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The ketogenic diet in patients with myoclonic status in non-progressive encephalopathy

Roberto Caraballo[a,*], Francesca Darra[c], Gabriela Reyes[a], Marisa Armeno[b], Araceli Cresta[b], Graciela Mestre[b], Bernardo Dalla Bernardina[c]

[a] Department of Neurology, Hospital de Pediatría "Prof Dr Juan P Garrahan", Buenos Aires, Argentina
[b] Hospital de Pediatría "Prof Dr Juan P Garrahan" Buenos Aires, Argentina
[c] Servizio di Neuropsichiatria Infantile, Policlinico G.B. Rossi, Universita degli Studi di Verona, Italy

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ABSTRACT

Myoclonic status in non-progressive encephalopathy (MSNPE) is characterized by the recurrence of long-lasting atypical status epilepticus associated with attention impairment and continuous polymorphous jerks, mixed with other complex abnormal movements, in infants suffering from a non-progressive encephalopathy. The ketogenic diet (KD) has been used as an alternative to antiepileptic drugs (AEDs) for patients with refractory epileptic encephalopathies.

Purpose: In this study we assess the efficacy and tolerability of the KD in patients with MSNPE.

Methods: Between March 1, 1980 and August 31, 2013, 99 patients who met the diagnostic criteria of MSNPE were seen (58 patients in Verona and 41 patients in Buenos Aires). Six of these 99 patients were placed on the KD using the Hopkins protocol and followed for a minimum period of 24 months.

Results: Twelve months after initiating the diet, three patients had a 75%–99% decrease in seizures, two had a 50%–74% decrease in seizures, and the remaining child had a less than 50% seizure reduction. In five patients with a seizure reduction of more than 50%, the myoclonic status epilepticus disappeared within 6 months after starting the diet. All patients had very good tolerability and no adverse events were identified. In most of the patients AEDs were reduced.

Conclusion: The KD is a promising therapy for MSNPE, with most of our patients showing a more than 50% seizure reduction. In patients that responded well to the diet cognitive performance and quality of life also improved.

1. Introduction

The ketogenic diet is the most common non-pharmacologic therapy for patients with refractory epilepsy, not only children but adults as well [1].

It has been suggested that the KD is beneficial for seizure control in specific epileptic syndromes, most importantly epileptic encephalopathies [1–10]. Over the past years, there has been a remarkable appearance in the concept of using dietary therapy for emergency management of pharmacoresistant seizures [11,12]. The KD is effective in all types of epileptic seizures [1,13].

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 more than 50% reduction in seizures [1,13–16].

Myoclonic status in non-progressive encephalopathy (MSNPE) is characterized by the recurrence of long-lasting atypical status epilepticus associated with attention impairment and continuous polymorphous jerks, mixed with other complex abnormal movements, in infants suffering from a non-progressive encephalopathy, constituting a well-defined and unusual epileptic syndrome [17]. The etiology may be genetic, such as a defect in chromosome 15q 11-q13 (Angelman syndrome), deletion of the short arm of chromosome 4 (Wolf-Hirschhorn syndrome or 4p-syndrome), Rett syndrome, Prader Willi syndrome, and others. Prenatal or perinatal anoxic insults and bilateral polymicrogyria have also been described [17,18].

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

* Corresponding author at: Department of Neurology, Hospital de Pediatría "Prof Dr Juan P Garrahan", Combate de los Pozos 1881, C.P. 1245, Buenos Aires, Argentina.
E-mail address: rhcaraballo@arnet.com.ar (R. Caraballo).

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2. Material and methods

Between March 1, 1980 and August 31, 2013, 99 patients who met the diagnostic criteria of MSNPE were seen (Verona 58 pts, and Buenos Aires 41 pts). Six of these 99 patients were placed on the KD using the Hopkins protocol and followed for a minimum period of 24 months. Three patients were treated in Verona and three in Buenos Aires. Two patients received the oral formula of the KD (ketocal) due to their severe general neurological state at the moment of diet initiation.

