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Long-term outcome and tolerability of the ketogenic diet in drug-resistant childhood epilepsy—The Austrian experience

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ABSTRACT

Purpose: To evaluate the long-term efficacy/tolerability of the ketogenic diet (KD) in paediatric drug-resistant epilepsies.
Methods: Data from children who were treated between 1999 and 2008 and had continuous follow-up of at least 6 months after initiation of the KD were analysed retrospectively. Response was defined as ≥50% seizure reduction. Treatment effects on EEG, developmental outcome and the "outcome-predictive" value of various clinical factors were also assessed.
Results: 50 children (22 boys; mean age 4.5 years ± 3.55) were included. Mean follow-up was 3.93 ± 2.95. 50% of the patients were responders, 48% of them became seizure free. 50% were non-responders, 20% of them deteriorated. In responders, EEG background activity improved significantly ($p = 0.014$) and a significantly lower rate of epileptic discharges ($p = 0.009$) was seen after 6 months. In addition, neurological examination findings demonstrated significant developmental progress ($p = 0.038$).

Favourable treatment outcome was associated with a shorter disease duration ($p = 0.025$) and generalised tonic clonic seizures ($p = 0.059$). No further significant outcome predictors were detected. However, response was 44% in patients with infantile spasms, 62.5% in those with Dravet syndrome and 50% in Lennox-Gastaut-syndrome.

Side effects occurred in 28%, but discontinuation of the KD was not required in any case. They most often observed with concomitant topiramate ($p = 0.001$) and valproate ($p = 0.046$).
Conclusion: Despite the retrospective nature of the study and the inhomogeneous patient sample, we found good long-term effects of the KD on seizure frequency, EEG and neurological development.

1. Introduction

The ketogenic diet (KD) has been used in the treatment of childhood epilepsy since the 1920s.[1] Today – although the evidence consists almost exclusively of uncontrolled studies[2] and although knowledge concerning its exact mechanism of action is still lacking[3] – the KD is recognised as a safe and effective alternative treatment option. It is therefore recommended for children with refractory epilepsy who are not candidates for epilepsy surgery.[4] In addition, the diet has become the first line treatment of GLUT-1 deficiency, pyruvate-dehydrogenase complex deficiency and phosphofructokinase deficiency.[5]

Besides its anticonvulsant properties, a growing number of studies has recently demonstrated neuro-protective effects of the KD in various neuro-degenerative disorders (including Alzheimer's and Parkinson's disease, mitochondrial disorders, Rett syndrome), brain tumours, traumatic brain injury and stroke.[6,7]

The KD has been performed with varying outcome at the Vienna University Hospital, Department of Paediatrics since March 1999. Aim of this retrospective hospital-based chart review was therefore (1) to assess the overall long-term efficacy and tolerability of the KD at our centre and (2) to identify patients' characteristics associated with (un-)favourable treatment outcomes.

2. Methods

Clinical charts of all children treated with the KD between March 1999 and May 2008 and an observational period of ≥6 months after initiation of the KD were reviewed.

The KD was performed following the Johns Hopkins' protocol (in infants and toddlers without fluid restriction).[8] Vitamins,

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calcium, selenium and zinc were supplemented. The KD was administered add-on, and concomitant antiepileptic drugs (AEDs) were subsequently tapered if possible.[9]

All information relevant for further analysis was abstracted retrospectively from patients' medical records and the EEG data base. Aetiology was classified into cryptogenic and symptomatic categories. Seizure types and epilepsy syndromes were classified according to the criteria proposed by the International League against Epilepsy (ILAE).[10,11]

Routine EEGs (including hyperventilation, photic stimulation and sleep) recorded before and 3–6 months after initiation of the KD (or when the KD was stopped) were re-analysed with respect to background activity (1: background activity present yes/no, 2: frequency: cycles/s) and the presence of interictal spikes (yes/no).

Parental seizure counts 8 weeks before initiation of the KD (baseline) were compared with those reported at follow-up visits 6 months after initiation of the diet. In case of response to the KD, seizure counts reported 12 months after initiation of the diet were also considered.

