Epilepsia, 52(7):e54–e57, 2011
doi: 10.1111/j.1528-1167.2011.03107.x

BRIEF COMMUNICATION

Ketogenic diet also benefits Dravet syndrome patients receiving stiripentol: A prospective pilot study

*†‡Rima Nabbout, *Cristiana Copioli, *Mathilde Chipaux, *Nicole Chemaly, *Isabelle Desguerre, *†‡Olivier Dulac, and *†‡Catherine Chiron

*APHP, Department of Neuropediatrics, National Referral Center for Rare Epilepsies, Necker-Enfants Malades Hospital, Paris, France; †Inserm, U663, Paris, France; and ‡Paris Descartes University, Paris, France

Summary

We aimed to test the efficacy of ketogenic diet (KD) in patients with Dravet syndrome (DS) not satisfactorily controlled by antiepileptic drugs (AEDs). We included prospectively 15 DS patients aged >3 years with partial response to AEDs including stiripentol. All patients had a seizure diary and clinical examination with Conners and Achenbach scales before KD, at 1 month following onset and every 3 months thereafter. At 1 month, 10 patients (66%) had a decrease of seizure frequency ≥75%. Efficacy was maintained in eight responders at 3 and 6 months and in six responders at 9 months. Five patients (33%) remained on KD over 12 months, and one was seizure-free. In addition to efficacy on seizure frequency, KD was beneficial on behavior disturbances including hyperactivity. This effect was reported in all responders and in a few nonresponders. KD might have a double effect, on seizure control and on hyperactivity and behavior disturbances in patients with DS.

KEY WORDS: Dravet syndrome, Ketogenic diet, Stiripentol, Hyperactivity, Behavioral disturbances.

Patients with Dravet syndrome (DS) present with seizures in the first year of life, usually in a febrile context. Within a few months they develop intractable epilepsy. The combination of stiripentol, clobazam, and valproate significantly reduces seizure frequency and duration (Chiron et al., 2000). This therapy is accepted today as the gold standard for this syndrome. Some efficacy of topiramate and levetiracetam was also reported (Nieto-Barrera et al., 2000; Striano et al., 2007). Despite these therapeutic improvements, patient with DS often fail to become seizure-free, particularly in infancy and early childhood. In addition to pharmacoresistant seizures, patients with DS present usually with hyperactivity, behavioral disturbances, and poor relational capacities (Wolff et al., 2006). These aspects have a major impact on the quality of life and are a clue complaint of the families and rehabilitation teams (Nolan et al., 2008). Efficacy of the ketogenic diet (KD) was reported in two retrospective series of patients with DS and in a few DS patients included in a controlled randomized study (Neal et al., 2009), but none following the administration of stiripentol (STP) (Caraballo et al., 2005; Kang et al., 2005). Our aim was to test prospectively the efficacy of KD in DS patients unsatisfactorially controlled by antiepileptic drugs (AEDs) (stiripentol, clobazam, and valproate).

Accepted March 28, 2011; Early View publication May 13, 2011.
Address correspondence to Rima Nabbout, Department of Neuropediatrics, Centre de reference epilepsies rares, Hôpital Necker Enfants malades, 149 rue de Sèvres, 75015 Paris, France. E-mail: rimanabbout@yahoo.com, rima.nabbout@nck.aphp.fr

Methods

We included prospectively patients with (1) the diagnosis of DS (Dravet et al., 2005); (2) followed at our institution since this diagnosis; (3) aged >3 years; (4) having more than eight seizures per month; (5) having received for over 6 months the combination of stiripentol, clobazam, and valproate. We quantified only the seizures that had a clonic component (generalized, unilateral, or focal) and that parents were able to identify easily. Parents were also asked to report myoclonic fits and atypical absences, although no attempt at quantification of the latter was attempted.

Patients received a classical 4:1 ketogenic diet, based on an adapted diet with the possible use of ready formula KetoCal (Nutricia, Gaithersburg, MD, U.S.A.). KD was initiated without fasting during a 4-day hospital stay dedicated to initiate the diet and ensure diet education for parents and child.

