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Efficacy and tolerability of the ketogenic diet in Dravet syndrome — Comparison with various standard antiepileptic drug regimen

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Summary There is strong evidence for the use of the ketogenic diet (KD) in Dravet syndrome (DS). The purpose of this study was to evaluate both effectiveness and tolerability in comparison with various antiepileptic drugs (AEDs).
Methods: 32 children (19 males) with genetically confirmed DS treated at our center since 1999 were analyzed retrospectively. Data collected from patients' files included type of mutation, age at treatment initiation and treatment lag, overall seizure frequency and frequency of different seizure types, especially prolonged seizures and status epilepticus (SE). Efficacy and safety of the KD were evaluated. In addition, the effect on seizure count was compared with that of various AED regimen and the vagus nerve stimulation (VNS).
Results: Overall response to the KD was 70% at 3 months and 60% at 12 months. No SE occurred while patients were on the diet, and the frequencies of prolonged generalized and myoclonic seizures were reduced. No severe side effects requiring withdrawal of the KD were observed. Although the effect of the KD was independent of age at initiation, it had to be withdrawn due to noncompliance more frequently in solid fed older children compared with infants treated with the liquid ketogenic formula. The KD was not significantly inferior to the current gold

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standard AED triple combination of Stiripentol + Valproate + Clobazam (89%), Bromides (78%), Valproate alone (48%), Topiramate (35%) and VNS (37%) and significantly more effective than Levetiracetam (30%; $p = 0.037$, Pearson's Chi-square).
Significance: These data suggest that the KD ranks among currently used AEDs as an effective treatment for seizures in DS. According to our results (good effect on SE and prolonged seizures, good tolerability, less compliance problems due to formula treatment) the KD should be considered as an early treatment option in infants with DS.

Introduction

Dravet syndrome (DS) is a rare genetic infantile onset epileptic encephalopathy with multiple seizure types, recurrent status epilepticus (SE), developmental slowing and cognitive impairment (Scheffer, 2011; Ragona et al., 2011).

DS is almost invariably refractory to most conventional antiepileptic drugs (AEDs). Sodium channel-blockers — i.e. carbamazepine (CBZ), oxcarbazepine (OXC), and lamotrigine (LTG) — aggravate both seizures and interictal EEG (Genton, 2000), and may also provoke status epilepticus (SE). Stiripentol (STP) was licensed under the European orphan drug scheme in 2001 and — in combination with Valproate (VPA) and Clobazame (CLB) — is currently regarded as the ''gold standard treatment'' (Chiron et al., 2000; Wirrell et al., 2013). Other AEDs such as Bromides (Lotte et al., 2012; Oguni et al., 1994), Levetiracetam (LEV) and Topiramate (TPM) are reported to be effective but to a lower degree than the ''triple combination'' STP + VPA + CLB (Chiron, 2011; Korff et al., 2007; Kroll-Seger et al., 2006). There are only limited data on Vagus-Nerve-Stimulation (VNS) in DS. However, good efficacy and only mild short and long term side effects were reported from small case series (Cersosimo et al., 2011; Spatola et al., 2013; Zamponi et al., 2011).

The KD has been well established as a treatment option for childhood epilepsies since the 1920s, and efficacy was also documented in a recently published randomized trial (Neal et al., 2008). There is strong evidence that the KD effectively controls seizures in patients with DS (Caraballo, 2011; Caraballo et al., 2005; Kang et al., 2005; Korff et al., 2007; Laux and Blackford, 2013), especially when added to the gold standard triple combination (Nabbout et al., 2011). Further, the diet has been reported to exhibit neuroprotective effects (Dutton et al., 2011; Luan et al., 2012) and to control long lasting SE refractory to conventional AED treatment (Nabbout et al., 2010).

Despite this long-standing clinical efficacy of the KD in DS, the diet has not yet been evaluated in comparison with or in combination with other treatment regimen currently recommended for DS. This study was therefore performed to determine the place of the KD among other treatment options currently available.

Methods

Clinical records of all children with a genetically confirmed diagnosis of DS treated at our center since 1999 were examined retrospectively. Demographic as well as genetic data were used. Detailed seizure diaries had to be available.

Evaluation of treatment outcome: Seizure frequency three months before initiation of any new treatment was defined as ''baseline''. The duration of any new treatment after initiation had to be at least three months. In order to prevent bias, treatment periods with baseline regimen including potentially aggravating agents (i.e. sodium channel blockers) were excluded from further analysis.

