Review article

The ketogenic diet in children with epilepsy

D. Papandreou[1]*, E. Pavlou[2], E. Kalimeri[3] and I. Mavromichalis[1]

[1]*2nd Pediatric Clinic, Medical School of Aristotelion University of Thessaloniki, Greece*
[2]*Neurology Department, 2nd Pediatric Clinic, Medical School of Aristotelion University of Thessaloniki, Greece*
[3]*Nutrition Department, General Hospital of Kozani, Greece*

Children with epilepsy, especially those facing intractable seizures, experience a great impact on the quality of their lives. Effective treatment is essential, and although new anti-epileptic drugs have shown an improved profile of action, still a substantial number of children look for more efficacious ways of treatment that are far away from potential toxicity and ineffectiveness. The ketogenic diet is a dietary therapy for epileptic children based on manipulation of metabolism principles and brain energetics. This regimen aims to produce a controlled ketonaemia through excessive dietary fat intake, little carbohydrates and adequate (for growth) protein. The present paper is a review of previous and current papers regarding the proposed mechanisms of the ketogenic diet's action, and the efficacy of the regimen on epileptic children. Unfortunately, a few small studies in sample size and duration tried to evaluate the potential risks of this regimen and their results were rather inconclusive. Further research needs to be done in order for the exact mechanism of the ketogenic diet to be clarified which will help to improve the diet's application, especially for vulnerable epileptic children as far as their growth is concerned.

Epilepsy is a neurological disorder consisting of recurrent spontaneous seizures (Holmes & Ben-Ari, 2001; Cunnane *et al.* 2002), caused by an imbalance between cerebral excitability and inhibition. This imbalance is implicated for a tendency towards uncontrolled excitability (Holmes & Ben-Ari, 2001). Clinical manifestation of epilepsy occurs with epileptic seizures which can be defined as 'a disordered yet rhythmic firing of a population of neurons resulting in a behavioural change' (Cunnane *et al.* 2002) and can be symptomatic, idiopathic or cryptogenic (Anonymous, 1981). It is well known that during a seizure, neurons undergo a prolonged depolarisation which results in changes of the epileptic focus with alterations of γ-amino butyric acidanergic function, increases in synaptic excitation, changes of K^+ or Ca^{2+} currents and extracellular ion concentrations (Holmes & Ben-Ari, 2001). Recurrent severe seizures can lead to brain-cell death (Lipton & Rosenberg, 1994). Epilepsy affects 1–2 % of the child population (Cunnane *et al.* 2002). The incidence of seizure seems to be higher in young individuals than in adults. Although the immature brain seems to be relatively more resistant to epilepsy-induced brain damage than the mature, it is more susceptible to the harmful consequences of repeated seizure activity (Holmes & Ben-Ari, 2001). Children with epileptic seizures, especially those with intractable seizures, experience a great impact on

their quality of life and on psychosocial function (McEwan *et al.* 2004). Intractable epilepsy is defined by inadequate control of seizures despite optimal treatment with conventional medications (Lefevre & Aronson, 2000). In such populations, mortality and accident rates are higher. In addition, children have to face the reality of a poor cognitive function, a low school performance, a social stigmatisation and isolation from their peers (Wheless *et al.* 2001).

Thus, effective treatment is essential for the confrontation of epileptic seizures and the establishment of a better quality of life, especially for children. The usual way of treatment is the provision of anti-epileptic drugs (AED). As intractable is characterised, it is the type of epilepsy that has persistent seizures, although two or more drugs appropriately chosen are provided in a gradual manner alone or in combination until toxicity can be detected (Cunnane *et al.* 2002; Sheth & Stafstrom, 2002). Although new AED have shown an improved profile as far as seizure control and side effects are concerned (Shorvon & Stephan, 1997), placebo-controlled studies from a review paper showed that only 15–40 % of patients with refractory epilepsy were favoured by the addition of a new AED and a small proportion of them stayed free of seizures (Marson *et al.* 1997). Moreover, most of the trials that test new AED have short duration, and thus it is impossible to know the long-term consequences of their

usage (Marson & Chadwick, 2001). Taking into account the aforementioned and the necessity of a better quality of life, an inclination towards new ways of treatment is justified. The ketogenic diet (KD) is thought to be an alternative way of treatment.

