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Comparison of seizure reduction and serum fatty acid levels after receiving the ketogenic and modified Atkins diet

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ABSTRACT

The ketogenic diet (KD) and the modified Atkins diet are effective therapies for intractable epilepsy. We compared retrospectively the KD and modified Atkins diet in 27 children and also assessed serum long chain fatty acid profiles. After 3 months, using an intent-to-treat analysis, the KD was more successful, with >50% seizure reduction in 11/17 (65%) vs. 2/10 (20%) with the modified Atkins diet, $p = 0.03$. After 6 months, however, the difference was no longer significant: 7/17 (41%) vs. 2/10 (20%) ($p = 0.24$). We observed a preventive effect of both diets on the occurrence of status epilepticus. After 1 and 3 months of either diet, responders experienced a significant decrease in serum arachidonic acid concentration compared to non-responders. The KD and modified Atkins diet led to seizure reduction in this small pilot series, with slightly better results after 3 months with the KD, but not after 6 months. The decrease of serum arachidonic acid levels might be involved in the anticonvulsive effects of KD or modified Atkins diet.

1. Introduction

Approximately 30% of patients with epilepsy have refractory epilepsy, i.e. seizures persist despite accurate diagnosis and carefully monitored treatment with antiepileptic (AEDs) drugs.[1,2] The ketogenic diet (KD) is a high-fat, adequate-protein and very low-carbohydrate diet that has been used for many years to treat intractable epilepsy in children. The KD has been shown to be effective in retrospective, prospective and randomized controlled studies.[3–6] In a randomized controlled trial, after 3 months of the KD, 38% of patients had >50% seizure reduction compared with 6% of the controls, while 7% of patients had >90% seizure reduction compared with none of the controls.[5] In Korean and American multicentric studies, more than 40–50% of patients had a >50% reduction in seizure frequency after 6 and 12 months.[6,7]

More recently, the modified Atkins diet has been used to treat intractable epilepsy.[8–13] The modified Atkins diet induces ketosis without fluid, calorie or protein restriction, nor the requirement for fasting or food weighting. Daily carbohydrates are limited and high-fat intake encouraged. The modified Atkins diet was designed to be a less restrictive alternative than the KD. Early studies have suggested efficacy and safety in both children and adults.[8–13]

The mechanisms by which the KD and modified Atkins diet exert their anti-seizure effects are not clear. Among the possible mechanisms of action, it has been hypothesized that various fatty acids, by influencing neuronal excitability, may constitute part of beneficial effects of KD on seizure control.[14–21] In a study of 9 children on KD, elevated blood polyunsaturated fatty acid (PUFA) was found. The rise in arachidonic acid (AA) was correlated with seizure control.[22] However, a decrease in serum AA and an increase of linoleic (LA) and eicosapentaenoic (EPA) acids were found in another study including 25 patients.[23] In the latter, no correlation between serum fatty acids levels and seizure control was found.

We report our experience using both classic KD and modified Atkins diet in children with refractory epilepsy. Our aim was to compare the relative efficacy of the diets and to evaluate serum long chain fatty acids profiles.

2. Methods

2.1. Patients

This retrospective study took place at the Pediatric Neurology Department in Lille University Hospital, France. The subject cohort

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consisted of 27 patients with intractable childhood epilepsy who had been experiencing more than 2 seizures per week which could not be controlled by at least three anticonvulsant drugs. All seizure types were permitted. No child with prior exposure to either the KD or the modified Atkins diet was included.

2.2. Study design

The seizure frequency was determined from parental and medical notes (seizure calendar) at baseline (1 month) and during the follow-up (1, 3, 6 and 12 months on the diet). Children with a ≤50% seizure reduction were classified as non-responders and those with a >50% seizure reduction as responders.

The occurrence of convulsive status epilepticus was compared before and after the start of the diets. We included in this analysis the patients that remain at least 3 months on diet.

At our institution, a non-fasting KD protocol was used from September 2002 to January 2007 but was later replaced by the modified Atkins diet. The classic KD was introduced without initial fasting and fluid restriction. The total caloric amount was given in three days (day 1: 1/3; day 2: 2/3; day 3: 3/3). All patients received the KD with a lipid-to-nonlipid ratio of either 4:1 or 3:1.

The modified Atkins diet consisted of 60% fat, 30% protein, and 10% carbohydrates by weight, without the restriction of recommended daily calories according to patient age. The modified Atkins diet was also introduced without initial fasting. As suggested by Kossoff et al.,[12] for the first month carbohydrates were restricted to 10 g/day, but were permitted to increase by 5 g/day at intervals of at least 1 month when the child was having difficulty with the restriction of carbohydrates, to a maximum of 10% carbohydrates per day by weight.

Following the start of either diet, all patients were advised to remain in the hospital for 3–4 days to ensure adequate diet adaptation. A qualified dietician (EB) also educated the caregivers/parents about preparation of the diet at home. Follow-up clinic visits at 1, 3, 6 and 12 months after initiating either diet were obtained to assess efficacy, tolerability, and associated serum long chain fatty acid profile.