Treatment response was defined as the absolute reduction in seizure frequency of $\geq$50% three months after initiation of a new treatment compared with ''baseline''. Patients who had <50% reduction in seizure frequency were defined as non-responders. Aggravation was defined as $\geq$50% increase in the frequency or severity of existing seizures, emergence of new seizure types, or the occurrence of SE. The total seizure count at three months compared to baseline was assessed for the following treatment regimen: KD add-on, VPA mono-therapy, ''triple combination therapy'' with STP + VPA + CLB, add-on treatment with TPM, LEV, Bromides and VNS.

For the KD, additional variables were evaluated: age, treatment-lag and efficacy on different seizure types (generalized tonic clonic seizures (GTCS), SE, myoclonic seizures (MS)), as well as side effects and growth data (body weight and length). Long-term treatment response to the KD was defined as a reduction in seizure frequency at 6 months, 12 months and at last follow up compared with baseline.

Statistical analysis

Statistical analysis for this retrospective cross-sectional observation study was performed using the IBM Statistical Package for Social Science (SPSS Statitistics Version 21). Descriptive statistics (mean, minimum, maximum, standard deviation, and median-when appropriate) were used. Student's *t*-test was applied for parametric data, Pearson's chi-square and Fisher exact test for all non-parametric data, respectively.

Results

Patients' characteristics

32 children (19 male) with DS were treated at our center since 1999. Genetic testing exhibited 31 SCN1A mutations (16 missense mutations, six truncating mutations, two deletions, four splicing mutations, and three frame-shift mutations) and one GABRG2 mutation (missense mutation) (Table 1). Follow-up was mean 6.89 years $\pm$ 5.93 (min. 0.15—max. 17.80) and age at last follow-up was mean

Table 1 Patients' characteristics (ID — identification of cases, F — female, M — male, SCN1A — sodiumchannel, FS — febrile seizures, GTCS — generalized tonic clonic seizures, SE — status epilepticus, MS — myoclonic seizures, MYO — myoclonias, AS — absence seizures, CPS — complex partial seizures, AT S — atonic seizures, KD — ketogenic diet, AED — antiepileptic drug, VPA — Valproic Acid, STP — Stiripentole, CLB — Clobazam, LEV — Levetiracetam, TPM — Topiramate, CNZ — Clonazepam, LCM — Lacosamid, PRM — Primidon, ESLI — Eslicarbazepin, LOR — Lorazepam). *Cases in bold letters were on the KD.

ID	Sex	Age	Mutation	Phenotype	Onset of epilepsy	Seizure types	KD-duration	Current AEDs
001	M	8	SCN1A Missense	DRAVET + autism	1.41	FS, GTCS, SE, MS	—	VPA
002	F	19	SCN1A Truncation	DRAVET	0.45	FS, GTCS, SE, MS, AS	—	STP + VPA + CLB
003	M	15	SCN1A Missense	BORDERLINE DS	0.75	FS, GTCS, AS	—	VPA
004*	M	8	SCN1A Truncation	BORDERLINE DS	0.59	FS, GTCS, SE, MS	Since 09/2007	KD, LEV
005	M	10	SCN1A Missense	DRAVET	0.22	FS, GTCS, MS	—	LEV, STP + VPA + CLB
006	F	7.5	SCN1A Missense	DRAVET	0.33	FS, GTCS, SE, MS, AS	—	VPA, TPM
007	M	9	SCN1A Deletion	DRAVET	0.17	FS, GTCS, MS, AS, CPS	Since 09/2006	KD, STP + VPA + CLB
008 2nd mut.	M	1.2	SCN1A Missense SCN1A Missense	DRAVET	0.17	FS, GTCS, SE, MS, CPS, AT S	—	TPM
009	F	12.5	SCN1A Missense	DRAVET	0.42	FS, GTCS, SE, MS, AS, AT S	—	STP + VPA + CLB
010	M	14	SCN1A Truncation	DRAVET	0.96	FS, GTCS, CPS, AT S	—	VPA, CLB
011	F	15.7	SCN1A Splicing	DRAVET	0.48	FS, GTCS, SE, MS, AS	05/1999—08/1999	TPM, VPA, CNZ
012	M	15	SCN1A Missense	DRAVET	0.75	FS, GTCS, SE, MS, AS	—	STP + VPA + CLB
013	M	2	SCN1A, SCN2A, SCN9A Deletion	DRAVET	0.25	FS, GTCS, MS, AS,	06/2011—03/2012	VPA, LEV, CLB
014	M	9	SCN1A Missense	BORDERLINE DS	2.76	FS, GTCS, MS	—	0
015	F	5	SCN1A Splicing	DRAVET	0.32	FS, GTCS, SE,	—	LEV
016	F	17.5	SCN1A Truncation	DRAVET	0.31	FS, GTCS, SE, MS, AS, CPS	01/2000—04/2002	TPM, STP + VPA + CLB
017	M	20.5	SCN1A Truncation	DRAVET	0.39	FS, GTCS, SE, MS, CPS, AT S	11/1999—06/2000	STP + VPA + CLB
018	F	19	GABRG2 Missense	DRAVET	0.72	FS, GTCS, SE, AS, AT S	—	LEV
019	M	15	SCN1A Missense	DRAVET	0.20	FS, GTCS, MS, AS, CPS	—	LCM
020	F	5.5	SCN1A Missense	DRAVET	1.33	FS, GTCS, MS, AS, CPS, AT S,	—	VPA
021	F	19	SCN1A Missense	DRAVET	0.42	FS, GTCS, SE, MS, AS, AT S	—	LCM
022	M	3.8	SCN1A Frameshift deletion	DRAVET	0.37	FS, GTCS, SE, MS, AS	—	PRM, TPM
023	F	1	SCN1A Splicing	DRAVET	0.29	FS, GTCS, SE, MS, AT S,	05/2011—03/2012	LEV

