Diet transiently improves migraine in two twin sisters: possible role of ketogenesis?

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Summary

The ketogenic diet (KD) was introduced in 1921 to improve drug-resistant epilepsy (Wheless, 2008), but its benefits in other neurological disorders, such as migraine, remain unclear (Maggioni et al., 2011). From the 1970s, many physicians proposed modified KD regimens, characterized by low-carbohydrate and low-fat intake (adipose tissue catabolism accounted for the ketone body production), as a means of achieving rapid weight loss since this is promoted by the anorectic effect of ketosis and protein-induced sense of satiety (Astrup et al., 2004). We describe the case of two twin sisters whose high-frequency migraine was found to benefit from a weight-loss KD. This accidental, retrospective observation prompted us to hypothesise that a KD might be useful for migraine patients.

Introduction

The ketogenic diet (KD) was introduced in 1921 to improve drug-resistant epilepsy (Wheless, 2008), but its benefits in other neurological disorders, such as
patients followed a transitional low-calorie, non-keto-
genic low-carbohydrate diet. During ketogenesis, the patients were under medical supervision and had laboratory blood tests every two weeks (alanine aminotransferase, aspartate aminotransferase, gamma glutamatic transpeptidase, lactic dehydrogenase, alkaline phosphatase, bilirubin, blood urea nitrogen and creatinine), which were always normal. After the third transitional period, a balanced diet was prescribed to allow the patients to maintain their new weight (Patient 1: 58 kg, BMI 21.30; Patient 2: 59 kg, BMI 21.67).

Both sisters, using headache diaries, kept a daily record of their migraine-induced disability. They reported about five to seven attacks/month (14-16 days/month) in the two months prior to starting the KD (Fig. 1). In both cases, the disappearance of migraine coincided with each ketogenic period (headache disappeared as from day 3 after the KD was started/resumed) and returned during the transitional diet periods, albeit with reduced frequency, duration and intensity. During the observation period, reported in figure 1, the patients did not take any preventive medication. Tests for celiac disease were negative, thereby excluding a role of dietary gluten avoidance.

Discussion

We have described the case of a pair of twins who obtained a transient improvement of their migraine during a KD that was cyclically repeated as part of a weight loss dietary program. A previous report described a patient with MOH in whom a weight-loss KD surprisingly led to disappearance of the headache (Strahman, 2006), but the real efficacy of ketogenesis on migraine is still under scrutiny (Maggioni et al., 2011). In fact, available data on the effects of ketogenesis in migraine patients are discordant: although a good response to KD is often described in anecdotal reports, this finding is not confirmed by all authors (Maggioni et al., 2011). In particular, in a pilot study performed on adolescents with chronic daily headache (CDH) no protective effect of KD was obtained (Kossoff et al., 2010). However, this study was affected by several limitations: the normal-weight adolescents did not comply well with the diet; the fact that KD exposes patients to gastrointestinal problems that can reduce their compliance; the patients diagnosed with CDH could have included not only chronic migraineurs but also patients with other comorbidities (other types of headache and/or psychological problems).