Nature of the ketogenic diet

The existence of the KD dates back to old times. The idea that epilepsy could be cured by diet was first proposed as a 'water diet' – initially described by Rawlle Geyelin (1921) based on the work of Michigan paediatrician Hugh Conklic (1922) in which children would be fasted for as long as 3 weeks (Wallas & Farrell, 2004). Dr Wilder (1921) first described the use of a maintained diet to mimic this starvation (high fat and low carbohydrates). It is essentially the same KD that is in use now, as it was observed that starvation-produced ketosis could have an impact on brain disorders (Berryman, 1997; Freeman, 2003). Another researcher (Peterman, 1925) gave the first report about its application and efficacy, with 60 % of his patients being seizure-free and another 35 % having more than 50 % improvement (Vining, 1999; VanItallie & Nufert, 2000). Until then, the only efficacious drugs were phenobarbital and bromides (Wheless *et al.* 2001; Freeman, 2003). Modern pharmaceutical practice has displaced the diet for a while, because it was less convenient for patients and their families who had to adhere in a strict regimen and show compliance with its rules (Berryman, 1997; Wheless *et al.* 2001). The diet experienced its resurgence at the beginning of the 1990s (Stafstrom, 1999). Although many children responded well to conventional AED, still a substantial number was experiencing intractable epileptic seizures due to ineffectiveness (Lightstone *et al.* 2001), whilst potential toxicity from multiple AED (MacCracken & Scalisi, 1999) was another reason for this resurgence.

The classic KD starts with an initial period of fasting and fluid restriction until ketone bodies appear in the urine, followed by the introduction usually of high-fat (80 %), adequate-protein (15 %), low-carbohydrate foods (5 %) (Vining *et al.* 1998).

The diet may be provided in different ratios (fat:(carbohydrates + protein)) that range from 3:1 for infants, children and adolescents, whereas for adults the ratio usually is 4:1. This difference in ratios for younger ages aims to provide a higher protein content to assure adequate growth. As can be seen, 80–90 % of total energy intake comes from fat (Cunnane *et al.* 2002; Freeman, 2003), and the rest is given as protein (1–1·5 g/kg body weight), whereas the smallest amount of carbohydrates is provided (4–5 % of total energy intake) (Kwiterovich *et al.* 2003) in order to achieve sufficient ketosis (Cunnane *et al.* 2002).

Energy intake is reduced to 75–80 % (Freeman, 2003; Kwiterovich *et al.* 2003) of the RDA and fluid intake is calculated to meet 80 % of daily needs (Freeman, 2003).

Caution must be also paid to the type of the protein content, since a considerable percentage of amino acids are glycogenic, and thus can form glucose (VanItallie & Nufert, 2000). The ratio of branched-chain amino acids (BCAA) and aromatic amino acids (ARAA) in the plasma of children who are on the KD may also have an effect on seizures

(Jirapinyo *et al.* 2004). In this study, nineteen cases out of twenty had a significantly higher plasma BCAA:ARAA ratio during the KD than before the diet ($P < 0.001$), with a satisfactory result in the reduction of seizures. It was concluded that the KD produced an increased plasma BCAA:ARAA ratio and this increased plasma BCAA:ARAA ratio may play an important role in controlling epilepsy.

The diet is inadequate in trace elements, minerals and certain vitamins (DiMario & Holland, 2002) and thus supplementation is necessary in order to avoid nutritional deficiencies. Usually, the most important that must be supplemented are Ca, Zn, folic acid, Se, Fe and vitamin D at least at 100 % of the RDA (Bergqvist *et al.* 2003; Thiel & Fowkes, 2004; Hossain *et al.* 2005).

Another type of KD uses medium-chain triacylglycerols (MCT) (Thavendiranathan *et al.* 2000). It provides 60 % of MCT, 11 % of long-chain saturated fats, 10 % of protein and 19 % of carbohydrates. Carbohydrate provision is obviously increased (Liu *et al.* 2003) from that of the classical KD and this makes the MCT diet more palatable. However, it was seen that consumption of the MCT diet is implicated in greater adverse effects, but overall it can be as effective as the classic KD in controlling epileptic seizures (Prasad & Stafstrom, 1998). It is known that ketosis can be inhibited by the consumption of small amounts of carbohydrates, which directly can shift the metabolism to glycolysis (VanItallie & Nufert, 2000; McGhee & Neelam, 2001). This phenomenon can be seen in patients who do not take into account or are unaware of the carbohydrate content of some foods, supplements or medications. Especially for medications there are lists with the carbohydrate content of different medical drugs and supplements that can be received from epileptic individuals while on the KD (McGhee & Neelam, 2001).

Most of the studies (Kinsman *et al.* 1992; Lefevre & Aronson, 2000; Kang *et al.* 2005) show that the diet should be maintained for 2 years and then slowly withdrawn over a 6–9-month period. After this period, consumption of a regular diet is less likely to reinitiate seizure activity (Edelstein & Chisholm, 1996), but knowing that only approximately 10 % of the children on the diet become seizure-free it is difficult to adapt to such a decision (Vining, 1999).

