Epilepsy Research (2012) 100, 252—257

journal homepage: www.elsevier.com/locate/epilepsyres

Is the ketogenic diet effective in specific epilepsy syndromes?

Srishti Nangia[a,1], Roberto H. Caraballo[b,2], Hoon-Chul Kang[c,3], Douglas R. Nordli[a,*], Ingrid E. Scheffer[d,4]

[a] Children's Memorial Hospital Epilepsy Center, 2300 Children's Plaza, Box 29, Chicago, IL, 60614-3363, United States
[b] Servicio de Neurologia, Hospital de Pediatria Juan P Garrahan, Combate de los Pozos 1881, Buenos Aires CP, 1245, Argentina
[c] Pediatric Neurology, Pediatrics, Pediatric Epilepsy Clinic, Epilepsy Research Institute, Severance Children's Hospital, Yonsei University College of Medicine, 50 Yonsei-Ro, Seodaemun-Gu, Seoul, 120-752, Republic of Korea
[d] Florey Neuroscience Institutes and Departments of Medicine and Paediatrics, The University of Melbourne, Austin Health and Royal Children's Hospital, Melbourne Brain Centre, 245 Burgundy Street, Heidelberg, 3084, Australia

Received 13 October 2011; received in revised form 27 January 2012; accepted 28 January 2012
Available online 15 March 2012

KEYWORDS
Ketogenic diet;
Epilepsy syndromes;
Treatment;
Dravet syndrome,
Epilepsy with myoclonic—atonic seizures, Tuberous sclerosis

Summary Is the ketogenic diet (KD) more effective in certain epilepsy syndromes? The KD has been shown to be effective in treating multiple seizure types and epilepsy syndromes. We review the effectiveness of the KD in Dravet syndrome, epilepsy with myoclonic—atonic seizures, mitochondrial disease, tuberous sclerosis, late infantile and juvenile neuronal ceroid lipofuscinosis, and febrile infection-related epilepsy syndrome. In certain epilepsy syndromes, like epilepsy with myoclonic—atonic seizures, the diet should be considered early in the course of treatment.

Introduction

Is the efficacy of the ketogenic diet (KD) epilepsy syndrome specific? The KD has been shown to be effective in treating multiple seizure types and epilepsy syndromes. A recent randomized trial showed that the diet should be considered a therapeutic option in pharmacoresistant epilepsy, but is the diet particularly effective in specific epilepsy syndromes? (Neal et al., 2008).

Caraballo and colleagues in a recent retrospective, multicenter study assessed the efficacy and the tolerability of the KD for different epilepsy syndromes in 216 patients who were started on the diet between March 1, 1990 and December 31, 2010. 140 (65%) of the initial

* Corresponding author. Tel.: +1 773 883 6159; fax: +1 773 868 8904.
E-mail addresses: snangia@childrensmemorial.org (S. Nangia), rhcaraballo@arnet.com.ar (R.H. Caraballo), hipo0207@yuhs.ac (H.-C. Kang), dnordli@childrensmemorial.org (D.R. Nordli), scheffer@unimelb.edu.au (I.E. Scheffer).
[1] Tel: +1 773 883 6159; fax: + 1 773 868 8904.
[2] Tel: +54 11 9436116; fax: +54 11 9436116.
[3] Tel: +82 2 2228 2075; fax: +82 2 393 9118.
[4] Tel: + 613 9035 7344; fax +613 9496 2291.

0920-1211/$ — see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.eplepsyres.2012.01.015

patients remained on the diet 18 months after KD initiation. Seizure-freedom was achieved in 31/140 (22%) of the patients and 79/140 (56%) experienced a greater than 75% reduction in seizures. Two patients with GLUT-1 deficiency became seizure-free. The KD was most effective in treating patients with epilepsy with myoclonic—atonic seizures, Lennox-Gastaut Syndrome, and West Syndrome. The KD was also found to be of benefit in treating patients with Dravet syndrome, and structural focal epilepsy secondary to malformations of cortical development and tuberous sclerosis. Four children with febrile infection-related epilepsy syndrome (FIRES) and two children with epileptic encephalopathy due to continuous spike and wave during sleep (CSWS) had a significant decrease in seizures (Caraballo et al., 2011a).

We review the effectiveness of the KD in Dravet syndrome, epilepsy with myoclonic—atonic seizures, mitochondrial disease, tuberous sclerosis, late infantile and juvenile neuronal ceroid lipofuscinosis, and FIRES. Evidence of increased efficacy for certain epilepsy syndromes, such as epilepsy with myoclonic—atonic seizures, underpins recommendations that the KD should be considered early in the course of treatment in these disorders.