Table 1 (*Continued*)

ID	Sex	Age	Mutation	Phenotype	Onset of epilepsy	Seizure types	KD-duration	Current AEDs
024	M	2	SCN1A Missense	DRAVET	0.58	FS, GTCS, SE, MS	–	VPA, Bromide, CLB
025	M	14	SCN1A Missense	BORDERLINE DS	0.53	FS, GTCS	–	LEV
026	M	2	SCN1A Missense	DRAVET	0.25	FS, GTCS, SE, MS, CPS, AT S	–	STP + VPA + CLB
027	M	21	SCN1A Missense	DRAVET	0.59	FS, GTCS, SE, MS, AS, CPS,	06/2000–09/2000	PRM, ESLI, LOR
028	M	12	SCN1A Missense	DRAVET	0.88	FS, GTCS, MS, AT S	–	STP + VPA + CLB
029	F	15.4	SCN1A Truncation	DRAVET	0.38	FS, GTCS, SE, MS, AS, CPS	06/2000–09/2000	Bromide
030	F	10	SCN1A Frameshift deletion	DRAVET	0.42	FS, GTCS, SE, MS, AS, AT S	–	TPM, VPA, CNZ
031	F	4	SCN1A Splicing	DRAVET	0.94	FS, GTCS, SE, MS, AS, CPS, AT S	Since 08/2012	KD, VPA, LEV
032	M	5	SCN1A Frameshift deletion	BORDERLINE DS	0.76	FS, GTCS, SE	–	LEV

Table 2 Antiepileptic drugs (AEDs) used *(CBZ – Carbamazepine, OXC – Oxcarbazepin, LTG – Lamotrigin) ** (other drugs included – ST – Sulthiam, PRM – Primidon, ZS – Zonisamid, FBM – Felbamat, ETS – Ethosuximid, RUF – Rufinamid, CNZ – Clonazepam, LCM – Lacosamid, VIT B6 – Vitamin B6, GBP – Gabapentin, VGB – Vigabatrin, Prednison, ESLI – Eslicarbazepin, LOR – Lorazepam).

Antiepileptic drugs (AEDs) used	Number of children (%)
Valproate mono-therapy	31 (96.9%)
Phenobarbital	4 (12.5%)
Stiripentole + Valproate + Clobazam	9 (28.12%)
Bromides	9 (28.12%)
Topiramate	20 (62.5%)
Levetiracetam	20 (62.5%)
Sodium-channelblockers yes/no*	26 (81.3%)
Other drugs**	24 (75%)
Vagus-Nerve-Stimulation (VNS)	8 (25%)

10.60 ± 6.28 years (min. 0.96–max. 21.04). AEDs used are displayed in Table 2.

Treatment with the KD

From March 1999 to April 2014 127 children were placed on the KD at our center. From these 127 children, 9 children dropped out during the first days because of food refusal, none of them of our DS group. All children with DS remained at least 3 months on the diet. In total 10/32 (five male) children with a genetically confirmed DS have been treated with the KD since 1999. Age at seizure onset in these children was between 0.17 and 0.94 years (mean 0.44 ± 0.22). The mean age at initiation of the KD was 4.03 years ± 2.74 (min. 0.86–max. 9.76). The treatment lag from epilepsy onset to KD initiation was between 0.61 and 9.71 (mean 3.59 ± 2.69) years. Prior to the initiation of the KD, patients had used 1–13 AEDs (median 5.5).