Seizure frequency was evaluated with the patient seizure diary, during 2 month baseline, at 1 month, and every 3 months as long as they were on the diet. In addition to clinical examination and seizure diary report, all patients had a hyperactivity assessment with Conners scale and a

behavioral assessment with the Child Behavior Checklist (CBCL) (Achenbach). Parents and teachers responded separately to these questionnaires. There was no change in AED medication during the 2 month baseline and the first 3 months of KD therapy except for acute rescue therapy with benzodiazepines (diazepam or clonazepam). We considered responders the patients with a ≥75% decrease in seizure frequency on KD compared to baseline. We compared then the range of Conners scale and Achenbach scale before the diet and at 3 and 6 months after the diet in every patient. We considered as clinically significant a scale of 70 or above [≥2 standard deviation (SD)]. We considered as improvement a decrease >10 points (1 SD).

Patients

Fifteen patients were included in this study at a mean age of 5 years (range from 4–11 years). DS was diagnosed on the bases of clinical findings and electroencephalography (EEG) results. *SCN1A* mutation or rearrangements were found in 12 patients. Protocadherin 19 (PCDH19) sequencing did not show evidence of any mutation in the *SCN1A*-negative female patients. All patients had experienced a decrease in seizure frequency and mainly of episodes of status epilepticus when administered STP, clobazam (CLB), and valproate (VPA) at the respective mean doses of 40, 0.2, and 15 mg/kg per day. During the few months prior to inclusion, patients experienced a gradual increase in afebrile seizure frequency reaching >8 seizures (clonic or tonic–clonic) per month despite the adjustment of AED doses. During the 6 months preceding the diet, seven patients received topiramate (TPM) and three levetiracetam (LVT), in addition to their therapy. This adjunction gave a partial response in five (three with TPM and two with LVT). However, TPM was stopped in one patient because of severe anorexia. LVT increases the behavioral problems in one patient and was stopped after 2 months despite efficacy on seizure frequency.

Results

At KD onset, all patients were receiving STP, VPA, and CLB, combined with TPM in two and with LVT in one (Table 1). Patients presented with mild to severe mental delay. According to Conners and Achenbach parents and teacher's scales, 11 patients presented with hyperactivity and 6 had behavioral disturbances, mainly conduct problems (Table 1).

Ten patients were responders, with one becoming seizure-free. Parents reported a major decrease in atypical absences and myoclonic fits in all ten. Efficacy was maintained at 3 and 6 months for eight responders.

Ten patients presented with hyperactivity and attention deficit and five with behavioral disturbance (mainly impulsivity and aggressivity) prior to KD, and four presented both (Table 1). All responders had major improvement in behavior disturbances, attention, and hyperactivity that was reported by parents and therapists, and validated by Conners and Achenbach scales (Table 1). The range of the Conners scale decreased by more than 10 points compared to the range before the KD; this effect was maintained during follow-up. The same improvement was also reported and validated in three nonresponders in whom parents and therapists advised maintaining the diet (Table 1).

KD was maintained for at least 9 months in six patients, including the seizure-free patient. Two showed loss of efficacy (Patients 7 and 8). However, KD was maintained in

Table 1. Clinical characteristics of the patients and ketogenic diet data

Patient	Age at onset (first seizure) (months)	SCN1A/PCDH19	Age at KD (years)	Efficacy (months)				KD duration (months)	HA, BD (before KD/after diet)	Co-AEDs
				1	3	6	9			
1	4	+/ND	5	y	y	y	y	13	+/–, NS/NS	
2	7	+/ND	6	y	y	y	y	12	+/–, +/–	
3	7	+/ND	4	y	y	y	y	11	+/–, NS/NS	
4	6	–/–	11	y	y	y	y	14	NS/NS, +/–	
5	8	+/ND	4	y	y	y	y	12	NS/NS, –/–	+ TPM
6	7	+/ND	5	y	y	y	y	12	NS/NS, –/–	
7	5	+/ND	6	y	y	y	n	9	+/–, NS/NS	
8	9	–/–	4	y	y	y	n	7	+/–, NS/NS	
9	6	+/ND	7	y	n	n	n	1	+/+, +/+	
10	4	+/ND	8	y	n	n	n	6	+/+, +/–	
11	5	+/ND	5	n	n	n	n	7	+/–, NS/NS	
12	7	+/ND	4	n	n	n	n	10	+/–, –/–	+TPM
13	8	+/ND	7	n	n	n	n	2	NS/NS, NS/NS	
14	7	+/ND	7	n	n	n	n	1	+/+, +/+	+LVT
15	5	+/ND	5	n	n	n	n	2	NS/NS, NS/NS	