Metabolic pathways of the brain during starvation or using the ketogenic diet

Epilepsy itself induces changes in brain energy homeostasis, but these changes were thought to be manageable through manipulation of the body's metabolic principles. Since glycolysis was connected with seizure activity, the provision of ketones as energy substrate was thought to reduce glycolytic energy, and thus seizure susceptibility (Greene *et al.* 2000). Thus, the KD manipulates the changes in metabolism that starvation can induce in order to have an impact on the harmful changes that epileptic seizures can cause to the brain. Under physiological conditions, the brain derives most of its energy needs from the aerobic oxidation of glucose. Glucose is kept in sufficient levels in the central nervous system so as to be provided in appropriate amounts to neurons. Glucose transport is facilitated by glucose transporters that are expressed at the blood–brain barrier. Homeostatic control is changed in the epileptic brain, transporters' expression is

altered, the blood–brain barrier's nature is changed and thus K movement from blood to the brain can be observed, whereas cerebral blood flow can not meet the present metabolic demands (Bruehl *et al.* 1998). It was Cornford *et al.* (2002) who reported that glucose uptake and metabolism during epileptic seizures are profoundly increased and lactate, which is a precursor of glucose, is significantly increased as well, leading to a marked lactic acidosis. For very small periods of time, deprivation of glucose can lead to the production of glucose via hepatic gluconeogenesis or glycogenolysis. However, for longer periods of glucose deprivation, incomplete fatty acid oxidation can compensate for this energy deficit by providing an alternative source of energy to the brain, through its by-products, ketone bodies (VanItallie & Nufert, 2000). Haymond *et al.* (1983) demonstrated that although glucose production and utilisation are significantly diminished during ketosis, a basal requirement of glucose oxidation is essential for the brain as energy substrate and this was observed when glucose flux was corrected for estimated brain weight, but not when expressed per kg body weight. β-hydroxybutyrate, acetoacetate and acetone are classed as 'ketone bodies'. Acetone is a minor volatile ketone body which is produced mainly from the decarboxylation of acetoacetate (Likhodii *et al.* 2002) and to a lesser degree by the enzymic conversion of acetoacetate (Musa-Veloso *et al.* 2002), and although it had been given less importance than the other ketones, it may play a critical role in the mechanism of the KD's action (Likhodii & Burnham 2002). Once ketone bodies are formed, they are transported across the blood–brain barrier by monocarboxylate transporters (MCT1). Leino *et al.* (2001) indicated that the expression of monocarboxylate transporters in the adult rat brain can be induced several-fold with the implementation of the KD and that glucose transporters are also sensitive to the same factors that cause the up regulation of monocarboxylate transporters, namely fasting, ketosis and hypoglycaemia. However, this up regulation of monocarboxylate transporters

is lower than that found in suckling rats and this finding may imply a difference in substrate usage in different ages. Indeed, during the suckling period, the rat brain readily uses ketone bodies for energy metabolism, whereas a shift to glucose utilisation happens after weaning (Nehlig and Pereira de Vasconcelos, 1993). This is the reason why children can extract ketone bodies as energy substrates during the KD more easily than adults and why the KD is more effective in children (Wheless *et al.* 2001). Ketogenesis, which takes place in the liver, is represented in Fig. 1.