The effect of the KD on seizure frequency was classified into responders (≥50% reduction in seizure frequency) and non-responders (<50% reduction in seizure frequency or seizure aggravation (increase in seizure frequency and/or occurrence of new seizure types). According to the literature, not only complete seizure freedom, but already a seizure reduction of 50% can be considered as an improvement in children with drug resistant epilepsies.[12]

The effect of the KD on psychomotor development was evaluated based on the results of clinical neurological examinations performed immediately before initiation of the KD (baseline) compared with those at follow-up visits at 6–12 months and was quantified into the categories normal development, mild and severe impairment.

Variables evaluated with respect to their possible predictive value for (un-)favourable treatment outcomes were: sex, age at seizure onset, age at initiation of the KD, duration of epilepsy and number of AED failures before initiation of the KD, seizure type(s), aetiology, and epilepsy syndrome, seizure counts according to seizure diaries, fat:nonfat ratio, duration of treatment, concomitant AEDs, results of clinical neurological examinations (baseline and follow-up visits), compliance measured by plasma levels of beta-hydroxybutyrate (β-OHB), BMI, auxiometric and laboratory data, reported side effects, as well as EEG at baseline and follow-up visits).

All analyses were performed using the Statistical Package for the Social Sciences for Windows (version 15.0.1; SPSS, Inc., Chicago, IL): Student's *t*-test was used to compare continuous parametric data and χ^2 for non-parametric data ($p < 0.05$ was considered to be statistically significant).

3. Results

3.1. Clinical data

52 children and adolescents ≤18 years were treated with the KD at the Vienna University Hospital between March 1999 and May 2008. In 2 patients the KD was stopped after two, respectively, 6 days, because they refused the ketogenic meals. Thus, data from 50 patients ($n = 22$ boys, $n = 28$ girls) with a mean age of 4.5 years ± 3.55 (min. 0.4–max. 16.8 years) at initiation of the KD and a mean duration of 3.0 years ± 2.26 (min. 0.08–max. 8.36 years) of epilepsy before initiation of the KD were analysed. Detailed clinical characteristics are displayed in Tables 1 and 2.

25/50 patients (50%) were symptomatic, 25/50 (50%) were classified as cryptogenic (risk factors according to medical history and/or abnormal neurological examination, but MRI-negative). Seizure types and epileptic syndromes are shown in Tables 3 and 4.

Table 1
Patients' characteristics.

Gender	28 females (56%)	22 males (44%)
Aetiology	25 symptomatic (50%)	25 cryptogenic (50%)
Epilepsy syndromes	22 generalised 3 focal	24 generalised 1 focal
Febrile seizures	20% yes	80% no
Family history for epilepsy	6% positive	94% negative

Table 2
Mean values.

Age at epilepsy onset	1.44 years ± 2.53	Min. 0.0–max. 12.32
Age at KD start	4.44 years ± 3.55	Min. 0.39–max. 16.76
Timelag to KD	3.0 years ± 2.26	Min. 0.08–max. 8.36
Seizure frequency		
Before KD	557.2 ± 1981.5	Min. 0.46–max. 13.680
After 6 months	265.33 ± 663.08	Min. 0.0–max. 4320
AEDs before KD	Mean 5.77 ± 2.49	Min. 0.0–max. 13
Concomitant AEDs	Mean 1.88 ± 0.87	Min. 0.0–max. 3
AEDs post-KD 3–6 m	Mean 1.28 ± 1.16	Min. 0.0–max. 4

Before initiation of the KD patients had received up to 13 different AEDs (mean 5.77 ± 2.49). When starting with the KD patients were on maximum three AEDs (mean 1.88 AEDs ± 0.87). AEDs were reduced to 1.28 ± 1.16 at 3–6 months after initiation of the diet.