Dravet syndrome

Dravet syndrome (DS), previously known as severe myoclonic epilepsy of infancy, is a distinctive severe infantile-onset epilepsy syndrome (Dravet et al., 2002). However, the diagnosis of DS in the young infant may be challenging at initial presentation as the diagnosis becomes clearer with the evolution of the electro-clinical picture over time (Caraballo et al., 2005). However, earlier diagnosis of DS is increasingly occurring with increased awareness that an infant presenting with recurrent febrile status epilepticus under 14 months of age is at risk of having this disorder. With the second presentation of febrile status epilepticus, clinicians are appropriately considering *SCN1A* mutational analysis with mutations found in 75% of patients with DS. Between one and 4 years, other seizure types emerge including focal dyscognitive, absence and myoclonic seizures. Development slows after one year and intellectual disability is usual. Early diagnosis is important in order to control seizures which, in turn, may help to minimize cognitive deterioration and improve cognitive outcome.

Between March 1, 1990 and August 31, 2004, 52 patients who met diagnostic criteria for DS were studied by Caraballo and colleagues. Twenty were placed on the KD in conjuction with 1—3 AEDs and followed for a minimum duration of 1 year. Prior to starting the diet, the children had received a mean of 6.4 different AEDs and were taking a mean of 2.2 AEDs when the diet at the time of initiation. Thirteen (65%) of the 20 patients remained on the diet one year after initiation. There was a greater than 75% reduction in seizures in ten (77%) children with 2 (15%) becoming seizure free. In a multicenter experience, Kang and colleagues found similar results in 14 patients with DS (Kang et al., 2005). Caraballo and colleagues currently offer the KD after failing three or four adequate trials of AEDs (including stiripentol) in children with DS (Caraballo, 2011b).

Nabbout and colleagues in a recent prospective study initiated 15 DS patients receiving stiripentol, clobazam, and valproate for more than 6 months on the KD in conjunction with topiramate in two children and levetiracetam in one (Nabbout et al., 2011). The children were older than 3 years of age and had more than eight seizures per month. Generalized, unilateral, or focal clonic seizures were quantified; the patients also had myoclonic and atypical absence seizures. The impact on seizure frequency was assessed at 1 month and every 3 months for the duration of the diet. A Conners scale and a behavioral assessment with the Child Behavior Checklist were administered to each child in order to evaluate the impact of the diet on hyperactivity, inattention, impulsiveness, and aggression. Patients were considered to be responders if there was a >75% decrease in clonic seizure activity on the KD. 67% (10/15 patients) were responders and 1 patient became seizure-free. The diet continued to be effective 3 and 6 months after initiation. 40% of the patients were still responders at 9 months and 33% at 1 year. There was an improvement in hyperactivity and inattention in 10/18 (56%) patients and in impulsivity and aggression in 5/18 (28%) patients. This improvement was also noted in three children whose seizures did not respond to the KD. This study highlights that children with DS can show an improvement in both seizures and behavior with the KD.

Epilepsy with myoclonic—atonic seizures

Previously known as myoclonic—astatic epilepsy (MAE), epilepsy with myoclonic—atonic seizures was first recognized as a discrete epilepsy syndrome by Dr. Hermann Doose in 1970 (Doose et al., 1970). In 1989, the International League Against Epilepsy (ILAE) initially classified MAE as a cryptogenic or symptomatic generalized epilepsy. In 2001, The ILAE Task Force on Classification and Terminology reclassified MAE as an idiopathic generalized epilepsy (Engel, 2001). In 2010, the International League Against Epilepsy revised the classification and renamed MAE as ''epilepsy with myoclonic—atonic seizures'' (Berg et al., 2010).

Children with MAE have onset of a combination of seizure types including myoclonic, myoclonic—atonic, or atonic seizures between the ages of 7 months and 6 years, typically following previously normal development. The children can also have absence, clonic, generalized tonic—clonic seizures, and tonic-vibratory seizures may occur later in the course of the disorder (Commission, 1989; Kelley and Kossoff, 2010).

The KD has been effective in several series of patients with MAE. Oguni et al. (2002) recruited 81 patients with MAE from 3600 patients with childhood epilepsy. In 89% of the patients myoclonic—atonic seizures stopped within 1—3 years but generalized tonic—clonic or clonic seizures persisted. They found that the most effective treatment for the myoclonic—atonic seizures was the KD followed by ACTH and ethosuximide.

Laux et al. (2004) retrospectively studied 28 patients on the KD. Ten patients had MAE, 16 had epileptic encephalopathies including Lennox-Gastaut Syndrome, periodic spasms, and a diffuse encephalopathy with multifocal seizures, and 2 patients had focal epilepsy of unknown cause. Seventy-percent of the patients with MAE had an