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REVIEW ARTICLE

Ketogenic diet and epilepsy: an up-date review

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Abstract: Background and Aims: Ketogenic diet is currently a therapeutic option for the treatment of epilepsy other than anticonvulsant drugs, for which there is a growing interest in Europe and worldwide, mainly due to the persisting number of refractory patients and the adverse side effects of antiepileptic old and new drugs. Aim of the present article is to review literature data regarding the use of the diet in the different types of epilepsies and epilepsy syndromes, trying to better understand the main evidence-based indications for its use.
Material and Methods: A literature search was based on a Medline search of published retrospective, not-controlled prospective and randomized controlled trials on the use of the ketogenic diet for the treatment of epilepsies and antiepileptic encephalopathies. In some instances, case reports were also included. A search on standard textbooks and review articles on the use of the ketogenic diet was considered as well. A summary and a critical appraisal of what emerged from the literature for each epileptic syndrome will be discussed in this review.Conclusions: Ketogenic diet is considered as the primary treatment of GLUT-1 deficiency syndrome and pyruvate-dehydrogenase deficiency. It is so far included as secondary option for the so called "catastrophic epileptic encephalopaties of childhood", and should be a potential treatment against a wide variety of other seizure types and epilepsy syndromes as well as many symptomatic localization-related epilepsies. The best evidence of its efficacy regards refractory infantile spasms, Dravet syndrome and myoclonic-astatic epilepsy as well as epileptic encephalopathies due to cortical migration disorders. There is also a growing interest for dietary treatments for epilepsy other than ketogenic diet, such as the modified Atkins diet and the low glicemic index diet , both providing a daily amount of fat less than the ketogenic diet. Presently, some authors prefer to use the ketogenic diet in infants and younger children, leaving the other two diets for the treatment of older children, adolescents and young adults.

Key words: **ketogenic diet, epilepsy**
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Introduction

Literature data regarding the ketogenic diet treatment for epilepsy and epileptic syndromes come mostly from retrospective, not controlled prospective, and two more recent randomized, controlled trials. As it concerns seizure type, ketogenic diet was as much effective in focal as in generalized seizures, though it seems to work somewhat better in generalized seizures [1,2]. More recently, Neals et al. [3], in a large randomized controlled study with the ketogenic diet, did not find significant differences between generalized and focal symptomatic syndromes. Further, Villeneuve et al. [4] report a particularly positive response in recently worsened focal seizures.

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Ketogenic diet and infantile spasms

Nordli et al., [5] first report on the early treatment with the ketogenic diet in children aged less than 2 years, affected by refractory seizures. The best response was reached in patients with infantile spasms whose seizures decreased by 50 to100% in 12 out of 17 children (70.6%).

Twenty-three children with infantile spasms [6], aged between 5 months and 2 years, were fed a classical ketogenic diet for at least one year. Thirty per cent of IS were symptomatic (tuberous sclerosis complex, mitochondrial diseases, Down syndrome, focal cortical dysplasia, dismyelinating disease, gene translocations). At 3,6,9, and 12 month follow-up, 67%, 72%, 93%, and 100% of the patients showed a seizure decrease more than 50% (3 of them were seizure-free at 12 months).

In 2005, Kang et al. [7] reported on 39 children with refractory infantile spasms included in a larger series of patients treated with ketogenic diet. Fourteen out of 39 patients remained on the diet up to 12 months and 13 were seizure-free, while one more patient showed a seizure improvement by 50%.

In another retrospective trial [8], an all liquid, 3:1 ketogenic diet led to seizure control in 23 of 43 children (53.5%) with persisting infantile spasms, and to 90% seizure decrease in other four patients. Spasm reduction was associated with a significant improvement of EEG findings and psychomotor development.

Further, a retrospective case-control study of the diet compared to ACTH was made by Kossoff et al. [9] in children with newly diagnosed infantile spasms. Thirteen children were treated with KD and twenty with high doses of ACTH. Eight of 12 (62%) became seizure-free after a month on the diet, while 18 of 20 (90%) were controlled with ACTH.

While patients on ACTH showed a normal EEG more frequently at one month follow-up, adverse side effects (31% vs 80%) and frequency of recurrence (12.5% vs 33%) were less in the ketofed group.

Ketogenic diet and Lennox-Gastaut syndrome

Ketogenic diet decreased seizure frequency in anecdotic LGS patients as reported by Wheless et al. [10] and Schmidt et al. [11]. Freeman et al. [12] had previously described 17 patients with atonic or myoclonic seizures who showed an early seizure reduction by 50% or more on the diet. In five patients with LGS [13], ketogenic diet was not or poorly effective associated with a bad compliance to the diet.

Kang et al. report 75 patients with LGS included in a larger series of 119 patients treated with ketogenic diet [7]. Thirty-three out of 75 (44%) remained on the diet at least 12 months: 22 were seizure-free, 2 had a 90% and other 6 a more than 50% seizure reduction. The best results were found against generalized tonic, atonic and myoclonic seizures.

Finally, Freeman et al. [14] treated with the diet 20 patients with LGS, with mean age of 3.6 years. Patients were randomized to blindly receive, in addition to the diet, 60 gr. per day of glucose or 60 gr. of saccharin. Patients, crossed over the other treatment after one week, showed only a milder seizure decrease on saccharin than on glucose.

Noteworthy, Freeman et al. [15], in a review on the ketogenic diet, did not include patients with Lennox-Gastaut syndrome among the best candidates for this dietary treatment.

