Ketogenic diet and childhood neurological disorders other than epilepsy: an overview

A Verrotti, G Iapadre, S Pisano & G Coppola

To cite this article: A Verrotti, G Iapadre, S Pisano & G Coppola (2016): Ketogenic diet and childhood neurological disorders other than epilepsy: an overview, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2017.1260004

To link to this article: http://dx.doi.org/10.1080/14737175.2017.1260004

Accepted author version posted online: 14 Nov 2016.
Review

Ketogenic diet and childhood neurological disorders other than epilepsy: an overview

Authors: Verrotti A¹, Iapadre G², Pisano S³, Coppola G⁴.

1. Department of Pediatrics, University of L'Aquila, San Salvatore Hospital, L'Aquila, Italy. Electronic address: alberto.verrottidipianella@univaq.it

2. Department of Pediatrics, University of L'Aquila, San Salvatore Hospital, L'Aquila, Italy. Electronic address: giuliah@live.it

3. Department of Child and Adolescent Neuropsychiatry, University of Salerno, Italy. Electronic address: pisano.simone@gmail.com
Abstract:

INTRODUCTION: In the last years, ketogenic diet (KD) has been experimentally utilized in various childhood neurologic disorders such as mitochondriopathies, alternating hemiplegia of childhood (AHC), brain tumors, migraine, and autism spectrum disorder (ASD). The aim of this review is to analyze how KD can target these different medical conditions, highlighting possible mechanisms involved.

AREAS COVERED: We have conducted an analysis on literature concerning KD use in mitochondriopathies, AHC, brain tumors, migraine, and ASD.

EXPERT COMMENTARY: The role of KD in reducing seizure activity in some mitochondriopathies and its efficacy in pyruvate dehydrogenase deficiency is known. Recently, few cases suggest the potentiality of KD in decreasing paroxysmal activity in children affected by AHC. A few data support its potential use as co-adjuvant and alternative therapeutic option for brain cancer, while any beneficial effect of KD on migraine remains unclear. KD could improve cognitive and social skills in a subset of children with ASD.
1. Introduction

1.1 Ketogenic diet: composition and metabolism

Ketogenic diet (KD) is high in fat, moderate in protein and low in carbohydrate dietary regimen. Classic KD is performed on a ratio of grams of fat to grams of protein plus carbohydrate (generally, 4:1, but also 3:1, 2:1, and 1:1 are possible) [1]. Daily energy intake is generally restricted to 80-90% of recommended values. The classic long chain triglyceride (LCT) diet is the more largely used, even if the medium chain triglyceride (MCT) type is to prefer in some cases [2]. In fact, MCT oils provide more ketones per kilocalorie of energy, moreover they are more efficiently absorbed and rapidly transported to the liver; unfortunately, they can cause more frequently gastrointestinal discomfort [3]. For all these reasons, a modified MCT diet, with 30% of energy deriving from MCT and 30% from LCT, is more widely accepted [4]. Another form of KD is the modified Atkins diet (MAD); it includes a ketogenic ratio of 1:1, a very slow and gradual implementation of carbohydrate daily consumption and no limitations on proteins, fluids and calories, making it easier to adhere to the dietary regimen [5]. KD can be administered also as an all-liquid, formula based diet, even to
enterally fed children and to infants not yet weaned. Once initiated, KD should be maintained for at least 3 months; if successful, its discontinuation should be considered after a time of 2 years; (greater periods can be evaluated in children diagnosed with Pyruvate dehydrogenase deficiency (PDHD) or intractable epilepsy)[4].

1.2 Limitations of Ketogenic diet

As for all medical treatments, KD has also potential adverse effects: fortunately, in most cases, only minor side effects have been reported (gastrointestinal symptoms, hyperuricemia, hypomagnesemia, renal calculi, dyslipidemia) [6], which are commonly transient and easy to manage, not requiring KD discontinuation [4]. Anyway, KD has not the same level of efficacy and safety for different neurological disorders. There are specific conditions in which KD has been reported as particular beneficial, such as two distinct disorders of brain metabolism, glucose transporter type 1 deficiency syndrome (GLUT1-DS) and PDHD. KD has also shown great efficacy in certain epilepsy and genetic syndromes, including Dravet Syndrome, infantile spasms, myoclonic-astatic epilepsy and tuberous sclerosis complex. In all these medical conditions, KD can be offered early. On the other hand, KD is contraindicated in many specific disorders of fatty acid transport and oxidation; therefore, before initiating KD, inborn errors of metabolism that could lead to a severe metabolic crisis, should be ruled out [4]. Finally, the best candidates for KD should be appropriately selected, basing on the presence of prerequisites to start the diet in order to ensure safety and to maximize the chance of success. In this regard, it is crucial counseling families before initiating the diet, the dietary supplementation, and the management of children on KD with respect to nutrition, laboratory evaluation, potential adverse effects and possible discontinuation. Thus, a successful management of children receiving KD requires a strict medical evaluation that must be performed in experienced specialized centers.