ND, not determined; TPM, topiramate; LVT, levetiracetam; y, yes; n, no; HA, hyperactivity; BD, behavior disturbances.
Conners and Achenbach scale: +: clinically significant scale ≥70; –: decrease >10 points in the scale; NS: scale <70, not clinically significant.

one of the two (Patient 7) because of the benefit on attention and behavior. At last follow-up, five responders had fulfilled more than 1 year on KD with a maintained efficacy, with one patient seizure-free (Patients 1–5).

In our series, we were careful about reducing AEDs in responders and did it only slightly for responders after 6 months of maintained efficacy, mainly in VPA.

None of our patients had to stop KD for side effects. Transitory anorexia and vomiting occurred in two patients during the first week of KD (day 3 and 4, respectively) that resolved a few days later. For two patients on TPM, urine analysis and renal echography performed at 3 and 9 months were normal. In one patient, hyperlipidemia was present at 6 months and resolved after the diet was withdrawn for seizures recurrence. He had a family history of hyperlipidemia and his levels before the diet were at the upper limit of normal range.

Discussion

This short but prospective series in a homogeneous epilepsy syndrome showed that KD can benefit patients with DS, even when receiving the gold standard therapy (STP + VPA + CLB with in some patients TPM or LVT) and unsatisfactorily controlled. KD reduced clonic seizure frequency by ≥75% and decreased myoclonic fits and atypical absences. Fifty percent of our patients were responders at short term (3 and 6 months) and 40% at long term (9 months). Efficacy was maintained in one third for over 1 year, and responders who achieved a follow-up >12 months were still on KD at last visit. This efficacy range seems inferior to the range reported previously (Caraballo et al., 2005; Kang et al., 2005). In the first study, 1 year after starting the diet, 13/20 patients (65%) remained on the diet. Ten of them (50%) achieved an >50% decrease in seizures frequency, with two patients seizure-free (Caraballo et al., 2005). In the second study, authors reported that 11/16 patients (69%) were continuing the diet at 12 months but only 39% achieved >90% seizures reduction and 52% a >50% reduction. We considered as responders patients who experienced a decrease of ≥75% of seizure frequency since the classical cutoff of >50% was considered insufficient for patients who were on polytherapy. In our series, 33% of patients still had a ≥75% decrease in seizure frequency at 1 year. Patients reported in the two previously mentioned studies could have been more easily controlled, since they did not receive STP and only few had received TPM. Although we observed a loss of efficacy during follow-up, five patients were still responders at 1 year of KD, with one patient seizure-free. This loss of efficacy could not be explained by a lack of compliance.

Children cotreated with KD and carbonic anhydrase inhibitor AEDs including TPM and zonizamide are theoretically at a higher risk for urolithiasis because both are risk factors for this complication. However, in retrospective studies, this suspected cumulative risk failed to be confirmed (Kossoff et al., 2002; Caraballo et al., 2005; Paul et al., 2010). Patients cotreated with KD and TPM did not present any symptom related to a possible urolithiasis and had normal urine examinations and renal ultrasound. However, preventive measures should be encouraged in case of this comedication (Paul et al., 2010).

