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Ketogenic Diet in the Treatment of Seizures Associated With Hypothalamic Hamartomas

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Abstract

Seizures associated with hypothalamic hamartoma (HH) are notoriously intractable to medical therapy, and while surgical resection affords most affected patients with complete or near seizure-freedom, there remains a need to identify alternative treatments. In this retrospective study, we identified six patients from a large cohort of 220 patients with HH who were treated with the ketogenic diet (KD). Four patients had a 50–90% reduction in multiple seizure types (including gelastic, partial-onset and atonic seizures), and two individuals failed to respond. In order to study possible mechanisms, we then performed microelectrode recordings of small neurons in surgically-resected HH tissue slices. Exposure to ketone bodies decreased spontaneous firing in 5 of 7 small HH neurons. These preliminary results suggest that seizures associated with HH may respond favorably to the KD, and that ketone bodies might directly modulate the intrinsic epileptogenicity of HH tissue.

Introduction

Hypothalamic hamartoma (HH) is a rare cause of epilepsy with an estimated prevalence of 1 in 200,000 children and adolescents (Brandberg et al., 2004). Patients with HH exhibit gelastic seizures which are medically intractable, and they often suffer from a severe epileptic encephalopathy (Kerrigan et al., 2005). While surgical intervention can lead to seizure freedom in greater than 50% of patients, there are yet no broadly effective non-invasive treatments for HH patients that could be offered prior to definitive surgery or in the context of post-surgical recrudescence of seizure activity (Kerrigan et al., 2005).

Since 2003, the Barrow Neurological Institute (BNI) has treated more than 150 HH patients, originating from throughout the world, enabling us to develop an extensive clinical database. As HH has been shown to be recalcitrant to antiepileptic drugs, we asked retrospectively whether the ketogenic diet (KD) might demonstrate preliminary efficacy in this unique patient population. Furthermore, using fresh surgically-resected HH tissue specimens, we investigated whether ketone bodies – the hallmark metabolic substrates produced during KD treatment – might affect the spontaneous pacemaker-like firing of small HH neurons that

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have been implicated in a conceptual model of seizure genesis within HH (Fenoglio et al., 2007).

Methods

Following informed consent, patients are enrolled into a prospective, proprietary database under a protocol approved by the St. Joseph's Hospital & Medical Center Institutional Review Board. We identified patients who reported a prior history of KD treatment to control their intractable epilepsy. Multiple factors regarding prior medical and surgical treatment are entered at the time of study enrollment, including a database entry field for prior treatment with KD. Identified patients were contacted by phone or e-mail, and then completed a study-specific questionnaire confirming additional history relating to KD treatment, including age at treatment, duration, efficacy, adverse events, and possible changes in development, behavior or school function. The reasons for discontinuing the diet were also queried.

Electrophysiological methods were modified from Kim et al. (2008). Briefly, HH tissue samples were collected from 4 HH patients (without a prior history of KD treatment). HH slices (300 μ m) were cut using a standard vibratome. Each slice was loaded into a recording chamber attached to an Axioskop FS2 microscope and infused with artificial cerebrospinal fluid (aCSF) warmed to 34 °C. For gramicidin (20 μ g/ml) perforated patch recordings, electrodes were filled with a solution containing in mM: 135 KCl 10 HEPES, 0.5 CaCl₂, 2 MgCl₂, and 5 EGTA, pH 7.25. A tight-seal configuration achieved in small HH neurons (diameter, 10–16 μ m) under infrared-differential interference contrast (IR-DIC) optical illumination. Data were acquired using a Multiclamp 700A amplifier (Axon Instruments, Union City, CA, USA), and were digitized/sampled at 50 μ s intervals (Digidata 1322 A, pClamp V9.2, Axon Instruments). All chemicals used in this study were acquired from Sigma-Aldrich (St. Louis, MO, USA).

Results

Ten patients (4.5%) of 222 patients in the HH database had been treated with the KD. We were unable to contact 4 of 10 patients to complete the KD-specific questionnaire. The remaining six patients agreed to participate in this retrospective study. All patients had attempted the diet prior to evaluation at Barrow Neurological Institute and were started on the diet due to intractability to antiepileptic medications. Five of the six patients ultimately underwent resective HH surgery. As seen in Table 1, the median age at which the KD was initiated was 12 years. While patients remained on the diet for a median of 9 months, one patient in whom the KD was particularly effective has continued the diet for approximately 14 years. The traditional ketogenic diet had been attempted in each patient with 4 patients recalling achieving ketosis. 4 of 6 had at least a 50% improvement in total seizure frequency. Of the four patients who responded to the KD, two had a reduction in multiple seizure types (including complex partial, simple partial and atonic seizures). No beneficial effects were seen in 2 patients.

Two patients experienced subjective improvement in their school performance while on the diet. Despite experiencing minimal side-effects, the KD was discontinued in 3 out of 6 patients due to either weight loss (8–10 pounds for those two patients) or elevated cholesterol levels. Three patients found the diet too restrictive for their amount of clinical improvement.