1.3 Ketogenic diet and childhood neurological disorders: an overview

KD is a generally accepted and effective nonpharmacological treatment for children with refractory epilepsy [2,7-10]. Nevertheless, in the last decade it has been tested for a wide range of neurological
disorders. For example, among the large spectrum of mitochondrialopathies, KD is currently considered as the treatment of choice for PDHD [4]; more recently although based on case studies, KD has been reported to have positive effect, especially in reducing seizure activity, also in children with respiratory chain complex (RCC) defects [11] and other mitochondrial diseases. Patients affected by alternating hemiplegia of childhood (AHC) could benefit from KD, too, as reported in small case series [12-14]. Concerning autism spectrum disorders (ASD), there are some data suggesting its potential role not only in treating epilepsy related to autism, but also in modifying clinical course of disease in terms of social and cognitive skills, although in this field we are at a very early stage [15,16]. Data to support its use as a coadjuvant, alternative, therapeutic option for malignant brain tumors are available, but still based on small case series [17-21]. Its efficacy in reducing frequency and intensity of migraine attacks has been reported in few cases, for which further studies are required [22-24].

The aim of this review is to evaluate advantages and efficacy of KD in some childhood neurologic disorders, in order to individuate new fields of KD employment for the future.

The article is the result of the analysis of literature concerning the use of KD in various childhood neurologic disorders starting from 1975. A research has been conducted on PubMed search indexed for MEDLINE and EMBASE to identify studies using terms “ketogenic diet”, “mitochondrial diseases”, “PDH deficiency”, “alternating hemiplegia”, “brain tumors” “migraine”, “autism”, as key words. Only articles in English language have been reviewed and bibliography has been used for the research of other manuscripts of interest. The date of our latest research was July 2016. We have examined 187 articles focusing on year of publication, author, pediatric studies, number of patients, and type of articles. The different data have been compared and evaluated critically by all authors.

2. Ketogenic diet and Mitochondrial Diseases

2.1 Mitochondrial diseases: role of Ketogenic diet
Mitochondrial diseases are a heterogeneous group of genetic disorders affecting different organs (brain, muscles, heart, etc). They are caused by mutations located in genes either in the mitochondrial DNA (mtDNA) or in the nuclear DNA (nDNA) which code mitochondrial proteins, leading to mitochondrial dysfunction [25]. Although for many years mitochondrial diseases have been considered rare diseases, more recent epidemiological studies suggest that at least 1 in 5000 children can be affected [26]. Though the prevalence of individual mutations is much higher, approaching 1 in 200 live births, [27,28], but only a small proportion of individuals harbouring these mutations develops disease [29]. Indeed, because of the presence of multiple copies of mtDNA in each cell (1000 to 100000), both wild type mtDNA and mutant mtDNA molecules can coexist in variable amount, a condition known as “heteroplasmy”. Hence, the biochemical defect in the cell and the phenotypic expression of disease depend on the percentage of mutant mtDNA which must exceed the tissue-specific critical threshold level. More than 300 mutations have been reported to be involved in the large spectrum of mitochondrial diseases [30]. Although during the last two decades, several new mutations of mtDNA and nDNA have been identified, and our understanding of their underlying pathological mechanisms has been considerably improved, this has not lead to the development of an effective therapy; in fact, currently no curative treatment exists for mitochondrial disorders, except for primary deficiency of coenzyme 10.

However, several symptomatic strategies, including dietary measures and changes in lifestyle, pharmacological treatments and gene therapy can be adopted in order to improve the quality of life and to achieve a better outcome. Therapeutic strategies available for this group of diseases generally tend to increase mitochondrial biogenesis, regulate mitochondrial autophagy, inhibit mitochondrial apoptosis, scavenge toxic compounds, and bypass electron transfer chain defects and nuclear transfer [31].

