistant focal epilepsy disappeared after CR (a sign of poor response according to Plouan is a sign of the effectiveness of the diet [2]

Side effects

Side effects are noted in 63% of cases, mild and managed by symptomatic treatment. In the follow-up of the first few days, they were dominated by digestive disorders: constipation in 38 patients (100%), a treatment based on nursing, hydration and a laxative treatment allowed her to return to order. Vomiting was found in 11 patients, or 28.94%. These were related either to transient intolerance, non-acceptance of the diet or food straining, often attributed to ketoacidosis and disappeared with the correction of the latter. Ketoacidosis was noted in 3 patients with drowsiness, vomiting, polypnea, with 4-cross ketosis in the urine chemistry: We sensitized the parents to this complication, maintaining a ketosis between 2 and 3 crosses in the urine strip, if the acetone is at 4 crosses, with the symptoms mentioned above, we proceeded to a resugaring by half a box of Rouïba juice.

Side effects were dominated by renal lithiasis noted in 2 patients on renal ultrasound at 12 months, a urinary ionogram and calciuria on urinary creatinuria was performed with a nephrologist's opinion was requested, ketonuria performed every 3 months. These stones disappeared with hydration and alkalinization of the urine. Hypercholesterolemia was noted in two patients on the 3- and 12-month follow-up assessment, having disappeared on the follow-up assessment afterwards.

These effects did not stop the diet in any case, and the continuation of the diet at 12 months, is an indirect indicator of the tolerance of the ketogenic diet.

Studies on CR report side effects that vary according to the authors and without serious consequences hindering the continuation of treatment such as ACTH[4,5]: in 33% according to a study by Hong vs. 55.5% and 23% according to Eun and Numis[8,13,] respectively .

These effects are dominated by minor signs that can range from minor signs to rare but serious complications occurring with the implementation of the diet. Digestive signs: vomiting in 25% according to Eun 2006 and constipation in 7 patients according to Hong 2010. Medium- and long-term effects such as kidney stones in 2 cases according to Kang[9] hypercholesterolemia in 17 cases in Wong's study.

Our strategy of setting up the diet on an outpatient basis without prior fasting (with significant ketosis leading to vomiting) and our prior education on the occurrence of these effects and our telephone counselling allowed for good management of these effects and did not result in any interruption of the regimen.

Our study noted is also in agreement with the studies of EUN and HONG for kidney stones and hypercholesterolemia which disappeared after the use of olive oil (medium chain fatty acid) and good hydration for lithiasis

The reduction in the mean number of antiepileptic drugs was noted from 2.66 before diet to 1.68 after diet is in agreement with that of Hong with change in AE from 3.6 before diet to 1.4 after diet. [10,11]

Evaluation of the efficacy of the treatment on Neurodevelopment

If we group normal patients with mild delays, and medium delays with severe ones, we see that the number of normal patients and those with slightly impaired development remained the same at 28 patients or 73.6%. The latter rate corresponds to the rate of 72.6% (seizure-free patients (47.1%), patients with frequency reductions of more than 50% to 25.5%).

It has been found that two patients with severe retardation have become mean retardation after dieting

There is a positive correlation between electroclinical seizure suppression and improved neurodevelopment. [10,11]

CONCLUSION

The ketogenic diet has a positive impact on the eletroclinical reduction of spasm bursts with statistically significant results. The latter are correlated with the disappearance of hypsarrhythmia and the improvement of psychomotor development, making the latter an essential therapeutic option of choice

Tolerance with mild side effects and reduction of AEs are secondary objectives to be aware of for their prevention, review of the type of diet and the strategy for setting up the diet.

Appendix

Table 1. Reponse (reduction of crisis) after ketogenic diet

Crisis Reduction	**1 month of KD N (%)**	**3 months of KD N (%)**	**12 months of KD N (%)**
□ 10%	4(10,6)	0 (0,0)	0 (0,0)
10% to 49%	12(31,6)	1(2,6)	0 (0,0)
50% to 89%	18 (47,4)	15(39,5)	14 (36,8)
Seizure-free	4 (10,6)	22(57,9)	24 (63,2)
Total	38(100)	38(100)	38(100)
p-value	**0.01**	**0.0001**	

Table 2: Neurodevelopmental delay before and after KD

Neurodevelopmental delay	
Before the Ketogenic Diet N (%)	**After the Ketogenic Diet N (%)**
22 (57,9)	**30 (78,9)**

RND	**Before KD N (%)**	**After KD N (%)**
RNDL	12 (31.5)	20 (52,6)
RDNM	5 (13,2)	7 (18,4)
RNDS	5 (13,2)	3 (8)

