Epilepsia, 51(6):1086–1089, 2010
doi: 10.1111/j.1528-1167.2010.02543.x

BRIEF COMMUNICATION

Type 1 diabetes and epilepsy: Efficacy and safety of the ketogenic diet

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Summary

Diabetes type 1 seems to be more prevalent in epilepsy, and low-carbohydrate diets improve glycemic control in diabetes type 2, but data on the use of the classic ketogenic diet (KD) in epilepsy and diabetes are scarce. We present 15 months of follow-up of a 3 years and 6 months old girl with diabetes type 1 (on the KD), right-sided hemiparesis, and focal epilepsy due to a malformation of cortical development. Although epileptiform activity on electroencephalography (EEG) persisted (especially during sleep), clinically overt seizures have not been reported since the KD. An improved activity level and significant developmental achievements were noticed. Glycosylated hemoglobin (HbA1c) levels improved, and glycemic control was excellent, without severe side effects. Our experience indicates that diabetes does not preclude the use of the KD.

KEY WORDS: Ketogenic diet, Epilepsy, Type 1 diabetes, Malformation of cortical development.

Epileptic (primarily hypoglycemic) seizures are common in children with diabetes mellitus type 1, and electroencephalography (EEG) abnormalities are well recognized (O'Connell et al., 2008). Studies have also reported an increased occurrence of diabetes in patients with epilepsy, especially with idiopathic generalized epilepsy (IGE) (McCorry et al., 2006).

However, with the exception of a case report on a child with pyruvate dehydrogenase deficiency (PDH) and diabetes on the ketogenic diet (KD) (Henwood et al., 2006), no data exist to date concerning the efficacy and tolerability of the KD in patients with both epilepsy and diabetes.

However, studies on a low-carbohydrate KD in patients with diabetes type 2 showed beneficial effects in reducing body weight, achieving glycemic control, low-density lipoprotein (LDL) cholesterol, triglycerides (Trig), total cholesterol (chol), and urea (Dashti et al., 2007; Kirk et al., 2008).

We report the long-term experience with the KD in a child with epilepsy and diabetes type 1.

Accepted January 22, 2010; Early View publication March 19, 2010.
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Case Report

This girl was born in March 2004 to healthy nonconsanguineous Austrian parents. Family history was unremarkable for diabetes and epilepsy. Ultrasound detected placenta detachment in the second month of pregnancy and intraventricular midline cysts 3 weeks before term. Delivery was spontaneous at term; no complications were reported. At 9 months, right-sided spastic hemiparesis was diagnosed. At the same age tonic seizures were noticed during sleep. The girl's subsequent global development was delayed. At 18 months of age she presented with diabetic ketoacidosis [pH 7.25, blood glucose 702 mg/dl, glutamic acid decarboxylase (GAD) Ab 24.56 U/L (normal <1 U/L), insulin autoantibodies (IAA) 8.0 U/L (normal <1 U/L), autoantibodies against tyrosin phosphatase (IA2) Ab 8.9 U/L (normal <0.75 U/L)] and diabetes type 1 was diagnosed. After metabolic stabilization, continuous subcutaneous insulin infusion (CSII) and a standard low-fat high-carbohydrate diet was started. Diabetes education was provided to the parents.

Because of an increase in seizure frequency (1–2 seizures per week) the patient was seen at the epilepsy department in September 2006 at 30 months of age:

Clinical neurologic examination showed a right-sided spastic hemiparesis, dysdiadochokinesia, inability to stand on the right foot, and a better hand function showing a median pincer grasp but almost no manipulation of objects.

Magnetic resonance imaging (MRI) (Fig. 1) showed a widespread malformation of the left hemisphere. Signal changes and calcifications were also seen in the hippocampus and anterior lobe of the right hemisphere. Both cerebral peduncles were small, probably due to Wallerian degeneration. The widespread anomalies, especially the temporopolar hyperintensities and calcification suggest an intrauterine infection; cytomegalovirus (CMV), however, was not identified in the serologic examination.