There is only scant information regarding the impact of the KD on the pharmacokinetics of AEDs. There is however a historical perception that adding the KD to the short-chain fatty acid valproic acid (VPA) and/or the carbonic anhydrase inhibitors topiramate (TPM), sulthiame (ST) and zonisamide may cause unfavourable interactions. As there is no good evidence for automatic discontinuation of these anticonvulsants prior to KD initiation, it is recommended to add the KD to the existing regimen of drugs, but to monitor patients when receiving the above mentioned anticonvulsants.[13]

At our centre (especially when we started to use the KD), we considered withdrawal of these drugs (especially TPM and STM) before initiation of the KD if possible. Despite this, 21 of the patients had to remain on VPA, 8 on TPM, and 4 on STM throughout the KD.

Table 3
Seizure types.

Seizure types
36 (72%) generalised tonic clonic seizures
21 (42%) myoclonic seizures
13 (26%) complex partial seizures
9 (18%) atonic seizures
8 (16%) astatic seizures
3 (6%) simple partial seizures
2 (4%) tonic seizures

Table 4
Epilepsy syndromes.

Epilepsy syndromes
20 (40%) not classifiable
9 (18%) infantile spasms
8 (16%) SMEI (Dravet syndrome)
4 (8%) Lennox-Gastaut syndrome
3 (6%) CSWSS
2 (4%) temporal lobe epilepsy
1 (2%) myoclonic astatic epilepsy
1 (2%) pseudo Lennox syndrome
1 (2%) progressive myoclonic epilepsy
1 (2%) occipital lobe epilepsy

The diet was started at the classic 4:1 or 3:1 ratio in 31 children (62%), at a 3.5:1 ratio in 4 children (8%), a 3:1 ratio in 13 children (26%), and a 2.5:1 ratio in 2 children (4%). In the last 2 patients blood ketone levels were rather high (5–6 mmol/L) with the 3:1 ratio, so that they were switched to 2.5:1 KD ratio. Moreover, one of these children suffered from diabetes type I and blood glucose levels were quite low with a risk of hypoglycaemia with the 3:1 ratio.[14] Mean duration of the KD was 1.18 years ± 1.06 (min. 0.06, max. 3.87), in 30 children (60%) the KD was maintained >6 months, 20 children (40%) were on the KD <6 months. Follow-up after initiation of the KD was 6 months to 10.86 years (mean 3.93 ± 2.95 years). Follow-up longer was longer than 1 year in 43 children (only 7 children were lost to follow-up after 6–11 months).

3.2. Efficacy (Fig. 1)

25 children (50%) were responders: 12 (48%) of them became completely seizure free, another 13 (52%) had ≥50% reduction in seizure frequency. 25 children (50%) were non-responders. 6 (24%) of them reported a decrease in seizure frequency of <50%, 14 (56%) reported absolutely no effect of the KD and 5 children (20%) reported an increase in seizure frequency, but no new seizure types were observed. In addition, those children continued to have more seizures after the diet was stopped and other treatment options were tried (so it remains unclear if seizure aggravation was due to the KD or to the natural course of the disease).

3.3. Long-term outcome

5/25 responders (20%) were lost to follow-up, 7/25 (28%) had a lower seizure frequency than before starting the KD and 6/25 (24%) fell back to baseline 12–24 months after discontinuing the KD. Among the responders, 5 of the initially seizure-free children showed recurrence of seizures: 4 children relapsed between 0.12 and 1.4 years after the KD had been stopped (mean 0.72 ± 0.61), 1 child relapsed before discontinuation of the KD (after 1.76 years on the diet). Seven patients remained seizure free for more than 12 months after discontinuation of the KD.

Prior to the initiation of the KD, only 4/50 patients (all of them responders) had normal neurological findings. The other 46/50 patients (including all non-responders) showed mild to severe impairment in neurological development ($p = 0.076$). Six months after initiation of the KD 1 additional responder showed normal neurological findings so that now 5 responders (20%) had neurological examination results without any pathological findings and 20 responders (80%) had either a mild or a severe neurological development delay compared to 100% non-responders ($p = 0.038$; Pearson's chi-square).