The first 5 DS patients were put on the KD prior to the introduction of a liquid ketogenic formula treatment in 2006. Further 5 children have been treated since then. Children who started with the KD before 2006 were significantly older at initiation of the KD than those starting after 2006: mean age was 6 years ± 2.44, min. 3.7–max. 9.8; versus (vs.) 2.03 years ± 1.22, min 0.7–max 3.7 ($p = 0.047$) and the treatment lag was significantly longer: mean 5.55 years ± 2.37, min 3.21–9.17 vs. mean 1.62 years ± 0.97, min. 0.61–max. 2.76 ($p = 0.008$). The number of AEDs used before the initiation of the KD was also higher in these children: median 8, range 4–13; vs. median 4, range 1–6 ($p = 0.060$).

The KD was started at the classic 4:1 ratio in six children and at a 3:1 ratio in the remaining four. Following the Johns Hopkins' guidelines (Lee and Kossoff, 2011) children remained at least 3 months on the KD to evaluate treatment response. Vitamins and Calcium were substituted, as well as potassiumcitrate administered to prevent kidney stones (Kossoff, 2008).

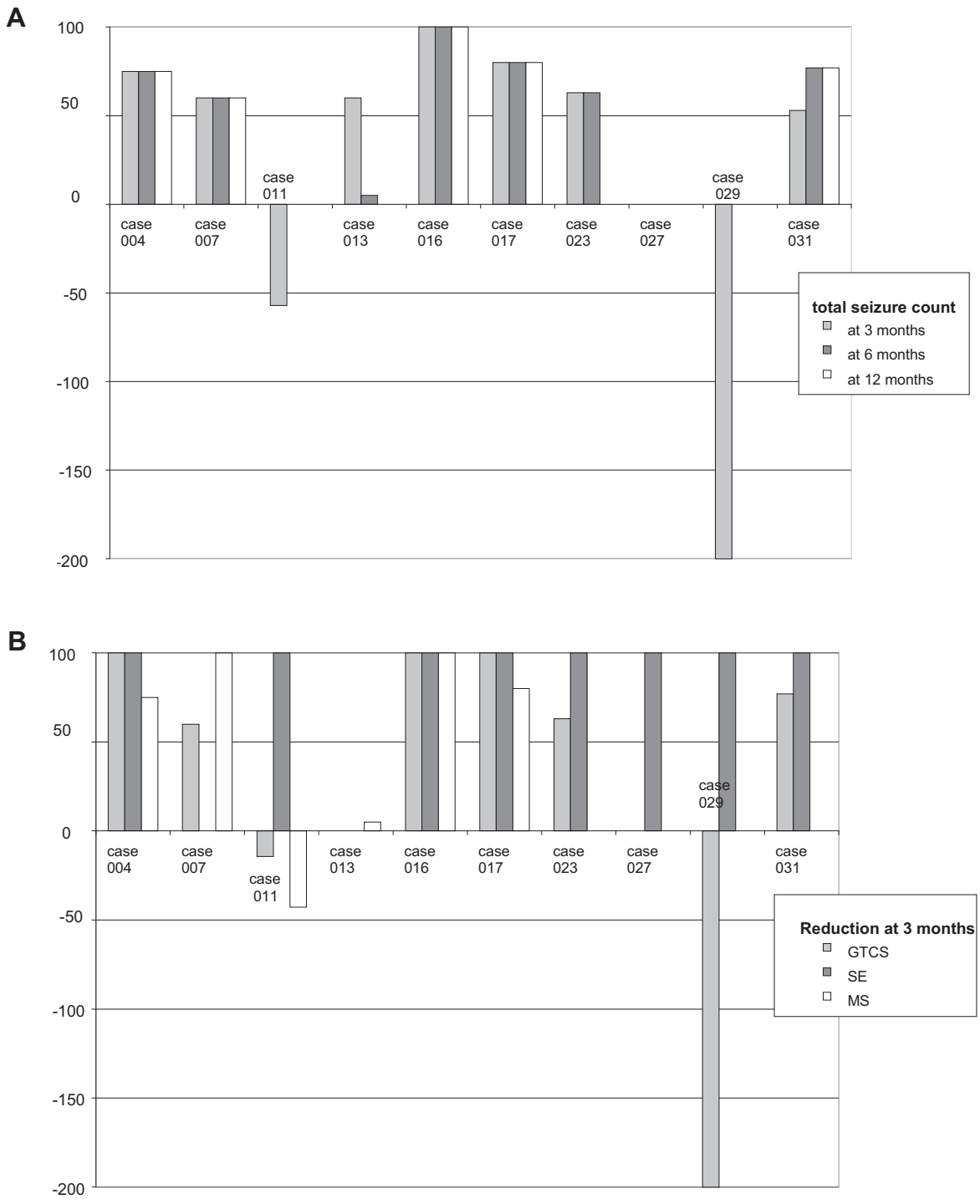

Figure 1 (A) %-Reduction of total seizure count at 3, 6 and 12 months compared to baseline on the KD. Minus indicates an increase in seizure frequency (seizure aggravation). (B) %-Reduction of different seizure types at 3 months compared to baseline on the KD (seizure types taken into account were generalized tonic clonic seizures (GTCS), status epilepticus (SE), and myoclonic seizures (MS).

