



SHORT COMMUNICATION

A pilot study of the modified Atkins diet for Sturge–Weber syndrome

Eric H. Kossoff^{a,b,c,*}, Jennifer L. Borsage^{a,b,c}, Anne M. Comi^{a,b,c}

^a The John M. Freeman Pediatric Epilepsy Center, Department of Neurology, Johns Hopkins Medical Institutions, Baltimore, MD, United States

^b The John M. Freeman Pediatric Epilepsy Center, Department of Pediatrics, Johns Hopkins Medical Institutions, Baltimore, MD, United States

^c The Hunter Nelson Kennedy Krieger Sturge Weber Center, Kennedy Krieger Institute, Baltimore, MD, United States

Received 13 July 2010; received in revised form 22 August 2010; accepted 13 September 2010

KEYWORDS

Ketogenic;
Atkins;
Sturge–Weber;
Children;
Ketosis;
Epilepsy

Summary The modified Atkins diet (MAD) is a dietary treatment for epilepsy which does not restrict fluids or calories. This theoretically makes the MAD safer than the ketogenic diet for children with Sturge–Weber syndrome (SWS). Five children aged 4–18 years with SWS and at least monthly intractable seizures were started prospectively on the MAD for 6 months. All children had urinary ketosis and seizure improvement, including 3 with >50% seizure reduction. © 2010 Published by Elsevier B.V.

Introduction

Sturge–Weber syndrome (SWS) is a sporadic condition presenting typically in infancy with seizures in 70–90% (Arzimanoglou and Aicardi, 1992; Sujansky and Conradi, 1995; Kossoff et al., 2009a,b). It is often associated with a facial port-wine birthmark (aka port-wine stain), glaucoma, seizures, stroke-like events, and typically unilateral leptomeningeal angioma. Medications are effective in controlling seizures for approximately 50%, but if not effective

then surgery (hemispherectomy or lobectomy) is advocated (Arzimanoglou and Aicardi, 1992; Sujansky and Conradi, 1995; Kossoff et al., 2002). However, there are some children with SWS that are either bilateral on neuroimaging or parents do not wish a potential functional deficit surgery might cause.

For these children, the use of the ketogenic diet may be advantageous, as it is for other children with intractable epilepsy. However, the ketogenic diet is often traditionally started with a brief fasting period as well as fluid and caloric restriction (Kossoff et al., 2009b). It can also lead to dyslipidemia. For these reasons, the ketogenic diet may be discouraged as an option for children with SWS due to risk of exacerbating stroke-like events. In addition, children who are surgical candidates due to a focal lesion(s), such as many with SWS, are less likely to become permanently seizure-free (Stainman et al., 2007). To our knowledge, there has been only one case of SWS with myoclonic–astatic seizures

* Corresponding author at: Suite 2158 - 200 North Wolfe Street, David M. Rubenstein Child Health Building, The John M. Freeman Pediatric Epilepsy Center, The Johns Hopkins Hospital, Baltimore, MD 21287, United States. Tel.: +1 410 955 4259; fax: +1 410 614 2297.

E-mail address: ekossoff@jhmi.edu (E.H. Kossoff).

treated with the ketogenic diet in the literature (Petit et al., 2008), and according to the Sturge–Weber Foundation, no child treated in their database (personal communication by Ball).

The modified Atkins diet (MAD) was designed as a less restrictive, outpatient-initiated dietary alternative to the ketogenic diet (Kossoff et al., 2006). It creates a ketotic state by providing high fat and low carbohydrate foods, but unlike the KD, it does not restrict protein, calories, or fluid, nor is there an admission or fasting period. We hypothesized that the MAD would be effective for children with SWS without any increased risk of dehydration or stroke-like events.

Methods

An open-label, non-blinded, prospective study design of 5 children was used. Inclusion criteria included age 2–18 years, radiographically-documented SWS, prior use of at least 2 anticonvulsants, and at least monthly, countable seizures. No child with prior use of the MAD for over 1 week was enrolled, nor were patients significantly underweight or with known hypercholesterolemia, kidney dysfunction, or heart disease. SWS scores were documented at study onset (Kelley et al., 2005).

The MAD basic protocol was used, however families were additionally counseled to encourage fluids throughout the day and carbohydrates were limited to 20 g per day in order to make the MAD less of a metabolic strain with less risk of initial over-ketosis (Kossoff et al., 2006; Kossoff et al., 2007). Anticonvulsant medications were not changed throughout the study.