2.3. Fatty acids profiling

Early morning blood samples were obtained from children prior to the initiation of the diet and were planned after 1, 3, 6 and 12 months on either diet. After addition of internal standard (C19:0; 20.2 μg/ml), serum lipids were extracted with chloroform/methanol (2/1, v/v) using a method adapted from this described by Folch et al.[24] Lipids were hydrolyzed and methylated with sulphuric acid and methanol. Fatty acid methyl esters obtained were separated by gas–liquid chromatography using a 30-m Supelco Omégawax ™ 320 fused-silica capillary column. Analysis was performed on a Varian 3400 gas chromatograph (Varian, Palo Alto, CA) equipped with flame ionization detector. Helium was used as carrier gas and column conditions were optimized to separate all the peaks of interest: C14:0, C16:0, C16:1, C18:0, C18:1, C18:2 *n*-6, C18:3: *n*-3, C20:3 *n*-6, C20:5 *n*-3, C20:3 *n*-9, C20:4 *n*-6, C22:6 *n*-3. Results are expressed as percentage of total fatty acids (mean ± S.E.M.).

2.4. Statistical analyses

Statistical Package for the Social Science (version 15.0) (SPSS Chicago, IL) was used for all statistical analyses and a p-value <0.05 was regarded as statistically significant. Categorical data were analyzed using Fisher exact test. Means (±S.E.M.) were analyzed using Mann–Whitney test.

3. Results

3.1. Patient demographics

Twenty-seven patients (15 females) were treated: 17 with the KD from September 2002 to January 2007 and 10 with the modified Atkins diet from January 2007 to June 2008 (Table 1). For 2 patients (patients 7 and 8), KD was replaced by the modified Atkins diet after 5 and 11 months, respectively. The median age at seizure onset was 6 months (range: birth-66 months). The epilepsy syndromes of the included patients were: 30% infantile spasms (8/27), 56% partial epilepsy (15/27), 11% generalized epilepsy (3/27) and 3% Lennox–Gastaut syndrome (1/27). A median of 7 AEDs (range: 3–14) had been attempted before diet initiation. The median age at KD onset was 32 months (range: 11–153 months) and at modified Atkins diet onset was 77 months (range: 4–182 months). Children were receiving a median of 3 AEDs at diet initiation (range: 2–4) (Table 2).

3.2. Treatment efficacy and duration

All children completed at least 1 month on diet. To date, 1 patient remains on the KD and 5 patients are still on the modified Atkins diet. The median diet duration was 5 months (range: 1–24) for the KD and 3 months (range: 1–6) for the modified Atkins diet. Twenty-nine percent remained on the KD after 12 months compared to 20% on the modified Atkins diet.

After 1 month, 10 of 17 (59%) children receiving the KD were >50% improved, compared to 5/10 (50%) of those receiving the modified Atkins diet ($p = 0.28$). Using an intent-to-treat analysis, after 3 months, 11 of 17 (64%) on the KD were improved, compared to 2 of 10 (20%) with modified Atkins ($p = 0.03$). After 6 months, the difference was no longer significant: 7/17 (41%) vs. 2/10 (20%) ($p = 0.24$). Ten of 17 children have stopped the KD (seizure free ($n = 3$), ineffective ($n = 7$), intolerance ($n = 1$)) whereas 5/10 stopped modified Atkins diet (ineffective ($n = 4$), intolerance ($n = 2$)). After 12 months, 8 patients were still on diet (6 KD; 2 modified Atkins diet). The comparison was not possible due to the small number of patients. None of our patient has had major side effects. We observed mild digestive disorders in 2 patients on KD and in 1 patient on the modified Atkins diet (Fig. 1).

There was no difference in the number of anticonvulsants before and after diet treatment. The occurrence of convulsive status epilepticus significantly decreased after the diet initiation (analysis done for 24 patients that remain at least 3 months on diet). Before either diet, the median occurrences of status epilepticus was 1 (range: 0–12) while the median was 0 (range: 0–2) while receiving dietary therapy ($p = 0.005$).

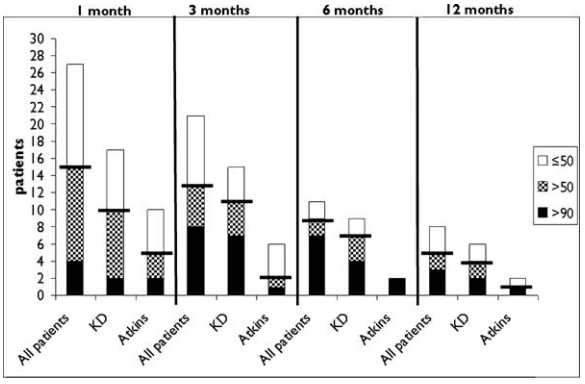

Fig. 1. Seizure reduction in patients remaining on KD and on modified Atkins diet at 1, 3, 6 and 12 months.