Under gramicidin perforated-patch recording conditions, a ketone cocktail consisting of 1mM β -hydroxybutyric acid (BHB) and 1 mM acetoacetate (ACA) completely suppressed

spontaneous firing in 2 of 7 small HH neurons, reduced the spontaneous firing in 3 out of 7 neurons, but did not affect the firing frequency in 2 of 7 cells (Fig. 1). Figure 1B demonstrates spontaneous firing resumed following a five minute washout period in the absence of ketone bodies. The test concentrations of BHB and ACA were chosen because prior studies have indicated that brain ketone levels may reach 0.5–1.6 mM after KD treatment (Kim & Rho, 2008).

Discussion

Seizures associated with hypothalamic hamartomas are generally refractory to anticonvulsant medications and are in part responsible for the devastating encephalopathy seen in many patients. Our study reviewed the utility of the ketogenic diet in this population. Many patients responded favorably to the diet with two-thirds of subjects reporting a reduction in seizures, with one patient having such a significant and sustained response that they declined surgical intervention with 14 years of follow-up.

The use of the ketogenic diet in the treatment of epilepsy associated with HH has been reported in a single patient by Palmini and colleagues, describing a 12 year-old girl with progressive deterioration after her second surgical resection. She was noted to have “obtained some improvement” after institution of the KD, but further details were not provided (Palmini et al, 2003). The present study – despite the small number of patients – adds to the available literature and supports the use of the KD as an alternative therapeutic option to AED therapy or surgical intervention. This may be particularly useful for patients in developing countries where management options may be limited (Papayannis et al., 2008). While surgical management offers the best chance for seizure freedom, KD might be considered after at least one AED trial has failed or while awaiting consideration for surgical intervention.

Our recent studies have demonstrated the possibility that the network activity between small HH neurons and large HH neurons in HH may play a critical role in seizure genesis (Fenoglio et al., 2007). Small HH neurons – which represent over 80% of all HH neurons – have been implicated as interneurons that may trigger abnormal network discharge (Fenoglio et al., 2007). In this study, our preliminary cellular electrophysiological observations – demonstrating a ketone-induced reduction in spontaneous firing of small HH neurons – are at first glance intriguing. While the mechanism of this attenuation of cellular firing by ketones bodies remains unclear, our data suggest that ketones might directly modulate the intrinsic epileptogenicity of HH tissue, possibly via an antioxidant action (Kim et al., 2007), in a manner that fits with our conceptual model of seizure genesis (Fenoglio et al., 2007).

There are significant limitations to our study, including a likely referral bias and recall bias. As a program specializing in surgical intervention, it is less likely that patients with good seizure control on either the KD or medications would be included in our HH database. This study is retrospective and uncontrolled, and depends, in large part, upon the ability of patients and families to recall their treatment history. The families appeared to easily recall their experience with the diet as it stood out among other treatments, but recall bias is clearly a significant limitation. Notwithstanding these limitations, our study nevertheless suggests that the KD may be an effective treatment for seizures associated with HH. Larger prospective (ideally multi-center) trials are necessary to establish the KD as a validated therapeutic option for HH patients.

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Figure 1.

Effect of ketones on the spontaneous firing of small HH neurons. (A) Representative tracing depicting the firing pattern of small HH neurons. Small HH neurons exhibited spontaneous rhythmic pacemaker-like neuronal activity. (B) In 2 out of 7 HH neurons, HH-induced spontaneous activity was fully suppressed by a cocktail of ketones (BHB + ACA, each 1 mM). Two vertical bars in the membrane trace indicate a 5 min washout period. (C) The ketone cocktail reduced, but did not completely abolish, the firing frequency in 3 of 7 small HH neurons. (D) No change of spontaneous firing occurred in 2 out of 7 HH neurons exposed to the ketone cocktail. BHB = beta-hydroxybutyrate, ACA = acetoacetate

Table 1

Summary of the clinical features of the HH patient population on the ketogenic diet

Patient Number	Age At Starting The KD (years)	Duration Of Dietary Treatment (months)	Clinical Effectiveness	Seizure Types For Which The KD Was Effective	Improvement in other areas	Reason for discontinuation
1	12	6	50–90% reduction	Gelastic, atonic, CPS	School functioning	SE (weight loss), TR
2	14	1	None		None	IE, TR
3	19	48	50–90% reduction	CPS	None	SE (high cholesterol), TR
4	12	168 (to present)	> 90% reduction	SPS	Behavior and school functioning	
5	10	6	50–90% reduction	Gelastic, atonic	None	Became IE, SE (weight loss)
6	4	4	None		None	IE

Abbreviations: CPS – complex partial seizures; SPS – simple partial seizures; SE – side effects; TR – Too restrictive; IE – ineffective.