Children were seen at baseline, 3, and 6 months, with food records and laboratory studies requested at each visit. Ketones were measured semiweekly and weight weekly. The study was approved by the Johns Hopkins Institutional Review Board and listed at www.clinicaltrials.gov (NCT00639730). Diet composition was analyzed using Food Processor for Windows™, EHSA Research, Salem, Oregon. Two-tailed *t* test was used to compare means. The significance level for all tests was $p=0.05$.

Results

Subject demographics

Five children, 3 male, were treated from October 2006 to April 2010 and all but one (Patient 3) completed all three study visits (Table 1). The age range was 4–18 years and seizures were occurring median 30 times per month (range: 4–100 per month) despite a median of 4 anticonvulsants tried (past plus current; range: 2–5). Seizures were complex partial in 4, atonic in 1. No child had prior dietary therapy nor had surgical resection of their angioma. Two (Patients 1 and 5) had prior stroke-like events, and all were on daily aspirin (range 81–325 mg/day).

Seizure outcome

At the 3-month visit, 3 (60%) had >50% reported seizure improvement with the other 2 having 25% seizure reduction (Table 2). Patient 3 discontinued the MAD after the 3-month visit and had a brief period of seizure worsening as a result according to parents, but they chose not to restart the MAD. At 6 months, Patients 1, 2, and 4 had 70–90% seizure reduc-

Table 1 Baseline patient demographics of children treated with the MAD for SWS.

Patient	Age at MAD onset (years)	Gender	Angioma location	SWS score	Number prior AEDs	Current AEDs	Baseline seizure frequency (per month)	Seizure type
1	4	Male	Left	11	4	Levetiracetam, topiramate	5	Complex partial
2	5	Female	Right	7	4	Carbamazepine, levetiracetam	8	Complex partial
3	10	Male	Right	5	5	Lamotrigine, levetiracetam	60	Atonic
4	13	Male	Right	5	2	Oxcarbazepine, topiramate	8	Complex partial
5	18	Female	Bilateral	10	3	Acetazolamide, carbamazepine, oxcarbazepine	40	Complex partial

Table 2 Outcomes of children treated with the MAD for SWS.

Patient	Baseline seizure frequency (per month)	3-Month seizure frequency (per month)	3-Month seizure reduction	6-Month seizure reduction	Urinary ketosis	Ketogenic ratio (6-month) ^a	Weight change (kg)	Diet duration (months)	Peak total cholesterol (mg/dl)
1	5	0	100%	90%	Moderate	2.3:1	+1.5	7 ^b	238
2	8	1	90%	100%	High	1.1:1	+0.7	13 ^b	206
3	60	45	25%	N/A	Moderate	N/A	+1.0	3	130
4	8	4	50%	70%	High	N/A	+0.9	9	155
5	40	30	25%	25%	Moderate	1.5:1	−3.6	12	268

N/A, not available.
^a Ketogenic ratio = fat:carbohydrate and protein (g).
^b Still on the MAD at this time.

tion and Patient 5 had 25% reduction with less severity. Two children (Patients 1 and 2) had 2–3 month periods of seizure freedom, which was unusual for them prior to the study. All of these 4 patients chose to continue the MAD after the study ended, and the two youngest subjects (Patients 1 and 2) remain on the MAD to date.

The two youngest children (ages 4 and 5 years) were also those with the greatest responses (>90% seizure reduction). The average ages of these children were slightly lower than the other 3, $p=0.054$. Gender, hemisphere involved, or number of anticonvulsants attempted did not correlate with >90% seizure reduction.

Diet analysis and ketosis

Three families provided 3-day food records at study visits for analysis. The MAD was similar in food record analysis to children treated with the MAD for other epilepsies (Kossoff et al., 2007). The mean ketogenic ratio after 6 months was 1.6:1 with 15.2 g of carbohydrates per day and 121.3 g of fat per day. Urinary ketosis was achieved in all children, and was moderate (40 mg/dl) in Patients 1, 3, and 5, and high (80–160 mg/dl) in Patients 2 and 4. There was no correlation of ketogenic ratio or ketosis with likelihood of a >90% seizure reduction.

Adverse effects

Over the 6-month study period, the median change in weight was 0.9 kg (range: −3.6 to 1.5 kg). Two families reported restrictiveness ($n=2$). No child had increased seizures compared to baseline during the study period. The median peak total cholesterol was 206 mg/dl (range: 130–268 mg/dl).

Only one child had a stroke-like event during the study period (Patient 1). This event of right arm weakness occurred during the final (fifth) month of the study. Prior to starting the study, he had 3 stroke-like events, and he was on aspirin treatment throughout the study period (Maria et al., 1998). This child had a brief complex partial seizure during this month, but it occurred 1 week after the stroke-like event had started. Parents did not attribute this to the MAD and as seizures were >90% improved they chose to continue the MAD after the 6-month study visit.