Diffusion tensor imaging and tractography showed white matter (WM) asymmetry with reduction of anteroposterior (green) running trajectories in the dysplastic left-sided temporal lobe. Areas of abnormal diffusion anisotropy reflecting abnormal myelination were found in the nondysmorphic hemisphere as well.

[18]Fluorodeoxyglucose positron emission tomography (FDG-PET) displayed diffuse hypometabolism of the entire left hemisphere, reduced volume, and e vacuo expansion of the left lateral ventricle, and reduced enhancement of the right mesiotemporal region. EEG-video monitoring showed interictal spike activity in electrodes C3 and P3, spreading to F3 and O1; clinically overt seizures were not recorded.

Antiepileptic drug (AED) management was started at the age of 2 years and 7 months with carbamazepine, which was stopped after 1 month because of thrombocytopenia and dizziness, by that time arriving at a daily dosage of only 14.5 mg/kg body weight. The subsequent therapy with oxcarbazepine, was stopped by the parents autonomously after 4 months (despite 1 month without overt seizures), because of fear of side effects (daily dosage 29.45 mg/kg body weight). They also refused to perform further presurgical evaluation, but agreed to try the KD as an alternative treatment.

To determine seizure frequency, video-EEG monitoring was performed before starting the KD and revealed that 1–2 seizures per week occurred with a mild tonic extension of the right hand and a rhythmic pattern in the left centrotemporal region; the mother reported only that the girl was anxious and could not bend her hand. Otherwise she did not observe clinically overt seizures.

Before starting the KD, basal insulin requirement on CSII was estimated, and then the diet was initiated at 3 years and 6 months without fasting. We followed the John Hopkins' protocol without fluid restriction (Freeman et al., 1998): total calories were approximately 1200 kcal; fluid intake was 800–1,000 ml/day; and fats, carbohydrates, and proteins were adjusted to a 3:1 ratio, and insulin requirement was reduced (see Table 1). To prevent a shortage of vitamins and calcium, these were supplemented. Within 2 days the girl became strongly ketotic (urine ketones > 4+, blood β-hydroxybutyrate >6.5 mmol/L, base excess (BE) −7.2 pH was within the range). Because strong ketosis persisted we lowered the ratio to 2.5:1 and the patient was dismissed after 13 days with a 1,200 kcal diet with 18 g proteins per day and 27.2 g carbohydrates per day.

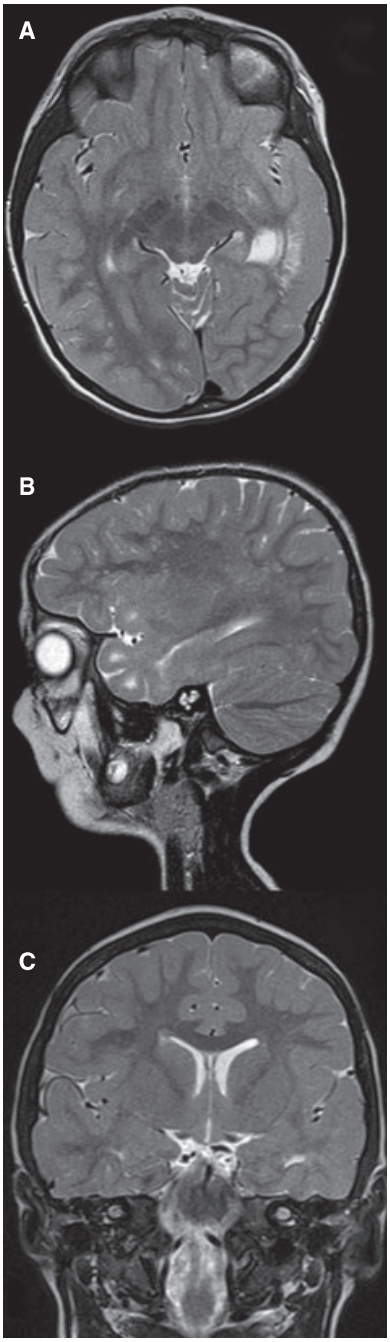

Figure 1.
Axial (**A**), sagittal (**B**), and coronal (**C**), T_2-weighted magnetic resonance (MR) images (1.5 Tesla) at the age of 4 years show a smaller left hemisphere with polymicrogyric and pachygyric aspects, predominantly in the temporal lobe. Abnormal hyperintense signal characteristics of the subcortical white matter are seen in both hemispheres as result of abnormal myelination (B). Note the abnormally high signal intensity of the right temporal pole, which has been described in various white matter disorders, in particular in cytomegalovirus (CMV)–associated white matter pathology.