Table 3 Efficacy and mean seizure reduction of the ketogenic diet (KD) in responders.

KD	Efficacy	Mean seizure reduction in %
At 3 months	70% (7/10)	70.14 ± 16.14 (min. 53—max. 100)
At 6 months	60% (6/10)	75.75 ± 14.37 (min. 60—max. 100)
At 12 months	60% (6/10)	78.40 ± 14.33 (min. 60—max. 100)

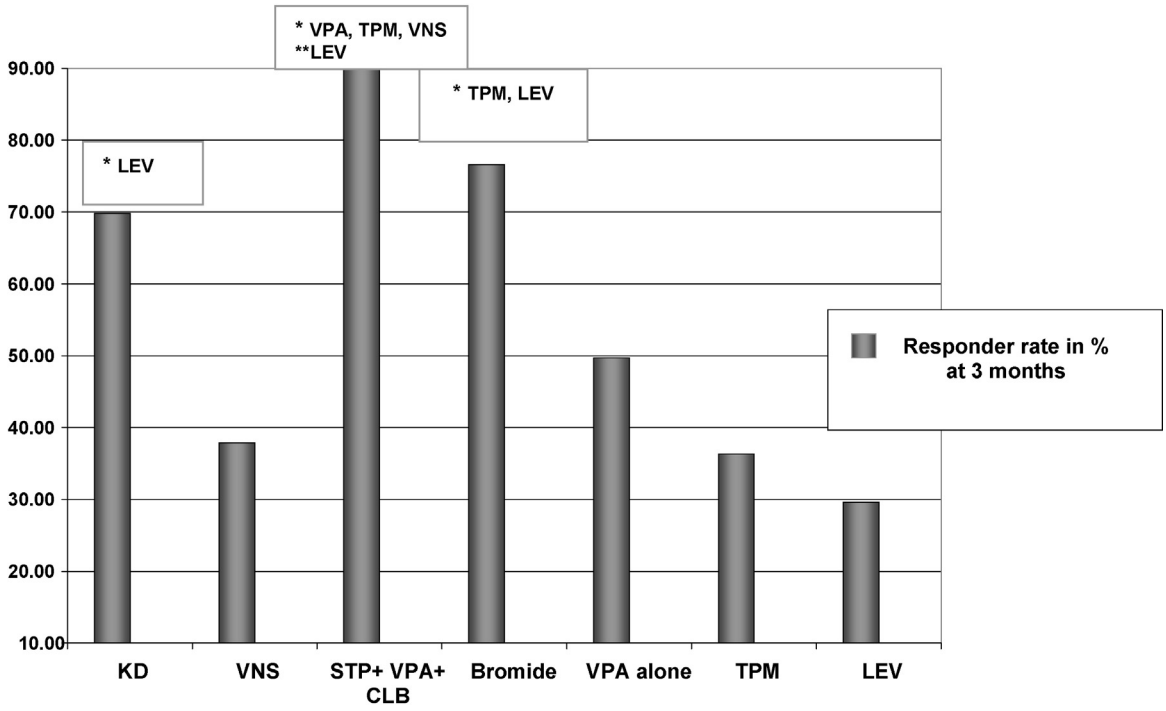

Figure 2 (A) Responder rate at 3 months. Total seizure count for all treatments was evaluated at three months and responders were defined as having a reduction in seizure frequency compared to baseline of at least 50%. Different treatments were compared using Pearson's chi-square and Fisher exact test (* significance level $p < 0.050$, ** significance level $p < 0.005$).

Efficacy of the KD is shown in Fig. 1A/B and Figure 2. Treatment duration of the KD is displayed in Fig. 3. Efficacy is shown in Table 3.

At 3 months, 7/10 of the patients (70%) were responders, one child became seizure free. 3/10 children (30%) were non-responders and therefore withdrawn from the diet: two of them showed an increase in seizure frequency (+200% and +57%), one child remained unchanged compared to baseline.