Comparing neurological findings prior to and 6 months after initiation of the KD, improvement was significantly better in responders than in non-responders (7 responders showed an improvement, 18 remained on their baseline performance, no patient got worse vs. 23 non-responders remaining on their baseline and 2 non-responders getting worse, Pearson's chi-square, $p = 0.008$)

EEG background activity was 4.87 ± SD 3.39 (range 0.00–9.00) cycles/s at the beginning and 5.79 ± SD 3, 12 (range 0.00–10.00) cycles/s at 6 months after initiation of the KD. In non-responders it was significantly higher at start (5.91 ± SD 3.04, range 0–9.0) vs. responders mean 3.92, SD ± 3.47 (range 0–8) cycles/s ($p = 0.041$; t-test), but did not differ from responders after 6 months (non-responders 6.17 ± 2.80, range 0–10 vs. responders 5.44 SD ± 3.41, range 0–10 cycles/s), background activity accelerated significantly only in responders (t-test, $p = 0.014$) after 6 months of treatment. In addition, a lower rate of epileptic discharges was observed in responders compared with non-responders after 6 months: in 9 responders (36%) but only 1 non-responder no epileptic discharges were present after 6 months ($p = 0.009$; Pearson's chi-square). In 7 responders epileptic discharges disappeared immediately after the initiation of the KD.

3.4. Side effects (Table 5)

Adverse effects occurred in only 14/50 children (28%): carnitine deficiency was treated, whereas growth impairment was moderate therefore not treated. One patient with kidney stones was prompted to drink more fluid. All these patients were monitored more closely and the side effects did not lead to an interruption of the KD in any case.

AEDs significantly associated with more side effects were TPM (metabolic acidosis) and VPA (carnitine deficiency, growth impairment): in 8 patients it was not possible to withdraw TPM before initiation of the diet and 6 of these patients showed side effects ($p = 0.001$). VPA had to be continued in 21 patients with 9 of them showing side effects ($p = 0.046$).

In patients with side effects body mass index (BMI) at onset was lower (BMI 13.85 ± 4.14 vs. BMI 15.70 ± 2.83; $p = 0.008$) and cholesterol (Chol) levels at start were significantly higher (Chol 200.14 ± 51.16 vs. Chol 172.15 ± 36.34, $p = 0.040$). Within 6 months on the KD triglycerides (Tri 107.70 ± 74.16 vs. Tri 273.35 ± 268.82; $p = 0.002$) and weight increased significantly in responders (15.47 ± 7.49 to 18.09 ± 9.08; $p = 0.000$), but there were no differences concerning BMI.

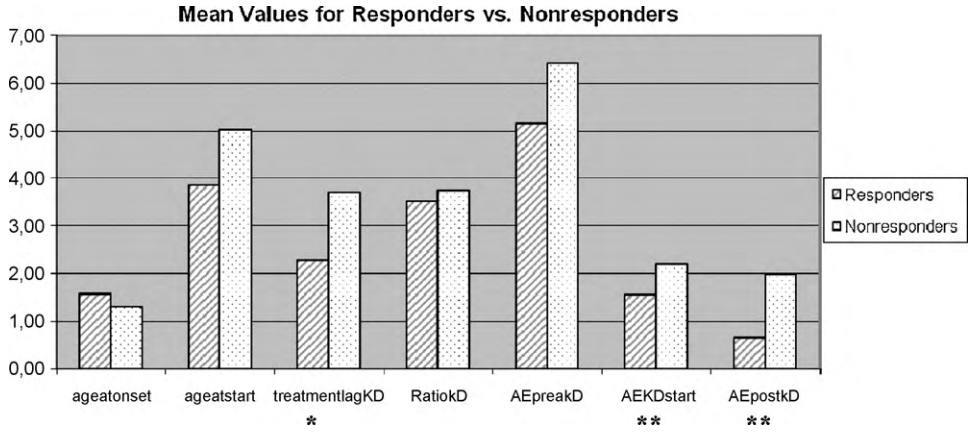

Fig. 1. Responders vs. non-responders.

Table 5
Adverse effects.