Table 1. Clinical and laboratory data before and under the KD

Time (months)	−6	−3	0	+3	+6	+10	+13
HbA1c rel %	6.6	7.0	7.9	6.6	6.7	6.8	6.2
Insulin International units (IU) (kg)	0.76	0.76	0.38	0.41	0.45	0.45	0.45
Fluid intake (ml)	–	–	1,000	1,000	1,000	1,250	1,300
Carbohydrates (g/kg)	10.5	8.7	2.26	1.93	1.90	1.90	1.90
Urine ketone	0	0	3+	3+	3+	3+	3+
Hemoglobin (g/dl) 11.5–15.0	–	–	12.4	13.3	–	12.5	12.5
Calcium^{2+} (mmol/L) 2.25–3.25	–	–	2.41	2.39	–	2.35	2.25
p(otential) of h(ydrogen) 17.37–7.42	–	–	7.34	7.41	–	–	7.36
Carnitine (μmol/l) 7–70	–	–	84	–	–	–	55.7
Triglycerides (mg/dl) 35–150	–	–	44	224	–	–	175
Cholesterol (mg/dl) 100–200	–	–	210	166	–	–	182
High-density lipoprotein (mg/dl) >35	–	–	77	–	–	–	124
Low-density lipoprotein (mg/dl) <127	–	–	41	–	–	–	106
Height (cm)	89.2	91.7	95	95	97.5	98.3	99
Weight (kg)	12.0	12.5	12	13.5	14.5	14.5	14.5
Partial pressure of carbon dioxide (mHg) 32–47	–	–	34	40	–	–	21.3
Plasma glucose	203	184	59	130	140	98	192
Seizures (week)	1–2	1–2	1–2	Not recorded	Not observed	Subclinical seizures recorded	Not observed

Immediately after initiation of the KD, no more events of tonic stiffening of the upper extremities were reported. A video-EEG after 4 months did not reveal any clinical or subclinical rhythmic patterns. Blood count, blood gas analysis serum electrolytes, and metabolic profile were normal. Clinical and laboratory data are displayed in Table 1. Height and weight gain was normal.

After 2 months we gradually increased the diet to 1,350 kcal and 20 g proteins per day, but because of reduced appetite and low acceptance of the fat, calories were lowered again at 3 months after initiation to 1200 kcal and proteins remained 20 g/day.

Developmental gain in language and motor skills was also observed, hand function improved showing a superior pincer grasp and manipulation on both sides, and standing on one foot was now possible for both sides. However, long-term video-EEG after 10 months (July 2008) showed continuous epileptiform activity over the left hemisphere and four nocturnal subclinical seizures with onset in the left frontocentral electrodes; however, physiologic sleep stages were preserved.

During the 15-month observation period, no severe hypoglycemia or ketoacidosis occurred, and metabolic control with glycosylated hemoglobin (HbA1c) (6.2%) was within the target range according to the International Society for Pediatric and Adolescent Diabetes guidelines (Rewers et al., 2007). Moreover, no deficit in selenium and zinc levels was present (selenium 55.6 μg/L, normal range 32–84 μg/L; Zinc 0.77 mg/L, normal range 0.64–1.10 mg/L), and uric acids were normal. Only one inpatient treatment was necessary because of tonsillitis.

After 15 months the child refused ketogenic meals and the family interrupted the diet.

No clinically overt seizures were reported, but subclinical patterns in EEG remained.

Discussion

The use of the classic KD is well established in various forms of drug-resistant epilepsy. In children older than 2 years the efficacy has been demonstrated, and regardless of seizure type and etiology, patients younger than 8 years (range from 4 months to 8 years) were more likely to achieve a greater than 50% improvement in seizure control, and seemed to stay longer on the diet than older patients (range from 8 to 16 years) (Freeman et al., 1998).