Efficacy of the ketogenic diet

Despite the lack of a well-established mechanism of action of the KD, there are many reports in the literature either on human patients or animals that highlight the efficacy of the diet in reducing or eliminating intractable seizure activity. Both types of KD show effectiveness in the treatment of refractory epilepsy. Particularly for an MCT KD it has been shown that the success rate in seizure control for children between the ages of 2 and 5 years is approximately 50 % (Edelstein & Chisholm, 1996). One of the early studies testing the efficacy of the KD was that of Schwartz *et al.* (1989*a, b*) who tried to establish the efficacy of three different kinds of KD in fifty-nine patients (aged 5–54 years old) with different seizure activity. They used the classic KD, the MCT KD and one modified MCT diet. Results indicated that all three regimens were equally effective in producing ketonaemia, but in the classic KD, the level of ketone bodies was the highest. In addition, testing the short-term clinical effects of the same three regimens on the same population for 6 weeks they showed a reduction in seizure activity >50 % in 80 % of the study population, and <50 % in the 20 % of the rest of the population (Schwartz *et al.* 1989*a, b*). Especially for the classical KD, the success rate of eliminating or decreasing seizure activity reached 67 % of the study population.
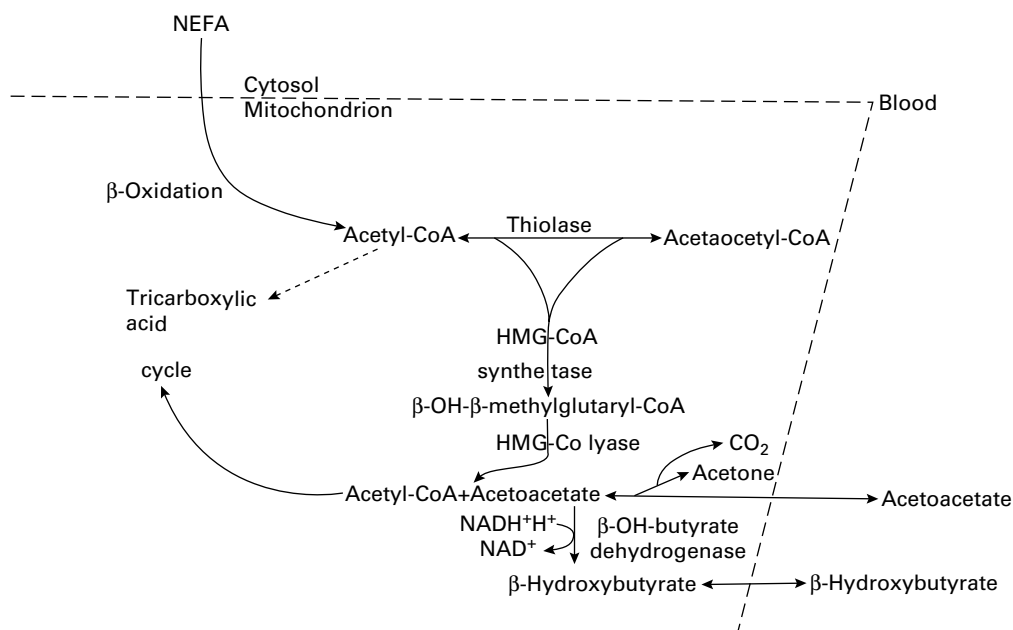

Fig. 1. Ketogenesis in the liver. HMG, β-hydroxy-β-methylglutaryl. (Adapted from Wheless *et al.* 2001.)

Gastrointestinal side effects were greater in the MCT diet, which proved to be more unpalatable, although it was mentioned that MCT diets due to higher carbohydrate content are more palatable (Prasad & Stafstrom, 1998). Seizure type did not interfere with the efficacy of the diet, but when age stood against efficacy it was shown that 84 % of those <11 years old had greater than 50 % improvement, whereas 77 % of those >11 years old showed greater than 50 % improvement.

In a difficult-to-control population with severe intractable epilepsy, Kinsman *et al.* (1992) proved that 67 % improved in seizure control, with 29 % having >90 % and 38 % having >50 % reduction in seizure frequency. Moreover, 64 % managed to reduce medication, in 36 % there was increased alertness and 23 % improved their behaviour. The diet was continued for 75 % of the responders for at least 18 months. Seizure type and length of time on the diet were not predictive of the efficacy of the diet. Results from this retrospective study confirm efficacy of the diet and long-term acceptability from a difficult-to-manage population. The efficacy of a non-MCT KD was assessed by reduction of seizure activity and medication usage in twenty paediatric patients (ages 15 months to 11 years) (Edelstein & Chisholm, 1996). During a 2-week period, seizure activity was diminished in 80 % of the population. Fifty percent were seizure-free for at least the first 2 weeks after their discharge. Illness or dietary unconformity led to relapse in 50 % of them. However, these patients managed to control seizures at the end of the study. As far as the AED are concerned, 15 % were able to wean off all medication and nine patients managed to reduce them. No patient discontinued the diet due to side effects. This trial showed that a non-MCT KD was an effective promising regimen for seizure relief in 80 % of the small study population, but its duration was short.

In a multicentre study of KD efficacy, Vining *et al.* (1998) evaluated seizure frequency in fifty-one children (mean age 4·7 years) at 3, 6 and 12 months. It was found that 10 % of the patients were seizure-free at 12 months whereas 54, 53 and 40 % of the study population had a greater than 50 % decrease in seizure frequency at 3, 6 and 12 months, respectively. There were no relationships when the KD's efficacy stood against age at diet initiation, seizure type or electroencephalographic findings. A greater than 50 % reduction in seizure activity at 12 months increased the probability of staying on the diet at about 80 %, whilst a less than 50 % improvement reduced the probability at 20 %. Compliance was increased due to minimisation of drug-related side effects. This study highlighted the efficacy of the diet across a wide variety of clinical settings and indicated that compliance with the diet goes along with efficacy and impact on the side effects of medication.