At 6 months, 60% were still responders. One child became a non-responder as the initial 60% reduction at 3 months

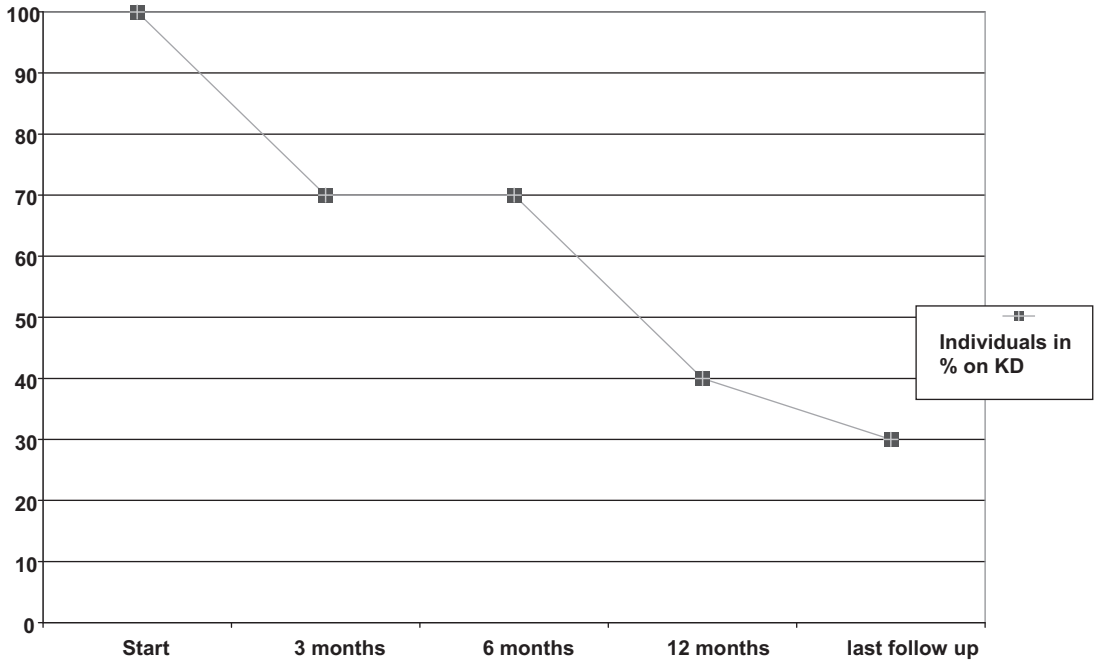

Figure 3 Treatment duration of the KD. The percentage of individuals on the KD is displayed at start, 3 months, 6 months, 12 months and at last follow-up visit.

dropped to 5% at 6 months and the KD was therefore withdrawn. In one child, reduction in seizure frequency increased further from 53% at 3 months to 77% at 6 months.

At 12 months, 6/10 (60%) children were still responders. One responder with an 80% seizure reduction at 3 and at 6 months became incompliant at 7 months and was withdrawn from the KD (seizure deterioration was not seen until 24 months follow-up). Another responder with a seizure reduction of 63% at 3 months started to refuse the KD when more solid ketogenic meals were introduced 6 months after initiation of the diet. The child was put on a whole diet with no sugars added after 7 months. No increase in seizure frequency occurred until the last visit at 13 months after initiation of the KD.

Duration of the KD >12 months/last follow up (Fig. 3): 4/10 children (40%) were on the diet for >12 months. In these four children, a persistent reduction in seizure frequency was observed (60%, 75%, 100% and 77% respectively). One initially seizure free child showed a relapse due to incompliance at 2.21 years after initiation of the KD. The remaining three children are still on the diet since 5.74, 6.72 and 2.04 years, respectively.

The mean duration of the KD in responders was 1.81 ± 2.42 (min. 0.58—max. 6.72) years. Mean follow-up after initiation of the KD was 7.51 ± 5.30 (range 1.08—12.82 years).

KD and concomitant AEDs

When starting the KD, children were on median 2.5 AEDs (max. 3, min. 1). Three of the responders had a co-medication with TPM, which has been previously hypothesized to show a synergistic effect (Caraballo, 2011).

In 4 responders AEDs were reduced from a median of 2.5 to a median of 0.5 during the course of the diet. In one child, co-medication was completely withdrawn after 2 years on the diet. This patient showed an increase in seizure frequency after five years and STP + VPA + CLB were added to the KD. He has then been seizure free for 20 months at last follow-up.