In addition to efficacy on seizures, behavioral and hyperactivity scales improved in all responders who exhibited abnormal values prior to the diet. This improvement did not seem to result exclusively from the anticonvulsive effect, since improvement also involved nonresponder patients and was maintained in one patient who showed seizure recurrence. Animal model data suggest that KD has a neuroprotective effect that could be applied beyond its treatment of epileptic conditions (Appelburg et al., 2009; Xu et al., 2010). Behavioral disturbances showed improvement in a few reported patients with Rett syndrome receiving KD (Kossoff et al., 2009) and this improved to some extent behavioral, social communication, and cognitive deficits in a pilot study for patients with autism (Evangeliou et al., 2003). In DS, this effect is highly warranted, since it could positively impact the rehabilitation therapy of the child and his socialization, two other major points in the treatment of DS (Nolan et al., 2008).

This is the first prospective study testing the efficacy of KD in a homogeneous cohort of DS unsatisfactorily controlled by the standard therapy including STP. Our results support that KD should be considered as an adjunctive procedure for these patients, either in case of pharmacoresistance or in case of major behavior disturbances. The timing of KD should be questioned and the reduction of associated AEDs may be considered in responders.

Disclosure

None of the authors has any conflict of interest. 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.

References

Appelburg KS, Hovda DA, Prins ML. (2009) The effect of ketogenic diet on behavioral outcome after controlled cortical impact injury in the juvenile and the adult rat. *J Neurotrauma* 26:497–506.

Caraballo RH, Cersósimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. (2005) Ketogenic diet in patients with Dravet syndrome. *Epilepsia* 46(9):1539–1544.

Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, Dulac O, Pons G. (2000) Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. *Lancet* 356(9242):1638–1642.

Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. (2005) Severe myoclonic epilepsy in infancy (Dravet syndrome). In Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P (Eds) *Epileptic syndromes in infancy childhood and adolescence*, 4th ed. John Libbey, London, pp. 89–114.

Evangeliou A, Vlachonikolis I, Mihailidou H, Spilioti M, Skarpalezou A, Makaronas N, Prokopiou A, Christodoulou P, Liapi-Adamidou G,

Helidonis E, Sbyrakis S, Smeitink J. (2003) Application of a ketogenic diet in children with autistic behavior: pilot study. *J Child Neurol* 18(2):113–118.

Kang HC, Kim YJ, Kim DW, Kim HD. (2005) Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. *Epilepsia* 46(2):272–279.

Kossoff EH, Pyzik PL, Furth SL, Hladky HD, Freeman JM, Vining EP. (2002) Kidney stones, carbonic anhydrase inhibitors, and the the ketogenic diet. *Epilepsia* 43(10):1168–1171.

Kossoff EH, Zupec-Kania BA, Rho JM. (2009) Ketogenic diets: an update for child neurologists. *J Child Neurol* 24(8):979–988.

Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross JH. (2009) A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia* 50(5):1109–1117.

Nieto-Barrera M, Candau R, Nieto-Jimenez M, Correa A, del Portal LR. (2000) Topiramate in the treatment of severe myoclonic epilepsy in infancy. *Seizure* 9(8):590–594.

Nolan K, Camfield CS, Camfield PR. (2008) Coping with a child with Dravet syndrome: insights from families. *J Child Neurol* 23(6):690–694.

Paul E, Conant KD, Dunne IE, Pfeifer HH, Lyczkowski DA, Linshaw MA, Thiele EA. (2010) Urolithiasis on the Ketogenic diet with concurrent topiramate or Zonizamide therapy. *Epilepsy Res* 90(1–2):151–6.

Striano P, Coppola A, Pezzella M, Ciampa C, Specchio N, Ragona F, Mancardi MM, Gennaro E, Beccaria F, Capovilla G, Rasmini P, Besana D, Coppola GG, Elia M, Granata T, Vecchi M, Vigevano F, Viri M, Gaggero R, Striano S, Zara F. (2007) An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. *Neurology* 69(3):250–254.

Wolff M, Cassé-Perrot C, Dravet C. (2006) Severe myoclonic epilepsy of infants (Dravet syndrome): natural history and neuropsychological findings. *Epilepsia* 47(Suppl. 2):45–48.

Xu XP, Sun RP, Jin RF. (2010) Effect of ketogenic diet on hippocampus mossy fibers sprouting and Glu5 expression in kainic acid induced rat model. *Chin Med J (Engl)* 119:1925–1929.