During the same year, at Johns Hopkins Hospital (Baltimore, MA, USA), efficacy of the KD was assessed in 150 children (mean age 5·3 years old) with intractable epilepsy that were treated with an average of 6·2 medications. At 1 year on the KD, 55 % of the initial population remained on the diet. Seventy-five of the 150 children appeared to have a persistent decrease in seizure frequency >50 %, 27 % had a greater than 90 % decrease whereas only seven children became seizure-free. There was no significant difference when efficacy stood against age. However, children older than 8 years were less likely to achieve an improvement of more than 50 %. Additionally, these children were also more likely to discontinue the diet before 12 months. Seizure type did not affect efficacy (Freeman *et al.* 1998). The results remained impressive for eighty-three children of the original population in a long-term follow-up at 3–6 years. Thirteen percent (twenty children) of the original population were still seizure-free. From those, one was still on the diet while nineteen discontinued the diet. An additional 14 % had a greater than 90 % reduction in seizure activity, twenty-nine were out of medications, twenty-eight were on one drug and fifteen were still on the diet (Hemingway *et al.* 2001).

Another retrospective study (Hassan *et al.* 1999), using the classical and MCT-modified KD, assessed seizure control based on the percentage change of patients' seizure frequency. Results indicated that only seven patients remained on the diet for more than 1 year and while on the diet, a greater than 50 % decrease in seizure frequency happened in thirty-five patients (67·3 %) of whom six (11·5 %) were seizure-free (Hassan *et al.* 1999). The KD failed to be effective in seventeen patients (32·7 %) (Hassan *et al.* 1999). There was no correlation between seizure control and serum concentration of β-hydroxybutyrate and this finding indicates that ketosis is necessary but rather insufficient to explain the anticonvulsant effect. AED decreased in 59·6 % of the patients and all of them had a greater than 50 % decrease in seizure frequency. Efficacy was not related to the age, duration of seizure activity, type of seizure or electroencephalographic findings. The diet was acceptable to the majority of the patients and adverse effects were infrequent. Death occurred in one patient on the diet; the role the diet played was unclear. The patient was a 19-month-old female in excellent health, except for longstanding multifocal seizures and significant developmental delay. After watching a television documentary about the KD the parents decided, on their own, to initiate the diet without medical supervision. Postmortem examination revealed diffuse gliosis of the brain, worst in the *hippocampi*, bronchopneumonia, and acute fatty infiltration of the liver; no evidence could be found for any underlying primary metabolic disorder (Hassan *et al.* 1999).

DiMario & Holland (2002), at Connecticut Children's Medical Center (Hertford, CT, USA), concluded for one more time that the KD is an effective treatment for intractable seizure activity and is well tolerated. Almost 25 % of those who started the KD discontinued it within the first 6 months. Of those who continued the diet, 39 % had 50 % or more reduction in seizure activity at 1 year and 22 % were seizure-free. Those results could not be explained by variables like age, sex or epilepsy aetiology. There were changes in electroencephalographic findings, suggesting that electroencephalography is a valuable method in assessing potential deterioration or improvement in patients while on the KD. Previous studies have not found changes in electroencephalography (Vining *et al.* 1998; Hassan *et al.* 1999). Moreover, patients that remained on the diet were able to reduce their medications. In a prospective study of three Italian Centres of Child Neuropsychiatry, fifty-six refractory young patients (aged 1–23 years) were assessed for the diet's efficacy taking into account seizure type, epilepsy form and age. At the first month, a seizure reduction of more than 50 % was seen in 42·8 % of the population. At 3 months, 75 %

discontinued the diet, 11 % were seizure-free, 27 % appeared to have a reduction of the number of seizures in a percentage between 50–90 % and 18 % continued the diet although seizure activity decreased less than 50 %. After 1 year, only 8·9 % were on the diet and none was free of seizures but all had a 50–90 % reduction in the number of seizures. Patients less than 8 years old tended to have better responses to the diet. Seizure type and sex failed to show any relationship with the efficacy of the diet. Positive behavioural changes, such as improvement of depression, hyperactivity, mental slowing and aggressiveness, were observed with the withdrawal of one or more anti-epileptic medications. No serious nutritional deficits of protein, minerals or vitamins were observed (Hassan *et al.* 1999).

Other studies tested the efficacy of the KD against different variables, such as developmental and behavioural status or type of epilepsy. In a pilot study, which was a part of the larger prospective study of Freeman *et al.* (1998), sixty-five children of the original 150 were tested for developmental and behavioural status while on the KD (Pulsifer *et al.* 2001). Development status at baseline was significantly delayed and 23 % of the cohort demonstrated significant emotional and behavioural problems. At 12 months, a significant improvement in overall developmental, physical and self-help functions was observed. Significant improvements were also observed in 'attention' and social problems that were problematic at baseline. These results for children being on the KD replicate findings of other studies, indicating increased mental alertness and improved behaviour on the KD (Kinsman *et al.* 1992; Maydell *et al.* 2001; Coppola *et al.* 2002). Further, the KD has been implicated in mechanisms similar to those that mood-stabilising drugs demonstrate, and thus the KD theoretically may act as a mood stabiliser in bipolar illnesses (El-Mallakh & Paskitti, 2001).