Safety of the KD

Side effects during the KD were only seen in 2/10 children: One child showed an increased weight gain of 6 kg during the first three months (BMI change from 15.7 to 19.93) with difficulties to return to baseline after the diet. In the other patients, BMI remained within the normal range (BMI after 3 months mean 16.38 ± 2.14, min. 12.56, max. 19.93). In another child, Carnitine deficiency occurred and was treated with an oral substitution of L-Carnitine. Fluid intake was within the normal range with a mean of $1092.56\,ml \pm 224.29\,ml$/day (min. 700, max. 1500). Cholesterole (Chol) levels and Triglycerides (Tgc) showed only a mild increase after 3 months (Chol mean 193.11 ± 81.58 mg/dl, min. 98—max 363; mean Tgc 241.33 ± 327.10, min. 55, max. 1097). In case 017 high Tgc levels decreased at 4 months to 759 and returned within the normal range at 6 months. No serious side effects with the need to stop the diet (e.g. steatosis hepatis or kidney stones) did occur.

Clinical characteristics of KD responders vs. non-responders

There were no statistically significant differences between responders and non-responders with respect to mutation type, age at epilepsy onset, age at initiation of the KD, the number of AEDs used before the KD and treatment lag (time between epilepsy onset and start of the KD). However, when comparing the children who started the KD before 2006 with those starting after 2006 the following differences were observed: The responder-rate was lower in those treated before 2006: i.e. 2/5 (40%) vs. 4/5 (80%). As mentioned above, the age at initiation was higher ($p = 0.047$) and the treatment lag was longer ($p = 0.008$) in patients treated before 2006. In addition, compliance was lower before 2006 — 2/5 (40%) vs. 4/5 (80%) as formula treatment was not available at that time.

The response of different seizure types to the KD is shown in Fig. 1B.

The mean reduction in seizure frequency compared with baseline was $28.69\% \pm 77.67$ (min. −150 to 100%) for generalized tonic clonic seizures (GTCS), and $38.04\% \pm 63.35$ (min. −85.71 to max. 100) for myoclonic seizures (MS). The effect on GTCS did not differ significantly from the effect on MS ($p = 0.520$) or on SE ($p = 0.053$), but the effect on MS differed from that on SE ($p = 0.036$). SE was present in 8/10 patients before initiation of the KD, and did not occur in any of them during the KD ($p = 0.000$). Even in non-responders SE were not observed during the diet. However, aggravation was seen for GTCS in 2 patients and for MS in 1 patient.

When looking at responders alone, the reduction in total seizure frequency at 3 months was $70.14\% \pm 16.14$ (min. 53—max. 100), for GTCS it was $77.57\% \pm 24.91$ (min. 50—max. 100), and for MS 78.00 ± 50 (min. 50—max. 100) (Table 3).

Efficacy of other treatment regimen (AEDs and VNS) compared with the KD at 3 months (Fig. 2)

STP + VPA + CLB showed a responder rate of 88.88% (8/9), with a mean seizure reduction of $73.45\% \pm 19.72$ (min. 40%—max.100%).

Bromide showed a responder rate of 77.77% (7/9) with a mean reduction of 66.58 ± 32.69 (min. 0%—max. 100%).

VPA monotherapy showed a responder rate of 48.4% (15/31 patients) with a mean seizure reduction of $40.97\% \pm 34.89$, min. 0—max. 100%.

TPM showed a responder rate of 35% (7/20) with a mean seizure reduction of 31.47 ± 26.68, min. 0—max. 80%.

LEV showed a responder rate of 30% (6/20) with a mean seizure reduction of $25.25\% \pm 31.71$, min. 0—max. 90%.

VNS showed a responder rate of 37.5% (3/8) with a mean seizure reduction of 27.88 ± 35.87 (min. 0—max. 87%).

The KD showed a responder rate of 70% (7/10), with a mean seizure reduction of $23.39\% \pm 90.55$ (min. −200 to max. 100).

In summary, statistically significantly higher responder-rates were observed with STP combined with VPA and CLB vs. TPM (Pearson's chi-square $p = 0.007$/Fisher exact $p = 0.014$),

LEV ($p = 0.003/p = 0.005$), VNS ($p = 0.027/p = 0.050$), and VPA mono-therapy ($p = 0.030/p = 0.054$), as well as with Bromides vs. TPM ($p = 0.033/p = 0.050$) and vs. LEV ($p = 0.017/p = 0.005$). The KD showed a significantly higher responder-rate than LEV ($p = 0.037/p = 0.054$). In addition, significantly higher reductions in seizure frequency were seen with STP combined with VPA and CLB vs. TPM ($p = 0.025$), vs. LEV ($p = 0.005$) and vs. VPA mono-therapy ($p = 0.017$), as well as with Bromides vs. VNS ($p = 0.009$), vs. TPM ($p = 0.016$) and vs. LEV ($p = 0.007$).