Frequency of the seizures was registered using daily seizure calendars kept by the parents. The parents were explained how to register the seizures and how to name the different seizure types. The authors also evaluated the seizure frequency considering the EEG-polygraphic recordings before and after KD initiation. Seizure frequency registration was started at least 3 months before the initiation of the diet.

Electroencephalograms and video-polygraphic-EEG recordings were performed during wakefulness and sleep at least three months before starting, while on, and after discontinuing the KD. The EEG recordings confirmed the myoclonic status in each patient prior to the initiation of the diet. The myoclonic status was continuous in the period between onset and initiation of the diet in four and intermittent in two patients. Baseline blood tests and lipid profiles were also obtained. Serum bicarbonate levels were measured in all patients.

Children started fasting in the hospital for 36–72 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 hospital for another five 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 to regulate the diet for optimal tolerance and seizure control. The ratio of the diet was progressively modified as needed to maintain 80–160 mg/dl urinary ketosis, and to avoid weight loss. Adverse events and reasons for diet discontinuation were recorded, as were changes in medication.

According to age and IQ level, all patients were psychometrically evaluated using the Wechsler Intelligence or Terman Merrill Scales.

3. Results

Six children with MSNPE, (4 girls and 2 boys) were placed on the KD as add-on to the use of one to three AEDs. All the patients were started on the diet while the myoclonic status was present. Age at diet initiation was between 2.5 and 9 years (mean, 5 years). The patients were followed for a period of 1 to 8 years (mean, 6 years).

All patients had more than one type of seizure before starting the myoclonic status epilepticus with age at onset ranging from 3 to 9 months (mean age, 6 months). The age at onset of myoclonic status was between 10 and 36 months (mean age, 20 months).

The children had previously received a mean of 6.5 different AEDs and were on a mean of 2 AEDs when the diet was begun.

In five of the six children placed on the KD the etiology of MSNPE was genetic; two had Angelman syndrome, one had Rett syndrome, in one the epileptic encephalopathy was secondary to a mutation in the *CDKL* gene, and in one genetic studies showed a *de novo* mutation in the *SCN8A* gene. In the remaining patient the etiology was unknown.

Regarding the neuropsychological aspects, during the myoclonic status, all six patients showed impairment of visual contact and loss of social abilities; in five of them behavioral disturbances and motor disabilities were also recognized.

Table 1 shows the electroclinical features, treatment, and evolution of the patients before diet initiation.

3.1. Duration on the diet

One of the six original children stayed on the diet for 12 months, one for 1 year and eight months, three children for 2 years, and one child for 3.5 years.

3.2. Efficacy of the diet, tolerability and adverse events

Twelve months after initiating the diet, three patients had a 75%–99% decrease in seizures, two patients had a 50%–74% decrease in seizures, and the remaining child had a less than 50% seizure reduction. In two patients with a seizure reduction of more than 50%, the myoclonic status epilepticus disappeared within the first 3 months and in three remaining patients within 6 months after starting the diet, respectively. In Table 2 the electroclinical features, treatment, and evolution of the patients while on the KD and at the last follow-up are shown with special emphasis on efficacy. Tolerability was very good in all patients and no adverse events were identified.

3.3. Electroencephalographic changes

After initiating the diet, the EEG abnormalities improved in four of six cases. In two patients with a 75–99% seizure reduction the electroclinical myoclonic status disappeared in the first months (Figs. 1 and 2), and in the remaining child with a 75–99% seizure reduction the EEG abnormalities persisted despite significant clinical improvement (Figs. 3 and 4). In both patients with a 50–74% seizure reduction the EEG improved during the first six

Table 1
The electroclinical features, treatment, and evolution of the patients before initiation of the KD.