Adverse effects
9 (18%) carnitine deficiency
3 (6%) growth deficiency
1 (2%) kidney stones

3.5. Factors associated with (un-)favourable response

There were no significant differences between responders and non-responders with respect to gender, age at initiation of the KD, and aetiology. Responders started after a significantly shorter duration of epilepsy with the KD than non-responders (treatment lag in responders 2.29 ± 1.62 years vs. non-responders 3.71 ± 2.61; $p = 0.025$). Tonic clonic seizures (GTCS) were overrepresented in responders (15/25 non-responders vs. 21/25 responders; $p = 0.059$, Pearson's chi-square).

There was no significant difference between responders and non-responders with respect to specific epilepsy syndromes (Table 1). However, in children with infantile spasms (IS) and in those with Lennox-Gastaut-syndrome (LGS) responder rates were 44% (4/9) and 50% (2/4), respectively (Table 4). Further, 5/8 (62.5%) children with Dravet syndrome (DS) responded to the KD.

There were no significant differences between the various AEDs used or certain drug combinations concerning treatment response. However, responders needed a significantly lower rate of concomitant AEDs ($p = 0.008$) and AEDs were reduced from mean 1.58 ± 0.88 to 0.66 ± 0.86 ($p = 0.002$) at 3–6 months from KD start.

There was no statistically significant difference between responders and non-responders concerning blood ketone levels (measuring compliance): blood ketone levels in responders compared with non-responders did not differ significantly at start of the KD (mean 2.93 mmol/L ± 2.22 vs. 2.85 mmol/L ± 2.55; $p = 0.922$) and after 3–6 months (mean 4.99 mmol/L ± 2.92 vs. 3.76 mmol/L ± 2.25; $p = 0.168$).

Further, there was no statistically significant difference between responders and non-responders concerning carnitine levels, aminoacids, organic acids and blood count.

4. Discussion

Published data on the efficacy of the KD in paediatric epilepsy patients have been remarkably consistent over the past decade[1,15,16] demonstrating cessation of all seizures in about 16% of patients, a greater than 90% reduction in seizure frequency in about 30–40% and a greater than 50% reduction in seizures in up to 60%. There are only a few randomised controlled trials published so far[2,17,18]: Neal et al. studied the benefits of the KD compared to no change in treatment in the control group; mean seizure frequency fell to 62% in children on the KD, whereas it increased to 137% of baseline in the control group.[2] Long-term beneficial effects were seen even after only a few months of use when the diet was discontinued. This potential anti-epileptogenic activity has been recently demonstrated in some animal studies as well.[19] The blinded, crossover study of the KD in children with the Lennox-Gastaut syndrome conducted by Freeman[17,18] aimed to confirm, by the addition of 60 g of glucose per day to negate the ketosis, that the effectiveness of the KD was neither the result of a placebo effect nor due to parental expectations and commitment. The authors found that the additional glucose did not significantly alter the frequency of electroencephalography-assessed events, but did decrease the frequency of parent-reported "drop" seizures ($p = 0.07$). The diet remained effective in decreasing seizures of the Lennox-Gastaut syndrome at 12 days, 6 months, and 12 months.

In our sample of children with drug-resistant epilepsies complete seizure freedom was achieved in 24%, seizure reduction of >50% in further 26%. Thus, efficacy was higher than previously reported.

To date only a few studies have tried to evaluate predictors for (non-)response to the KD[20,21]: starting the KD at a lower age and/or after less than three previous AEDs appeared to be a positive predictive factor. A trend for better outcome in patients with generalised compared to partial seizures was also observed.[21] Specific epilepsy syndromes which have been reported to respond most successfully to treatment with the KD included IS,[22] LGS,[17,18] severe myoclonic epilepsy of infancy (Dravet syndrome),[23] myoclonic astatic epilepsy (MAE),[24,25] Landau-Kleffner syndrome (LKS) where both seizure reduction and an improvement in language skills were seen,[26] and symptomatic epilepsy in various disorders including Rett syndrome,[27] cortical dysplasia[28] and tuberous sclerosis (TS).[29]