In summary, the KD was equally effective compared with the ''triple combination'' STP + VPA + CLB, bromides, VPA, TPM and VNS, and significantly more effective than LEV (Fig. 2) ($p = 0.037$).

Seizure freedom was observed in single cases: in one child on STP combined with VPA and CLB, in one child on Bromide, in one child on VPA monotherapy, and in one child on the KD, but not on TPM and not on LEV.

Discussion

This study investigated the treatment outcomes of various treatment regimens with special emphasis on the KD in a cohort of 32 patients with genetically ascertained DS.

The overall long-term responder rate for the KD at our center was 60%. Other centers observed higher responder rates from 63% to 66.5% (Caraballo, 2011; Caraballo et al., 2005; Kang et al., 2005; Korff et al., 2007; Laux and Blackford, 2013), but the children reported in these publications were younger than our cohort. Children treated with the KD at our center since 2006 were younger at initiation of the diet, the treatment lag was shorter and the number of AEDs used prior to the KD was smaller. In these children, the responder rate was higher (66.6%). However, seizure freedom was achieved in only 1/10 patients which is in line with the results obtained in other centers (Caraballo, 2011; Nabbout et al., 2010). Nabbout et al. (2010) observed an additional beneficial effect of the KD, when added to STP + VPA + CLB in 10/15 (66%) of their patients with 1 patient (6.66%) becoming seizure-free.

According to our results, responder rates of the KD at 3 months (70%) did not differ significantly from the triple combination STP + VPA + CLB (89%), bromides (78%), VPA mono-therapy (48%), TPM (35%) and VNS (37). In addition, the KD was well tolerated and in no case had to be withdrawn because of side effects.

The seizure type, responding best to the KD in this study was SE, which was not observed in any patient while on the KD (not even in children with responder rates <50%). SE is a neurologic emergency in DS patients, and is associated with high morbidity and mortality. Overall mortality is rather high in DS, especially around 2 years of age, ranging from 3.7% up to 20.8% (Genton et al., 2011b; Sakauchi et al., 2011; Skluzacek et al., 2011) with sudden unexplained death in epilepsy (SUDEP) accounting for more than a half of all events (53—59%) followed by SE with 14.3—36% (Akiyama et al., 2010; Genton et al., 2011a; Oguni et al., 2001; Skluzacek et al., 2011). Multiple SE during infancy have been reported to be followed by cognitive and behavioral impairment in up to 80% of DS patients (Brunklaus et al., 2012; Fountain, 2000). As SE is most prevalent during the first year after disease onset and because of its predictive value for unfavorable cognitive outcomes, treatment regimen that prevent infants from long-lasting convulsive seizures and SE are urgently needed.

Our data also demonstrated good effects of the KD on GTCS and MS. These results are similar to those reported from other centers and similar to our experiences with the KD in other epilepsy syndromes (Dressler et al., 2010; Kossoff et al., 2010; Maydell et al., 2001; Nabbout et al., 2010).

The efficacy of the KD was independent of sex, age nor type of mutation. The influence of the genotype on seizure outcome is discussed controversially in the literature (Ragona et al., 2011). In our sample, we did not observe a different response to any treatment with respect to the type of mutation.

Compliance problems were primarily observed in solid fed older children (4/10 = 40%) who frequently stopped the diet abruptly, even when they had initially responded. This problem was not encountered at all in younger children treated with the liquid formula.

Limitations and strengths

The study was conducted at a pediatric tertiary center, so the cohort was potentially biased toward severe outcome. The number of patients (32, 10 of them treated with the KD) was also small, but none of those 10 dropped out before finishing the 3 months period. Moreover, DS is an orphan disease.

Due to the retrospective study design, the effect of various treatment options on developmental outcomes of these children was not evaluated.

Finally, comparing different treatment regimen using retrospective data has significant limitations. However, there are currently no data available that highlight the place of the KD compared with other treatment options. The results obtained here seem promising and can serve as motivation for further prospective head-to-head studies.

Strengths of our study are the long observation period with detailed clinical data and that all patients were genetically confirmed.

Conclusion

Despite all the above mentioned limitations, our data showed equal efficacy of the KD compared with various AEDs currently available for the treatment of DS and compared with VNS. Further, only few and mild side effects and no neurotoxic effects were observed. There was an excellent effect of the KD on SE and prolonged GTCS. This result may perhaps provide a rational basis for considering the KD during infancy with the aim to reduce mortality and morbidity and to ameliorate cognitive outcome. In favor of an early application of the KD is also that compliance problems may limit the effect in older children.

Conflicts of Interest

None of the authors has any conflict of interest to disclose.

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