It has recently been proposed that weight loss could, in itself, improve migraine in obese women (Bond et al., 2013), however, this is not the case of the twin sisters reported here. Indeed, the fact that migraine improvement coincided with ketogenesis and recurred out of KD (Fig. 1) led us to consider this beneficial effect a consequence of the ketogenesis. Although several other factors (discontinuing analgesics, avoiding trigger foods and taking nutraceuticals) might have concurred to generate the unexpected outcome observed in these sisters, our experience corroborates and extends the observation that KD improves migraine, prompting several considerations. First, as already indicated (Fig.1), the migraine improved before the final weight loss, thus this improvement was not a consequence of the latter; on the contrary, the cyclic withdrawal of the KD was associated with recurrence of migraine, despite the ongoing weight loss. Second, nutraceuticals – magnesium, coenzyme Q10, riboflavin, alpha lipic acid (Sun-Edelstein and Mauskop, 2009) – presumably did not play a role in the migraine improvement, since they need to be assumed at higher concentrations and for a longer time in order to induce therapeutic effects. Third, migraine trigger compounds – phenylethylamine, tyramine, aspartame, monosodium glutamate, nitrates, nitrites, caffeine (Sun-Edelstein and Mauskop, 2009) – were not avoided during the KD. Hence, we attribute the improvement observed in these patients to ketogenesis, the sole event found to be time-locked to the disappearance (and recurrence) of their migraine attacks (Fig. 1); the improvement may be linked to modulation of cortical excitability (Whelch, 2008), dampening of inflammation and neuroinflammatory phenomena (Cullingford, 2004), and inhibition of oxidative stress (leading to reduced free radical formation) in neurons (Maalouf et al., 2007) and of the cortical spreading depression phenomenon (de Almeida Rabello Oliveira et al., 2008). Moreover, ketones are known to improve brain mitochondrial metabolism by enhancing mitochondrial genetic expression (Bough et al., 2006). Interestingly, mitochondrial genetics have already been related to the efficacy of riboflavin, a mitochondrial enhancer, in migraine prophylaxis (Di Lorenzo et al., 2009); a similar effect might be supposed to explain the improvement observed in migraineurs following a KD. Our report provides Class IV evidence (i.e. a clinical opinion) since our hypothesis that weight-loss KD results in migraine improvement is based only on retrospective observation of a couple of cases. However, in view of the cases here reported, we have designed a more extensive prospective observational study in a population of overweight patients recruited at a dietician’s clinic. Preliminary results of this study in 108 migraineurs (52 treated with KD and 56 with a low-calorie diet), presented to the Italian Society for the

Table I – Daily supplements of micronutrients taken by the patients.

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Daily Dose</th>
<th>Daily Dose</th>
</tr>
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<tbody>
<tr>
<td>Vit A</td>
<td>800 mcg</td>
<td>60 mcg</td>
</tr>
<tr>
<td>Vit B1</td>
<td>1.4 mg</td>
<td>5 mcg</td>
</tr>
<tr>
<td>Vit B2</td>
<td>1.6 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Vit B3</td>
<td>18 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Vit B5</td>
<td>6 mg</td>
<td>7.5 mcg</td>
</tr>
<tr>
<td>Vit B6</td>
<td>2 mg</td>
<td>0.6 mg</td>
</tr>
<tr>
<td>Vit B8</td>
<td>150 mcg</td>
<td>90 mg</td>
</tr>
<tr>
<td>Vit B9</td>
<td>200 mcg</td>
<td>1.75 mg</td>
</tr>
<tr>
<td>Vit B12</td>
<td>1 mcg</td>
<td>7.5 mg</td>
</tr>
</tbody>
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Study of Headaches (SISC) (abstract only), seem to confirm that ketogenesis and not weight loss improves migraine: there was a very high responder rate (about 90%) during a one-month KD, while two months after the four-week period of ketogenesis the KD group did not differ from the standard diet group in terms of headache reduction.  

Our observation, if confirmed by further, more extensive studies, may be an indication that overweight patients with high-frequency migraine can benefit from KD in repeated cycles: since most prophylactic treatments for migraine can potentially induce weight gain, the information we report could be very helpful for physicians caring for migraine patients.

Migraine improvement in twin sisters during ketogenic diet

Figure 1 - Diary chart:
The columns show the months, the rows the days. Patients recorded their degree of migraine disability daily on a 3-point scale: 1 = mild; 2 = moderate; 3 = severe.
In the “Weight” row, the patient’s weight, in kg, on the last day of the month is reported. The last row in each chart gives, month by month, the monthly migraine frequency (number of attacks), number of days with migraine in the month, and a monthly mean migraine disability index (sum of day-to-day disability divided the number of days with migraine in the month).
Neither patient experienced migraine attacks during the ketogenic diet, except for a non-migraine headache during menses and influenza in Patient 1 (*). The number of attacks, days with migraine, and the disability index all diminished during and after the ketogenic diet.
References