A significant reduction of interictal epileptiform discharges after 3 months on the KD has been reported (Hallbook et al., 2007), as well as beneficial effects on cognition and behavior (Pulsifer et al., 2001). In our case, the KD stopped all overt seizures, but did not influence subclin-

ical EEG activity. Subsequent development, however, improved significantly.

Carbohydrate restricted diets—comparable to the Atkins diet—have been used to reduce obesity and to improve blood control and insulin sensitivity in adults with diabetes type 2 (Dashti et al., 2007; Kirk et al., 2008). Lower insulin needs, fasting blood glucose, and HbA1c have been reported. However, diabetes type 2 does not tend to show ketoacidosis.

Despite the reported association between diabetes type 1 and certain epilepsy syndromes, for example, a fourfold increase in patients with IGE (McCorry et al., 2006), there are no studies evaluating the efficacy and safety of the classic KD in patients with both diabetes type 1 and epilepsy syndromes. There is only one report (Nielsen et al., 2005) about adult patients with diabetes type 1 without epilepsy on a low carbohydrate diet because of fluctuating blood glucose levels. After 12 months the rate of severe hypoglycemia was significantly lower despite a decrease of HbA1c from 7.5–6.4%. This improvement occurred while diabetes medication was successfully reduced.

Only in one case with PDH deficiency and epilepsy treated with the KD (Henwood et al., 2006), the child developed diabetes with ketoacidosis and KD was, therefore, interrupted. As her mental status deteriorated without the KD, she was again put on the diet, ameliorated, and continued with the KD for another 28 months together with insulin treatment, resulting in excellent glycemic control and significant developmental gains.

Hypoglycemia and ketoacidosis as well as serious infections are critical situations in individuals with diabetes type 1 and must be considered when using the KD in these patients. In our case no growth retardation or other side effects were observed, and electrocardiography (ECG) was normal. Only one episode necessitating intravenous antibiotic treatment occurred. Because of our experience the KD can be used without negative effects on metabolic control in children with epilepsy and diabetes type 1.

Acknowledgments

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

The authors indicate that they have no financial relationships relevant to this manuscript to disclose.

References

Dashti HM, Mathew TC, Khadada M, Al-Mousawi M, Talib H, Asfar SK, Behbahani AI, Al-Zaid NS. (2007) Beneficial effects of ketogenic diet in obese diabetic subjects. *Mol Cell Biochem* 302:249–256.

Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. (1998) The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. *Pediatrics* 102:1358–1363.

Hallbook T, Kohler S, Rosen I, Lundgren J. (2007) Effects of ketogenic diet on epileptiform activity in children with therapy resistant epilepsy. *Epilepsy Res* 77:134–140.

Henwood MJ, Thornton PS, Preis CM, Chee C, Grimberg A. (2006) Reconciling diabetes management and the ketogenic diet in a child with pyruvate dehydrogenase deficiency. *J Child Neurol* 21:436–439.

Kirk JK, Graves DE, Craven TE, Lipkin EW, Austin M, Margolis KL. (2008) Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. *J Am Diet Assoc* 108:91–100.

McCorry D, Nicolson A, Smith D, Marson A, Feltbower RG, Chadwick DW. (2006) An association between type 1 diabetes and idiopathic generalized epilepsy. *Ann Neurol* 59:204–206.

Nielsen JV, Jonsson E, Ivarsson A. (2005) A low carbohydrate diet in type 1 diabetes: clinical experience–a brief report. *Ups J Med Sci* 110:267–273.

O'Connell MA, Harvey AS, Mackay MT, Cameron FJ. (2008) Does epilepsy occur more frequently in children with Type 1 diabetes? *J Paediatr Child Health* 44:586–589.

Pulsifer MB, Gordon JM, Brandt J, Vining EP, Freeman JM. (2001) Effects of ketogenic diet on development and behavior: preliminary report of a prospective study. *Dev Med Child Neurol* 43:301–306.

Rewers M, Pihoker C, Donaghue K, Hanas R, Swift P, Klingensmith GJ. (2007) Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr Diabetes* 8:408–418.