Efficacy of the KD against seizure type (focal seizures *v.* generalised) was studied by Maydell *et al.* (2001). Results from 143 patients (mean age 7·5 years) indicated that patients with generalised seizures responded better to the diet than patients with focal seizures, but the difference between the groups was not significant. Approximately 25 % of those with focal seizures had >50 % improvement in seizure activity after 3 months and only six of them appeared to have greater than 90 % improvement. On the other hand, almost half of the patients with generalised seizures had at least 50 % improvement in seizure frequency with no significant differences between different types of generalised seizures. Findings from this study show that regardless of the seizure type, the KD is an effective treatment and a good option if surgery is not possible. The KD is an alternative way of treatment with side effects (acidosis, growth inhibition, kidney stones, increased cholesterol) and adjustments to the diet (for example, increased protein and polyunsaturated fats) can be made when necessary. Table 1 represents the most common and rare complications due to KD treatment being found in the aforementioned studies.

Mode of action of the ketogenic diet

Many studies have focused their research on the potential mechanism by which the KD exerts its protective effects on epileptic individuals. Unfortunately, none of the proposed

Table 1. Complications due to ketogenic diet treatment

Constipation
Vomiting
Diarrhoea
Dehydration
Acidosis
Hyperuricaemia
Hypocalcaemia
Hypertriacylglycerolaemia
Hypercholesterolaemia
Renal stones
Hypoproteinaemia
Oral candidosis
Leukodystrophy
Elevated liver enzymes
Gallstones
Hypoglycaemia
Weight loss and gain
Elevated uric acid
Nutritional disorders
Anorexia
Elevated blood urea N
Cardiomyopathy due to Se deficiency
Carnitine deficiency
Fanconi's renal tubular acidosis
Haemolytic anaemia

mechanisms was sufficient to explain how the KD works and this is obvious through the controversies in the research of explanation. Yudkoff *et al.* (2001) showed that ketosis is related to changes in brain amino acid metabolism, especially with regard to the transamination of glutamic to aspartic acid. Indeed, studies in epileptic mice have shown that aspartate may have a role in the pathogenesis of epilepsy (Flavin *et al.* 1991), and thus reduced formation of aspartate may favour γ-amino butyric acid synthesis, which is an inhibitory neurotransmitter. This happens because aspartate inhibits glutamate decarboxylase and less glutamate is converted to γ-amino butyric acid. KD-induced changes in neurotransmission can also include changes of the excitatory N-methyl-D-aspartate neurotransmitters which, due to their excitatory nature, are thought to be responsible for many forms of seizure activity. Alterations in tissue pH due to ketoacidosis seem to interfere with their receptors that are pH sensitive and thus block their excitatory activity. This interaction may be also facilitated through changes of pH in glial cells that during KD treatment prefer to metabolise glycogen. Glycogen metabolism produces lactate (lactic acidosis) and thus alterations in cell pH. But is there really a change in pH during KD treatment? If there is, then a hypothesis such as this would have a reasonable basis. Notwithstanding, some reports failed to show any changes in pH during chronic administration of the KD (Al-Mudallal *et al.* 1996; Novotny *et al.* 1997) and thus the question remains unanswered.

It is worth mentioning that ketogenesis may be impaired due to carnitine insufficiency, since it is well known that carnitine works as a transporter of long-chain fatty acids inside the mitochondria. The latter have to be esterified by carnitine, otherwise they cannot enter the mitochondria (VanItallie & Nufert, 2000). Low levels of total carnitine may decrease the process of ketogenesis, and thus the desirable KD state of ketosis (Stanley, 1995). It was Berry-Kravis *et al.* (2001) who showed that low levels of carnitine did not relate strongly

with seizure control. Although carnitine levels may decrease over the first few months of KD treatment, they seem to stabilise or normalise after a period of 6 months. Long-term treatment with the KD appears to maintain normal levels of carnitine, whereas the majority of KD-treated patients do not develop carnitine deficiency and thus they do not need supplementation. However, this finding does not exclude the possibility that supplementation may help patients with metabolic disorders that have been proven to be KD-intolerant to stay on the diet. β-Hydroxybutyrate and acetoacetate, after their formation in the mitochondria, are transported towards the brain via the monocarboxylic system (Leino *et al.* 2001). Fig. 2 represents the ketone body utilisation and oxidation in the brain after their transport.