In our sample, age at disease onset was lower in non-responders, but this was not statistically significant. However, responders showed a significantly shorter time from disease onset to KD start ($p = 0.025$). Thus, our results support suggestions from other centres that the KD should be used earlier.[1,30] As reported already by others, we found a non-significant trend towards a better response of GTCS,[21] but we were not able to reproduce the result reported by Than et al. recently[31] that complex partial seizures (CPS) are a negative predictive factor. Due to the small number in the various sub-groups we were not able to find a significant association between good/unfavourable outcomes and further seizure types or distinct epilepsy syndromes. However, we found a 44% and thus higher responder rate than reported in the literature in 9 patients with IS after 6 months treatment.[22] We also found a quite high responder rate (62.5%) for genetically verified DS and a high responder rate (50%) also for patients with LGS.[17,18] In contrast, 2/3 children with continuous spikes and waves during slow sleep (CSWSS) did not respond to the KD at all.

According to the literature, the KD seems to enhance the anticonvulsant effects of VPA, carbamazepine, lamotrigine, and phenobarbitale without affecting their pharmacokinetic and side-effect profiles.[32] In our sample, there was no association found between certain AEDs and the efficacy of the KD.[13] However TPM ($p = 0.001$) and VPA ($p = 0.046$) significantly increased the occurrence of side effects, and – as reported by Coppola et al.[33] – VPA increased the occurrence of secondary carnitine deficiency also in our population.

AEDs were successfully reduced in responders 3–6 months after initiation of the KD. As reported by others,[34] responders showed significantly improved EEG findings after 6 months with a significantly lower rate of epileptiform discharges and a significantly better background activity: in 17 children (34%) background activity was not present at all before initiation of the KD (hypsarhythmia in 6 patients) and was observed after treatment in 9 of these children. This is in our opinion a sign of a more physiological development.[35]

Children responding to the KD also showed a significantly better neurological outcome than the non-responder group as early as 3 months after initiation of the KD. However, this result is limited by the fact that it is based only on clinical examination findings and not on formal psychological testing.

Reports about correlations between ketone levels and the success of the KD are controversial: in several studies,[36] the effectiveness of the KD was independent from the measured blood ketone levels, but Gilbert et al.[37] and van Delft et al.[38] found that blood ketone levels correlate better with seizure control than urinary ketones at 3 and 6 months. However, in the study reported by van Delft et al. the only seizure-free patient showed low blood ketone levels. In our sample, there was no statistically significant

difference between responders and non-responders concerning blood ketone levels.

According to the literature, treatment with the KD seems to be relatively safe: nevertheless, early onset adverse effects such as dehydration, gastrointestinal discomfort, infectious disease, high lipids, hyperuricemia, symptomatic hypoglycemia, hyperproteinemia, hypomagnesemia, and hyponatremia have been reported. Late-onset adverse effects include growth retardation (which does not seem to be a problem when the KD is used less than 6 months[39,40]), progressive bone mineral content loss, renal stones, hydronephrosis, iron-deficiency anemia, secondary hypocarnitinemia and cardiomyopathy.[26,41] Compared to the literature, only few side effects were seen in our study population[38] and discontinuation of the KD was not necessary in any case. TPM and VPA were significant negative predictive factors for the occurrence of side effects ($p = 0.001$, resp. $p = 0.046$). Further significant negative predictors for side effects were a lower BMI ($p = 0.008$) and higher cholesterol levels ($p = 0.040$) at initiation of the KD.

5. Conclusion

In general, the KD proved to be an effective and safe treatment option for our patients, especially, when used early in the disease course. The KD proved to be effective in various seizure types, with the best efficacy seen in children with GTCS. Most important, the KD did not exacerbate any specific seizure type.

Although outcome results were not significant with respect to distinct epilepsy syndromes, we found good results in children with IS, LGS and DS, but almost no effect in patients with CSWSS. Although developmental outcome results were based on EEG and clinical neurological examinations only, our data demonstrate improvement in psychomotor development.

Our results are limited by the retrospective nature and the inhomogeneity of the analysed sample. The next steps are therefore prospective studies investigating the syndrome specific long-term treatment response of the KD, the effect of KD-monotherapy after AED withdrawal and the long-term effect of the KD on development using standardised instruments.

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

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