Patients	Age at onset of epilepsy (months)	Seizure types	EEG	Age at onset of MS (months)	EEG	AEDs
1	3	FS, ES	Hypsarrhythmia	15	Subcontinuous multifocal diffuse slow spike-waves	ACTH
2	3	FS, MA	Generalized spike and waves	13	Continuous polyspikes and slow waves	VPA, ETS
3	4	FS, MS		10	Continuous discharges of diffuse, asynchronous polyspike-waves	VPA, TPM
4	9	FS, SGS	Bilateral spikes	36	Continuous and diffuse slow waves with interposed spikes	VPA, LVT
5	8	MS	Generalized spike and waves	20	Subcontinuous multifocal diffuse irregular slow spike-waves	VPA, ETS
6	7	FS, MS	Bilateral spikes	26	Continuous and diffuse slow waves with interposed spikes	VPA,TPM, LVT

Table 2
The electroclinical features, treatment, and evolution of the patients while on the KD and at the last follow-up.

Patients	Etiology	Age at KD initiation (years)	EEG abnormalities at the last follow-up	AEDs	Side effects	Duration of KD and results (6 months)	Duration of KD and results (9 months)	Duration of KD and results
1	CDKL gene	2.5	Isolated spikes	VPA	–	50–75% seizure reduction and MSE disappeared at 2.5 months	75–99% seizure reduction	(1 year) 75–99% seizure reduction
2	***SCN8A* gene**	3.5	Bilateral spikes	VPA STM	–	75–99% seizure reduction and MSE disappeared at 2 months	75–99% seizure reduction	(3 years and 6 months) 75–99% seizure reduction
3	Unknown	2.5	Multifocal spikes	LVT	–	50–75% seizure reduction and MSE disappeared at 5 months	50–75% Seizures reduction	(1 year and 8 months) 75–99% seizure reduction
4	Angelman syndrome	6	Diffuse spikes and waves	VPA	Vomiting	50% seizure reduction	<50 Seizure reduction	(2 years) <50% seizure reduction
5	Rett syndrome	9	Occasional bilateral SW	VPA-CLB	–	50% seizure reduction and MSE disappeared at 4 months	50–74% seizure reduction	(2 years) 50–74% seizure reduction
6	Angelman syndrome	4	Bilateral posterior spike and waves	CLB LVT	Vomiting	50–75% seizure reduction and MSE disappeared at 5.5 months	50–74% seizure reduction	(2 years) 50–74% seizure reduction

Abbreviations: FS: focal seizures, ES: epileptic spasms, MS: myoclonic seizures, SGS: secondary generalized seizures, MA: myoclonic absences, MSE: myoclonic status epilepticus.