Consumption of the KD has been shown to improve brain energetics, seen as an increase of the ATP:ADP ratio (Ziegler *et al.* 2002). Adversely, ATP levels seem to decline during seizures. This has been suggested as a putative protective effect of ATP in controlling this chronic disorder (Ziegler *et al.* 2002). However, it is not clear how increasing the energy reserve in the brain could reduce brain excitability by increasing the seizure threshold (Bough & Eagles, 1999). Ziegler *et al.* (2002), by investigating basal protein phosphorylation in slices from different brain regions of young rats on a KD, found that they had approximately 40 % greater protein phosphorylation in all brain regions when compared with control rats. An increased ATP:ADP ratio was one of the explanations given for the accompanied elevated protein phosphorylation, whereas elevated ketone bodies were implicated in direct elevation of protein phosphorylation by changing phosphate uptake. Thio *et al.* (2000) also mentioned that ketone bodies *per se* do not directly result in alterations of the primary voltage and ligand-gated ion channels in cultured rat hippocampal neurons. Thus, these alterations may be caused due to changes in protein phosphorylation.

Potential role of polyunsaturated fatty acids

Some investigators examined the role of PUFA as an underlying mechanism of action of the KD. Fraser *et al.* (1993)

Fig. 2. Ketone body utilisation and oxidation in the brain. TCA, tricarboxylic cycle; OAA, Toxalo-acetate; GABA, γ-amino butyric acid. (Adapted from Wheless *et al.* 2001.)

demonstrated that provision of arachidonic acid in a concentration that ranged from 1 to 30 µM shifted Na^+ and Ca^{2+} channels to more hyperpolarised potentials resulting in diminished neuronal excitability. Yehuda *et al.* (1994) reported that the *n*-3:*n*-6 PUFA ratio was a critical variable in the inhibition of seizures induced by several epilepsy models using different doses of the chemical challenge of pentylenetetrazol. In another study involving childhood epilepsy and KD treatment, a positive correlation between elevated serum total arachidonate and seizure reduction was observed, as well as between β-hydroxybutyrate levels and serum total NEFA. Furthermore, elevated cortisol levels were observed in all children and this was thought to be another mechanism of action of PUFA since it is well known that provision of exogenous corticosteroids is considered as therapy for childhood epilepsy treatment (Fraser *et al.* 2003). Since free, non-esterified PUFA have been shown to inhibit seizures at an experimental level, raised plasma and increased transfer of NEFA into the brain may be a direct mediator of seizure control in the KD (Cunnane *et al.* 2002). Finally, changes that can be induced in the lipid composition of a neuronal cell's membrane can result in a series of changes that can inhibit or induce neuronal excitability (Yehuda *et al.* 1994).

Growth and nutritional status of children on the ketogenic diet

Many studies have confirmed the effectiveness of the KD in controlling intractable epilepsies in children; however, in our modern era there are few studies evaluating the potential risks of this regimen. Specific concern has been raised for the diet's impact on the growth and nutritional status of its users, since effectiveness of the diet can keep children on the KD for 2 years (Williams *et al.* 2002). The following studies give a small idea of how the KD can affect growth and nutritional status, but it is difficult to extract and generalise their conclusions because of their relatively small number of patients and their duration. Couch *et al.* (1999) evaluated the impact of the KD on the nutritional status and growth of twenty-six children for a period of 6 months. The diet administration followed a standard protocol at The Columbia-Presbyterian Medical Center (New York; Carroll & Koenigsberger, 1998) and was supplemented with multivitamins, Ca and folic acid so as to provide adequate growth. A polyunsaturated:saturated fat ratio of 3:1 was encouraged and provision of fluids was unrestricted. From baseline to 6 months, measurements of height and weight were taken and nutritional status evaluated with biochemical indexes. At 6 months it was observed that both weight and height increased significantly but mean percentile values of height, weight and standard weight for height remained similar to those at baseline. Only six patients experienced a decrease in standard weight for height but, as mentioned by the authors, 'no patient fell below 100 % of standard weight for height'. None of these patients fell below his or her original height for age or weight for age percentile after 6 months on the diet. Biochemical indexes which include analyses of Hb, packed cell volume, total cholesterol, total protein, albumin, and creatinine remained within normal values, with the exception of a decrease in blood urea N which was thought to be due to inadequate protein intake. Overall, linear growth was

maintained during a 6-month period which was indicative for optimal nutritional status. Longer follow-up may be needed to assess whether linear growth can be maintained in children for the duration of diet therapy.

In another retrospective chart review from Williams *et al.* (2002) on linear growth of children on a KD for almost 2 years, values of height and weight were plotted against standard values for age and sex. At 2 years, eighteen children out of twenty-one had their height percentiles fall below their initial values and only three children managed to maintain or exceed their initial percentile. No differences were observed in mean age, duration of the diet, protein and energy intake between those who managed to grow adequately and those who did not. Factors that might influence linear growth were unknown. Dietary protein intake did not correlate with weight and height changes and serum albumin levels were within normal levels. Furthermore, it is unknown if energy and protein intake might influence outcome and how much can be increased without influencing seizure control and without compromising linear growth. The study provides evidence that some children while on the KD may have their growth retarded. But still, results must be interpreted with caution. Close monitoring of children on the KD is important since growth of children may be suboptimal after 1·2 years on the KD.