KD ketogenic diet

RND Neurodevelopmental Delay

RNDLMild Neurodevelopmental Delay

RNDM Moderate Neurodevelopmental Delay

RNDS Severe Neurodevelopmental Delay

Table 3: Distribution by 12-month KD response by sex

	Crisis Reduction				P
Sex	10- 49%	50% - 90%	Seizure-free	Total	p = 0.088
M	1(4,5)	10 (45,5%)	11 (50,0%)	22 (100%)	
F	0 (0,0 %)	3 (18,8%)	13 (81,2%)	16 (100%)	
Total	1 (4,5%)	13 (34,2%)	24 (63,2%)	38 (100%)	

Table 4. Distribution of response at 12 months of KD by etiology

Etiologies	10% à 49%	50%- 90%	Crisis free	Total	P
Genetic	0 (0,0%)	2 (20,0%)	8 (80,0%)	10(100%)	0,042
Génétic Structural	0 (0,,0%)	2 (50,0%)	2 (50,0%)	4(100%)	
Structural congenital	1 (33,1%)	1(33,3%)	1(33,3%)	3(100%)	
Structural cquired	0 (0,0%)	8 (53,3%)	7 (46,7%)	15(100%)	
Metabolic	0 (0,0%)	0 (0,0%)	6 (100)	6(100%)	
Total	1(2,6%)	13(34,4%)	25(63,2%)	38(100%)	

REFERENCES

I. Dulac O. What is West syndrome? Brain Dev. Brain & development. 1 Dec 2001; 23:447-52.

II. Wong M, Trevathan E. Infantile spasms. Pediatric Neurology. 1 Feb 2001; 24(2):89-98.

III. Hrachovy RA, Frost Jr. JD, Kellaway P. Hypsarrhythmia: Variations on the Theme. Epilepsia. 1984; 25(3):317-25.

IV. Prezioso G, Carlone G, Zaccara G, Verrotti A. Efficacy of ketogenic diet for infantile spasms: A systematic review. Acta Neurol Scand. Jan 2018; 137(1):4-11.

V. Nabbout R. A risk-benefit assessment of treatments for infantile spasms. Drug Saf. 2001; 24(11):813-28.

VI. Song JM, Hahn J, Kim SH, Chang MJ. Efficacy of Treatments for Infantile Spasms: A Systematic Review. Clin Neuropharmacol. 2017; 40(2):63-84.

VII. Kossoff EH, Dorward JL. The modified Atkins diet. Epilepsia. Nov 2008; 49 Suppl 8:37-41.

VIII. Eun SH, Kang HC, Kim DW, Kim HD. Ketogenic diet for treatment of infantile spasms. Brain Dev. Oct 2006; 28(9):566-71.

IX. Osborne JP, Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, et al. The underlying etiology of infantile spasms (West syndrome): information from the United Kingdom Infantile Spasms Study (UKISS) on contemporary causes and their classification. Epilepsia. Oct 2010; 51(10):2168-74.

X. Hong AM, Turner Z, Hamdy RF, Kossoff EH. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. Epilepsy. August 2010; 51(8):1403-7.

XI. Eun SH, Kang HC, Kim DW, Kim HD. Ketogenic diet for treatment of infantile spasms. Brain Dev. Oct 2006; 28(9):566-71

XII. Pires ME, Ilea A, Bourel E, Bellavoine V, Merdariu D, Berquin P, et al. Ketogenic diet for infantile spasms refractory to first-line treatments: an open prospective study. Epilepsy Res. Jul 2013; 105(1-2):189-94.

XIII. Kang HC, Kim YJ, Kim DW, Kim HD. Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. Epilepsia. Feb 2005; 46(2):272-9.

XIV. Prezioso G, Carlone G, Zaccara G, Verrotti A. Efficacy of ketogenic diet for infantile spasms: A systematic review. Acta Neurol Scand. Jan 2018; 137(1):4-11.

XV. Fusco L, Vigevano F. Ictal clinical electroencephalographic findings of spasms in West syndrome. Epilepsy. 1993; 34(4):671-8.

XVI. 24-hour ambulatory EEG recording in epileptic infantile spasms - ScienceDirect [Internet]. [cited 2022 Dec 6]. Available on: https://www.sciencedirect.com/science/article/abs/pii/S0370447587800680

XVII. Maria Dahlin . The ketogenic diet influences the levels of excitatory and inhibitory amino acids in the CSF in children with refractory epilepsy. Epilepsy Research 64 (2005) 115–125