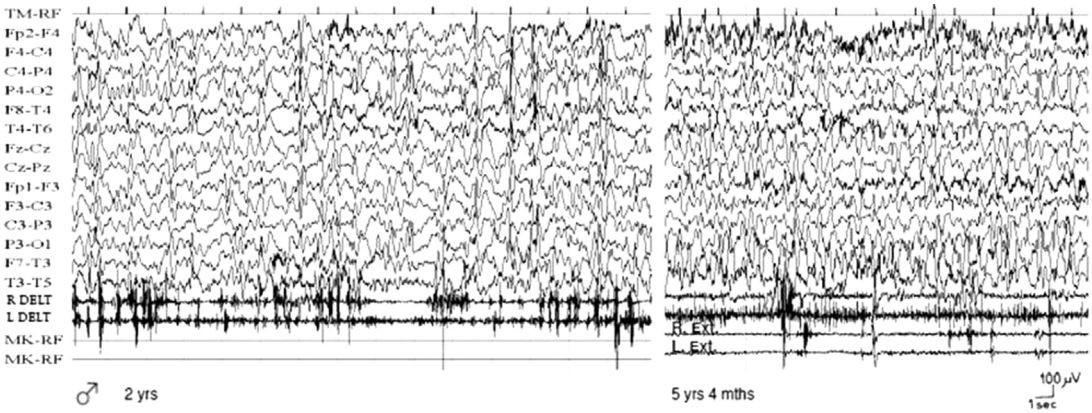

Fig. 1. Patient 1 (left side): On a background EEG with very slow and poorly organized activity, it is possible to recognize independent subcontinuous spikes in both hemispheres with frequent diffuse SW. Note the continuous synchronous and asynchronous myoclonias in both deltoid muscles related to the EEG paroxysms on the EMG. (Right side): Note the continuous discharges of unusual asynchronous spikes and waves in both hemispheres related to subcontinuous asynchronous myoclonias in both hemisomas, synchronous in the agonists and antagonists.

months of receiving the diet, while in the remaining child, who had a less than 50% seizure reduction, the EEG did not show a significant improvement.

3.4. Decreasing and discontinuing medications, and outcome

Medications were decreased non-systematically with the aim of the patient becoming medication free. In all the patients with decrease in seizures of more than 50%, AEDs were reduced from three to one or two. The neuropsychological profile improved significantly in all our patients, returning to baseline in four of them. Up to now, no recurrence of the myoclonic status epilepticus and neurological deterioration were registered in any patients in this series of patients after a mean of six years of follow-up. It is interesting to mention that the patient with MSENPE associated with the *SCN8A* gene had a 75–99% seizure reduction and no recurrence of the myoclonic status was observed. The girl with a severe encephalopathy of unknown etiology died at the age of 4

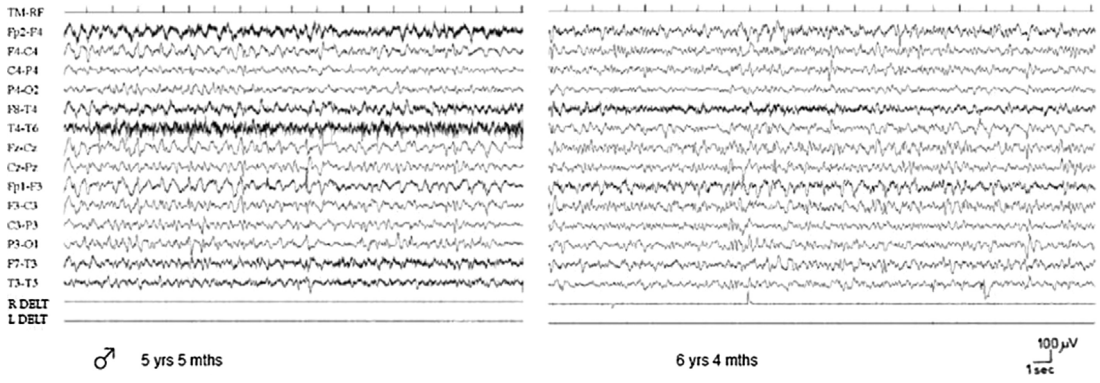

Fig. 2. Patient 2 (left side): Note the persistence of long sequences of theta activity in the fronto-central regions in the absence of diffuse discharges and clinical manifestations. (right side): Note the significant improvement of the EEG background activity with the persistence of isolated spikes in the central regions in the absence of clinical manifestations.

