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

Anastasia Dressler[a], Petra Trimmel-Schwahofer[a], Eva Reithofer[a], Angelika Mühlebner[a], Gudrun Gröppel[a], Edith Reiter-Fink[a], Franz Benninger[b], Roland Grassl[b], Martha Feucht[a,*]

[a] *Department of Pediatrics and Adolescent Medicine, Medical University Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria*
[b] *Department of Child and Adolescent Neuropsychiatry, Medical University Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria*

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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 Although the effect of the KD was independent of age at initiation, it had to be withdrawn due to noncompliance more frequently in solid fed older children compared with infants treated with the liquid ketogenic formula.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

* Corresponding author at: Epilepsy Monitoring Unit, Department of Pediatrics and Adolescent Medicine, Medical University Vienna, Waehringer Guertel 18-20, A-1090 Wien, Austria. Tel.: +43 1 40400 38050; fax: +43 1 40400 22770.
E-mail address: martha.feucht@meduniwien.ac.at (M. Feucht).

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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