Ketogenic diet and Dravet syndrome

Fejerman et al. [16] report on a significant response to the diet in 9 of 11 children with SMEI, throughout a 24 month follow-up. A

significant decline of the KD efficacy was observed in 2 cases. The same authors [16], refer a 50% or more seizure decrease in 13 of 20 patients, reason why they suggest that the ketogenic diet should be given early in these patients, having tried at least 3 antiepileptic drugs suitable for the syndrome. Further , 11 of 16 patients with this syndrome were fed a ketogenic diet by Kang et al. [7]; of them, 9 patients were seizure-free after a 12 month follow-up period, and one had a >50% seizure reduction.

Ketogenic diet and myoclonic-astatic epilepsy

Oguni et al.[18] report on an excellent or good response to the diet in 26 out of 218 patients with myoclonic-astatic epilepsy, treated with ketogenic diet, compared to ACTH or other AEDs including etosuximide, clonazepam, valproic acid and nitrazepam. The diet was ineffective in 7% of cases, never leading to seizure worsening.

More recently, Caraballo et al. [19] treated with the diet 11 of 30 patients with myoclonic astatic epilepsy; after a 18-month-follow-up, 6 patients (54.5%) were still on the diet and two of them were seizure-free.

Ketogenic deit and tuberous sclerosis

TSC is a pathological condition frequently associated with refractory epilepsy, often consisting of early-onset spasms, focal or polymorphous seizures (tonic, atonic and myoclonic).Ketogenic diet in TSC patients was first reported by Kossoff et al. [20] in 12 children, aged between 8 months and 18 years, affected by daily complex focal (4/12) or multiple seizure types (8/12). After a 6 month follow-up, 92% (11/12) had a seizure decrease by > 50% and 67% (8/12) by > 90%. Three patients were seizure-free. Similarly, 3 patients with TSC and focal seizures [21] showed a 90% (2/3) or a 50% (1/3) seizure reduction with the diet; the latter underwent then surgical removal of two left frontal tubers, becoming seizure-free. Four additional patients [22], aged 3 to 4 years, with secondary generalized focal seizures, had at least 50% seizure reduction 12 months after starting the diet.

Ketogenic diet and Landau-Kleffner syndrome

Kang et al., [7] report a good response in 2 of 4 cases with LKS included in a large series of 199 patients treated with ketogenic diet. The same authors describe [23] the case of a 5-year-old girl with a Landau-Kleffner-like syndrome including fluctuating sensory aphasia and bizarre behaviours together with mitochondrial respiratory chain complex-1 defect. This patient, previously refractory to different combinations of anticonvulsant drugs, ACTH and IVIG treatments, significantly improved with the ketogenic diet associated with Q10-Coenzyme, riboflavin, L-carnitine and high-dose multivitamins.

Ketogenic diet and Rett syndrome

Ketogenic diet was given by Haas et al. [24] in 5 girls aged between 5 and 10 years, with Rett syndrome and refractory seizures. Four of them showed a more than 50% seizure decrease and all of them had a behavioural improvement. Liebhaber et al.[25] report a significant decrease of atypical absences in a eight-year-old girl treated with ketogenic diet (4:1 ratio) combined to PB and sulthiame. Absences dropped from 30 per day to less than 5, together with a behavioral improvement. At age 11 years, stereotyped hand movements and polypnoea-apnoea episodes manifested.

Ketogenic diet in Lafora's disease and subacute sclerositing panencephalitis

A pilot study with ketogenic diet in 5 patients with Lafora's bodies disease [26], treated for 10 to 30 months (mean duration 16 months), did not show any significant effect on the

progression of the disease. Similarly, the diet was effective in a patient with PESS only in the first 2 weeks of treatment [27]; soon after, myoclonic jerks reappeared associated with an increasing cognitive impairment.

Ketogenic diet and status epilepticus

Francois et al. [28] report on the efficacy of the diet in 3 of 6 patients with refractory status epilepticus.

Ketogenic diet in early infantile epileptic encephalopathy with suppression-bursts (EIEE)

Three children with EIEE [7] did not respond to the diet, while another case [22] showed a > 75% reduction of seizures after 2 months on the diet that was nonetheless withdrawn 11 months later, due to persisting gastroesophageal reflux.

Ketogenic diet and mitochondrial diseases

In a retrospective assessment of a large series of patients treated with ketogenic diet [29,30], KD resulted well tolerated in 14 children with mitochondrial respiratory chain complex defects and epileptic syndromes including infantile spasms, Lennox-Gastaut syndrome, Landau-Kleffner syndrome or focal seizures. Half of the patients became seizure-free, and in three of them there was not seizure recurrence.

Interestingly, ketogenic diet was not effective in two cases of Leigh disease. These Authors state indeed for a potential efficacy and good tolerability of the ketogenic diet in mitochondrial disorders associated with epilepsy syndromes.

Conclusions

Ketogenic diet is currently a therapeutic option other than anticonvulsant drugs that should be preferably used as early as possible for the treatment of childhood refractory epilepsies. Table 1 synthetizes the clinical conditions for which the diet is particularly indicated.

Table 1. The role of the KD in the modern treatment of epilepsy

Primary therapy
GLUT1 deficiency syndrome
pyruvate dehydrogenase (E1) deficiency
Secondary treatment
generalised epilepsies (> VPA failure)
early myoclonic epilepsy
early infantile epileptic encephalopathy
myoclonic-absence epilepsy
severe epileptogenic encephalopathies
Lennox-Gastaut syndrome
Dravet syndrome
myoclonic-astatic epilepsy
refractory infantile spasms
Tertiary treatment
wide variety of seizure types and epilepsy syndromes
symptomatic localization-related epilepsies

There is a growing interest for the ketogenic diet worldwide as well as for other dietary treatments for epilepsy, such as modified Atkins diet and low glicemic index diet, both providing a daily amount of fat less than the ketogenic diet. Presently, some authors prefer to use the ketogenic diet in infants and younger children, leaving the other two diets for the treatment of older children, adolescents and young adults.

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