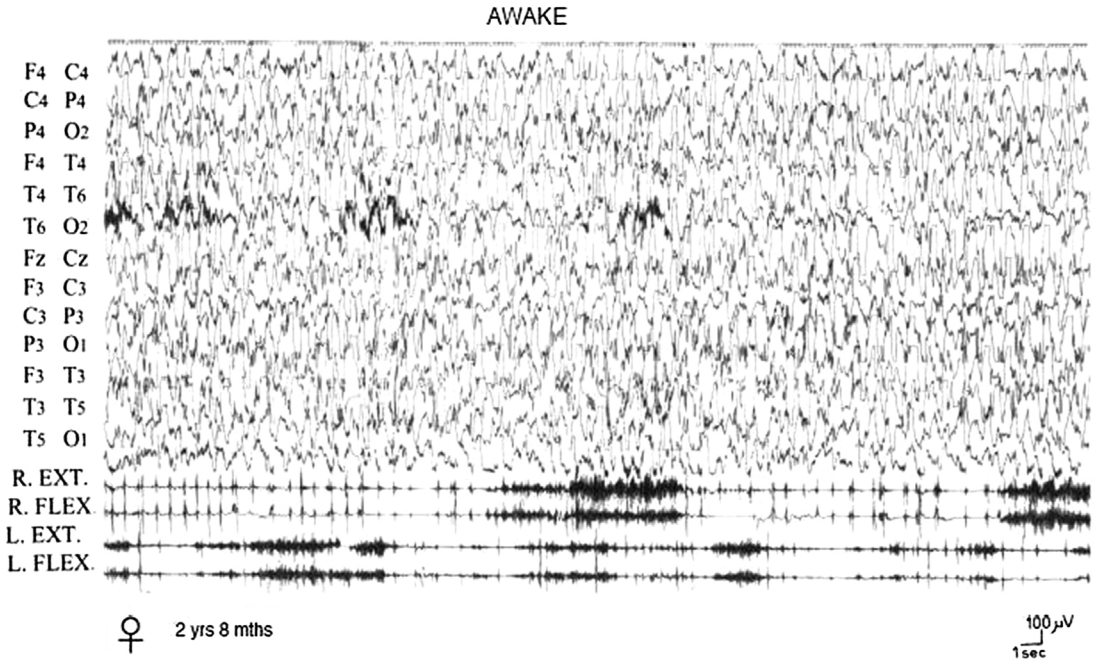

Fig. 3. Patient 3: Note the EEG continuous discharges of diffuse slow SW with frequent superimposed small fast poly-spikes and the continuous rhythmic positive myoclonias, synchronous in agonists and antagonists, asynchronous in both hemisomas.

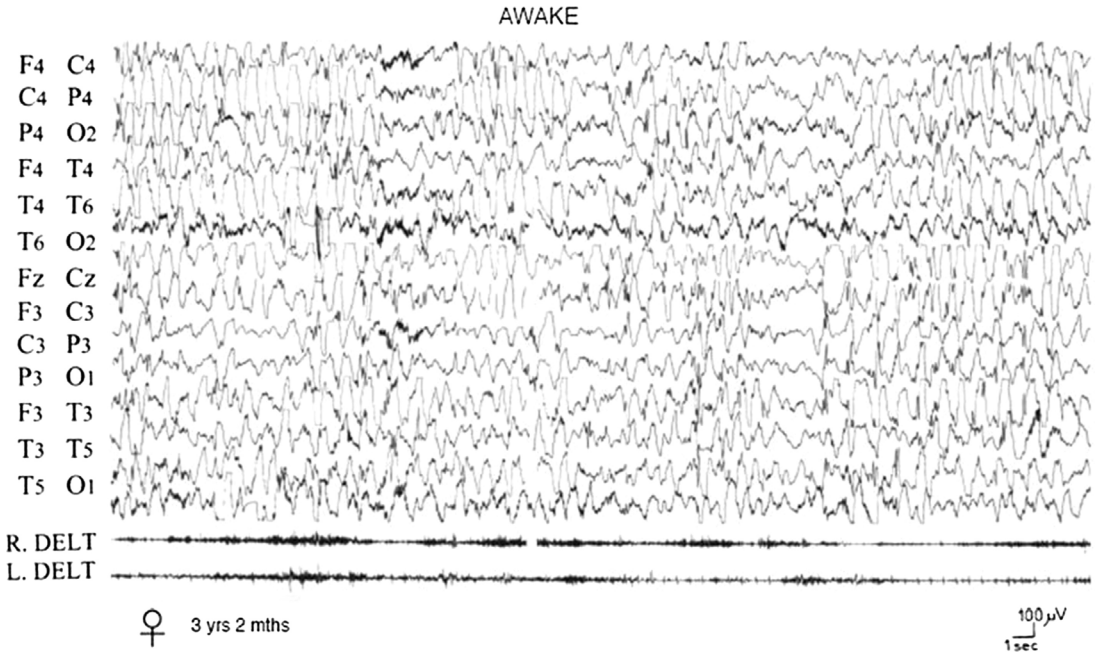

Fig. 4. Patient 3: Note the persistence of frequent EEG multifocal paroxysms in the absence of significant motor manifestations.

