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Can an early 24-hour EEG predict the response to the ketogenic diet? A prospective study in 34 children and adults with refractory epilepsy treated with the ketogenic diet

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ABSTRACT

Purpose: We examined whether early EEG changes in a 24-h EEG at 6 weeks of treatment were related to the later clinical response to the ketogenic diet (KD) in a 6-month period of treatment.
Methods: We examined 34 patients with heterogeneous epilepsy syndromes (21 children, 13 adults) and found 9 clinical responders (≥50% seizure reduction); this is a responder rate of 26%. We visually counted the interictal epileptic discharge index (IED index) in % during 2 h of wakefulness and in the first hour of sleep (method 1), and also globally reviewed EEG changes (method 2), while blinded to the effect of the KD.
Results: At group level we saw a correlation between nocturnal reduction of IED-index at 6 weeks and seizure reduction in the follow-up period. A proportional reduction in IED index of 30% from baseline in the sleep EEG, was associated with being a responder to the diet (Pearson Chi-square $p = 0.04$). EEG scoring method 2 observed a significantly larger proportion of patients with EEG-improvement in sleep in KD responders than in non-responders ($p = 0.03$). At individual level, however, EEG changes did not correlate very strongly to the response to the diet, as IED reduction in sleep was also seen in 15% (method 1) to 26% (method 2) of the non-responders.
Conclusion: Nocturnal reduction of IEDs is related to the response to the KD, however in daily clinical practice, an early EEG to predict seizure reduction should not be advised for individual patients.

1. Introduction

The KD is a high-fat, low-protein, low-carbohydrate diet used to treat patients with refractory epilepsy. The proportion of patients with ≥50% seizure reduction varies from 38–62% at 3 months after initiation of the KD to 27–58% at 6 months.[1–6] A randomized, controlled trial showed that 28 patients of the KD group had greater than 50% seizure reduction (38%), compared to four controls (6%) and five of the KD group had greater than 90% seizure reduction (7%), compared to none of the controls.[7] There were no statistically significant differences in outcome between patients treated with the MCT or classical KD.[7–9] The results of 30 studies with the MAD, of which one RCT demonstrated similar efficacy to the KD.[7–9] Although it is traditionally children who are treated with the KD, there is also evidence of its efficacy in adults.[6,10] The exact mechanisms underlying the effectiveness of the KD have not been elucidated. Because of the dietary changes, the KD is often experienced as a burden. If the response to the KD could be predicted in individual patients before or soon after its initiation,

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this could be helpful in selecting those patients who would potentially benefit from the KD and who should be encouraged to continue the diet.

The frequency of interictal epileptic discharges (IEDs) is a potential predictor for response to treatments. The occurrence of IEDs is correlated to seizure recurrence.[11,12] IED frequency is correlated with seizure-frequency, especially in patients with severe epilepsies.[13] In a recent study Kessler et al.[14] found that a response to the diet was 6 times more likely in children with a proportional IED index decline in wakefulness of ≥10% from baseline at one month of KD treatment.

In our centre, adults as well as children are treated with the KD. We examined whether early EEG changes during wakefulness or sleep 6 weeks after treatment initiation could be used to predict the response to the diet in subsequent months. We hypothesized that if a reduction of IEDs is seen soon after the initiation of the KD, this is related to a reduction in seizure frequency in subsequent months. Secondly, we examined whether baseline characteristics could predict the response to the KD.

2. Methods

2.1. Study design

We compared the IED-frequency in a 24-h ambulatory EEG after 6 weeks of treatment with the KD, to the IED-frequency in a baseline 24-h EEG one week before treatment (Fig. 1). A period of 4 weeks treatment is necessary to obtain stable ketosis. We registered at 6 weeks in order to be early in the treatment phase together with a high chance of all patients being in a steady ketosis at that moment.

A change in IED-frequency was compared with the clinical outcome as defined by the mean seizure frequency during a follow-up period ranging from at least 2 to a maximum of 6 months compared to 2 months baseline. Seizure counts in the first month of KD introduction were not used to define clinical outcome, because this period was necessary to obtain ketosis.

Antiepileptic drugs (AED) were continued unchanged during baseline and the first six months of treatment with the KD. The only allowed exception was an urgent medical reason.

The study was approved by the Medical Ethics Committee according to Dutch Governmental Guidelines.

2.2. Ketogenic diet

The KD was introduced during a 2-week hospitalization according to the Dutch guideline for KD[15]. This guideline does not include a fasting period. Usually the MCT (medium chain triglyceride)-diet was applied but if the insurance company did not refund the diet products, or at the subject's request, the classical diet or modified Atkins diet (MAD) was used. Changes could be made to the MCT-diet because of side-effects and other problems during the introduction phase. When tube feeding was given, a liquid form of the classical KD was used. The start of the diet was defined as the first change made to the daily nutrition. During the KD, ketosis was frequently measured. During the second 24-h EEG, the ketosis was measured in urine and blood or only in blood in cases of incontinence.

2.3. Clinical outcome

Patients and/or caregivers were asked to register seizures in a diary starting two months prior to the introduction of the KD.

The mean seizure frequency during the follow-up period after the 4 weeks of KD introduction was calculated and compared to the baseline mean seizure frequency. When the mean seizure frequency was reduced by ≥50%, the patient was defined as being a clinical responder. If seizure diaries were incomplete, the treating physician was asked to define the patient as a responder or non-responder, using patient's and/or caregiver's information.

2.4. EEG analysis

EEGs were recorded with the localizations Fp2, F4, C4, P4, O2, F8, T4, T6, Fp1, F3, C3, P3, O1, F7, T3, T5, Fp0, F0, C0, and P0. For the comparison of the IED-frequency before and after KD, two EEG scoring methods were used.

2.4.1. EEG scoring method 1

The number of IEDs was visually counted during 2 h of wakefulness (1 h during the day and the first hour after awakening). If possible, the selection was taken from the same hours of the day for EEG 1 and EEG 2, to minimize the effects of circadian rhythm or drug level fluctuations on the IED index. The mean number of IEDs in these 2 h was used to calculate a % of time of IEDs: (number of seconds containing IEDs/total number of

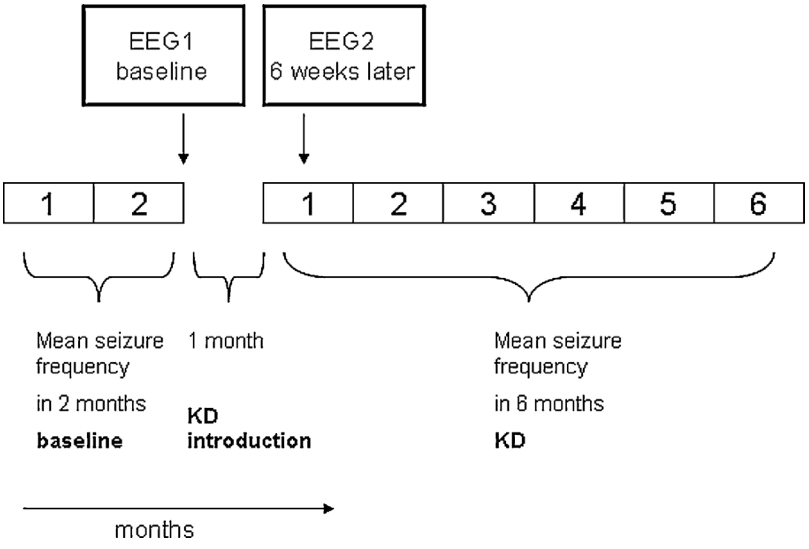

Fig. 1. Study design.