Growth, nutritional intake and biochemical indexes of children before and after 4 months of treatment with the classical and MCT KD were also evaluated in a prospective study (Couch *et al.* 1999). Nutritional intake was assessed by using 7 d weighed food records. Anthropometric measurements were compared with standards for linear growth. Results from the 4-month follow-up indicated that weight percentiles decreased on both diets, and especially on the classic KD, but differences on ideal body weight were not significant. Height was significantly increased for both diets and most of the children remained in the same percentiles. The KD group appeared to have an inclination towards lower values for mid-arm circumference, mid-arm muscle circumference and skinfold measurements. It was observed that energy intake remained stable but protein intake decreased for both diets without falling below RDA values. Both diets, if they had not been supplemented with minerals and vitamins, would have been inadequate. The classic KD conferred small increases in the atherogenic apo B, LDL and decrease in the anti-atherogenic HDL-cholesterol of the children but the MCT diet favoured lipid profiles. Furthermore, the MCT diet was more adequate in B vitamins and proved to achieve higher values of serum albumin. Normal growth was maintained for a small period of 4 months and both diets can support this linear growth, although the MCT diet appeared to be more adequate in nutritional support. Caution must be paid as far as the energy and protein provision are concerned for achievement of linear growth and seizure control, and caregivers should encourage the intake of PUFA (40 % dietary fat and 30 % MCT) in order for their children to maintain a good lipid profile (Liu *et al.* 2003).

Finally, Vining *et al.* 2002 evaluated the growth of children after 1 year on KD treatment. Results showed that both height and weight had significant differences between age groups but no differences were observed between boys and girls. Weight gain was minimal for all children throughout the study period.

Children that began the diet above median exhibited a continual decrease in weight scores. Children below the median at initiation lost weight but stabilised after 3 months. Overall, weights remained within normal percentiles for age, although children under 1 year of age showed less weight gain due to restriction of energy intake at 75 % of the RDA. Height was less impaired over the 1-year period. Overall, older children showed that their growth was almost normal compared with standards for linear growth derived from National Center for Health Statistics percentiles (Hamill *et al.* 1997). Specific interest was raised for younger children and for those that were more severely affected by epilepsy, who must be more closely monitored. Unfortunately, this study does not provide enough evidence about the efficacy of the diet to support normal growth, although its duration was longer than the ones previously mentioned.

Conclusions

It has been shown that nearly a third of cases with intractable seizures appear to be seizure-free, another third have a significantly reduced seizure frequency, whereas the remainder do not benefit significantly from the KD (Prasad & Stafstrom, 1998; Wheless *et al.* 2001; Cunnane *et al.* 2002). Overall, the aforementioned studies established the effectiveness of the KD as an alternative treatment for intractable epileptic seizures. In human studies, one could hypothesise that a meta-analysis of the published data could give the public a complete view of the efficacy of the KD, but such a hypothesis is probably not feasible due to a variety of study design (Prasad & Stafstrom, 1998; Wheless *et al.* 2001), difference in the interpretation of the outcomes (Lefevre & Aronson, 2000), differences in the age ranges and in the measured variables. Moreover, its effects on nutritional status and growth remain to be established and many parameters have to be taken into account. It is necessary to design studies that can evaluate growth and nutritional status after discontinuation of the diet, so the issue of 'catch-up' growth can be examined extensively. This would further help to conclude if the diet can safely be used in children without severe long-term effects, if the nutritional status is severely compromised, if the diet can be changed as far as its nutrients are concerned without altering its effectiveness or if there is an optimum time period for maintaining the diet without nutritional or growth consequences.

The KD is more effective in younger ages, but special concern should be given when the diet is prescribed to younger children (<1 year old), due to their greater vulnerability in growth impairment. Since the KD is considered as a therapy and not a fad diet, a patient should be placed on the diet after careful monitoring from a committed and experienced medical team. Children on the KD become more alert and exhibit better behaviour and cognitive function. Diminution or elimination of anticonvulsant drugs with their following side effects is another important factor associated with adherence to the diet. Undoubtedly, these changes have a positive impact on children's lifestyle. Further studies on animals are necessary to elucidate the exact mechanisms by which the KD exerts its effects. So far, what it is known is that ketonaemia derived from the lack of glucose cannot explain the effect of the diet on epileptic seizures. This phenomenon can only be

explored with invasive trials on animals. Realisation of the aforementioned study designs may favour our knowledge on the KD mechanism, and thus a safer and longer usage of the diet may be established.

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