Discussion

This pilot study demonstrates that the MAD can be successfully used for children with SWS. For those with uncontrolled seizures it appears to be a reasonable option. Children who were younger had slightly better seizure reduction, although with this small patient population it did not reach statistical significance.

The MAD was well-tolerated without obvious increased risk of stroke-like events, dehydration, or significant dyslipidemia. It is very possible that the traditional ketogenic diet would be equally well-tolerated as the MAD was if it was started without a fasting period (Bergqvist et al., 2005) or fluid restriction. It is also theoretically possible that switching these children to the ketogenic diet after the MAD might

have led to additional seizure control or even seizure freedom.

One additional challenge of this study was the low recruitment, with nearly 4 years required to enroll these 5 subjects, despite the historically high likelihood of intractability in SWS (Arzimanoglou and Aicardi, 1992). Recent evidence from our center suggests that children with SWS have a sporadic pattern of seizures, with 45% having at least 6 months between seizure clusters (Kossoff et al., 2009a). Many children evaluated at our SWS center failed to qualify for the study as they were not having at least monthly seizures. In this regard, the MAD may require prolonged periods of time for many children with SWS in order to judge efficacy.

Acknowledgements

This study was supported by a grant from the Vascular Birthmarks Foundation, who had no influence over data collection, analysis, or the writing of the manuscript. Dr. Kossoff has received consultant fees from Atkins Nutritionals, Inc.

References

- Arzimanoglou, A., Aicardi, J., 1992. The epilepsy of Sturge–Weber syndrome: clinical features and treatment in 23 patients. *Acta Neurol. Scand. Suppl.* 140, 18–22.
- Bergqvist, A.G., Schall, J.I., Gallagher, P.R., Cnaan, A., Stallings, V.A., 2005. Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. *Epilepsia* 46, 1810–1819.
- Kelley, T.M., Hatfield, L.A., Lin, D.D., Comi, A.M., 2005. Quantitative analysis of cerebral cortical atrophy and correlation with clinical severity in unilateral Sturge–Weber syndrome. *J. Child Neurol.* 20, 867–870.
- Kossoff, E.H., Buck, C., Freeman, J.M., 2002. Outcomes of 32 hemispherectomies for Sturge–Weber syndrome worldwide. *Neurology* 59, 1735–1738.
- Kossoff, E.H., McGrogan, J.R., Bluml, R.M., Pillas, D.J., Rubenstein, J.E., Vining, E.P., 2006. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia* 47, 421–424.
- Kossoff, E.H., Turner, Z., Bluml, R.M., Pyzik, P.L., Vining, E.P.G., 2007. A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet. *Epilepsy Behav.* 10, 432–436.
- Kossoff, E.H., Ferenc, L., Comi, A.M., 2009a. An infantile-onset, severe, yet sporadic seizure pattern is common in Sturge–Weber syndrome. *Epilepsia* 50, 2154–2157.
- Kossoff, E.H., Zupec-Kania, B.A., Amark, P.E., Ballaban-Gil, K.R., Bergqvist, A.C.G., Blackford, R., Buchhalter, J.R., Caraballo, R.H., Cross, J.H., Dahlin, M.G., Donner, E.J., Jehle, R.S., Klepper, J., Kim, H.D., Liu, Y.M.C., Nation, J., Nordli Jr., D.R., Pfeifer, H.H., Rho, J.M., Stafstrom, C.E., Thiele, E.A., Turner, Z., Veggjotti, P., Vining, E.P.G., Wheless, J.W., Wirrell, E.C., Charlie Foundation, and the Practice Committee of the Child Neurology Society, 2009b. Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group. *Epilepsia* 50, 304–317.
- Maria, B.L., Neufeld, J.A., Rosainz, L.C., Drane, W.E., Quisling, R.G., Ben-David, K., Hamed, L.M., 1998. Central nervous system structure and function in Sturge–Weber syndrome: evidence of neurologic and radiologic progression. *J. Child Neurol.* 13, 606–618.
- Petit, F., Auvin, S., Lamblin, M.D., Vallee, L., 2008. Myoclonic astatic seizures in a child with Sturge Weber syndrome. *Rev. Neurol. (French)* 164, 953–956.
- Stainman, R.S., Turner, Z., Rubenstein, J.E., Kossoff, E.H., 2007. Decreased relative efficacy of the ketogenic diet for children with surgically approachable epilepsy. *Seizure* 16, 615–619.
- Sujansky, E., Conradi, S., 1995. Sturge–Weber syndrome: age of onset of seizures and glaucoma and the prognosis for affected children. *J. Child Neurol.* 10, 49–58.