years and 2 months from a complicated bronchopneumonia; she was on the KD at that moment.

4. Discussion

Our preliminary experience with the KD in six children with MSNPE with a genetic etiology shows an overall good response in terms of seizure frequency, EEG improvement, and tolerability. To our knowledge, this is the first report on a series of patients with MSNPE treated with the KD. A single patient with MSNPE was published as part of a series of patients with epileptic encephalopathy treated with the KD [19]. Independently of the nosologic aspect of this particular electroclinical picture, when studying the effect of KD we refer to a definition of epilepsy based on etiology rather than on the electroclinical features only.

They did not present with recurrence of the myoclonus status epilepticus or neurological deterioration. Therefore, the KD should be considered earlier in patients with this syndrome. While the experience with the diet has been similar in patients with refractory myoclonic epilepsies and in those with similar genetic etiologies, it is important to emphasize the usefulness of the diet in patients with MSNPE.

The refractory myoclonic status epilepticus as well as the EEG abnormalities improved in most of our patients. In three children of the present series who had a seizure reduction of more than 75% the myoclonic status disappeared within the first month on the KD. This early response to the KD in cases with myoclonic status epilepticus has been reported by our group [20] in two patients, associated with refractory myoclonic epilepsy of unknown etiology not compatible with MSNPE in the first and associated with progressive encephalopathy in the second patient.

In two cases of our series, EEG abnormalities improved early after diet initiation. Similar EEG findings in patients with epilepsy treated with the KD have been reported [21].

It is well known that other epileptic encephalopathies associated with positive and/or negative myoclonic seizures, such as Dravet syndrome, epilepsy with myoclonic and atonic seizures, and epileptic encephalopathy with continuous spikes and waves during slow sleep, may have a good response to the KD [4,5,7,22].

Patients with refractory epilepsy associated with Angelman and Rett syndromes who responded well to treatment with the KD have been reported [23–25]. Some of these patients published probably had electroclinical features compatible with MSNPE. Patients with Angelman syndrome with refractory epilepsy have been treated with a low glycemic index diet with good results [26]; some of these may also have had an electroclinical picture of MSNPE.

In these patients with complex neurological conditions, peculiar behavioral disturbances, and severe epileptic encephalopathy the diet may seem very difficult to implement, but our experience as well as the results published in the literature suggest that the KD is a good alternative treatment in the management of children with MSNPE. Therefore, the parents should be specifically informed on the KD as a treatment option in these children. When the KD is selected as the appropriate therapy, the parents should be properly trained in the use of the diet to increase the success rate.

It is important to consider the KD earlier in the therapeutic scheme of patients with MSNPE. Future collaborative and prospective studies should be conducted to be able to draw more robust conclusions on the benefit of the KD in the management of the seizures in children with this particular epileptic syndrome. We would like to emphasize that the routine use of the polygraphic EEG recording is crucial to recognize the electroclinical pattern of MSNPE.

5. Conclusion

The KD is a promising therapy for MSNPE, with most of our patients showing a more than 50% reduction in seizures. The diet should be considered in the therapeutic scheme of children suffering from this syndrome considering that most of them are refractory to AEDs, regardless of the etiology. In patients who respond well to the diet, cognitive performance and quality of life also improves.

Conflict of interest

We have no financial and personal relationships with other people or organizations to disclose that could inappropriately influence this work.

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