KD can restrict glycolysis, increase fatty acid oxidation and provide ketones as an alternative fuel source for cerebral, cardiac and skeletal tissues; then ketone bodies are converted to acetyl-CoA that enters the tricarboxylic acid (TCA) cycle and is oxidized to feed the respiratory chain (RC) and produce ATP through oxidative phosphorylation (OXPHOS). Ketosis is also related to an augmented expression of OXPHOS genes,
probably due to a starvation-like response, which would determine the activation of several transcription factors and cofactors resulting in increased mitochondrial biogenesis [32].

KD has also been shown to influence the heteroplasmy rate in cells harbouring mtDNA mutations, resulting in the achievement of subthreshold levels. The exposition to ketogenic media of cybrid cell lines led to a decrease in the heteroplasmy rate of their mutant mtDNA and to a recovery of mitochondrial function [25], through a process of selective autophagy of mitochondria with a mtDNA mutation, carried out by lysosomal apparatus [33].

Several mechanisms have been proposed to explain the role of KD in reducing seizure activity; the increase of mitochondrial ATP production and the decrease of ATP, generated from glycolysis, can determine a selective activation of ATP-sensitive potassium channel resulting in a stabilizing effect on the neuronal cell membrane [34,35]. The neuronal hyperpolarization deriving from the disruption of excitatory glutamate synaptic transmission and the increase of inhibitory γ-aminobutyric acid (GABA) in the cerebral tissue would stabilize synaptic properties and lead to an increased resistance to epileptiform activity. KD is also associated with a neuromodulating activity ruled by circulating factors, which could modulate neuronal excitability altering the extracellular environment. In addition, increased polyunsaturated fatty acid levels could alter membrane composition, activate nuclear receptor proteins and diminish reactive oxygen species (ROS) production through the upregulation of mitochondrial uncoupling protein activity [34].

For all these reasons, in recent years, it has been hypothesized a potential role of KD in the treatment of several mitochondrial disorders. Data from literature over the last decades have reported that the exposition to a ketogenic environment for cultured human cells promoted a heteroplasmic shifting, an increase in the proportion of non-mutated mitochondrial DNA both among cells (intercellular selection) and within cells (intracellular selection), and an augmentation of mitochondrial proteins synthesis [36]. Hence, the effectiveness of KD in mitochondrial diseases due to complex I deficiency could derive from its ability to increase fatty acid β-oxidation that would shift reducing equivalents to complex II, and would bypass a deficient complex I [37].
2.2 Ketogenic diet and mitochondrial diseases: data from animal models

KD could have benefic effects even in lethal mitochondrial cardiomyopathy, as shown in a hypomorphic mouse with a missense mutation of one of the subunits of the Mediator, that showed a significant extend of the lifespan while on KD [38]. The Mediator is a transcriptional regulatory complex, which is essential for promoting preinitiation complex assembly. In mice, this kind of mutation causes a progressive and selective decrease in the transcription of genes necessary for OXPHOS and mitochondrial integrity, resulting in a progressive cardiomyopathy that invariably leads to cardiac failure. Probably, a small percentage of primary cardiomyopathies in human pediatric cases could be positively affected by KD in terms of morbidity and mortality. Also in the transgenic Deletor mouse, a disease model for progressive late-onset mitochondrial myopathy, KD was able to slow down progression of the disease. The authors reported a reduction of the amount of cytochrome c oxidase negative muscle fibers and a blockage of further mitochondrial ultrastructural abnormalities in the muscle. These findings can be related to an augmentation of mitochondrial biogenesis and a restoration of liver lipid levels; nevertheless, no changes have been found in the rate or the quality of mutant mtDNA [39].

2.3 Ketogenic diet and Pyruvate dehydrogenase deficiency

Among the large spectrum of mitochondrial disease, KD is recommended as treatment of choice for PDHD [4]. The Pyruvate dehydrogenase complex is a multienzyme complex, which plays a crucial role in cellular energy metabolism and acid base equilibrium, since it provides the link between glycolysis and the Krebs cycle. Non-sense mutations in one of its five component enzymes are generally responsible for PDHD; the most frequently involved subunit is the E1 subunit, which is encoded by the X-linked PDHA1 gene [40]. This enzyme normally catalyzes the oxidation of pyruvate to acetyl-CoA and its defect can lead to a variety of clinical presentations ranging from sever infantile lactic acidosis to chronic neurological dysfunction or ataxia [41], including recurrent demyelination [42]. In these patients, a strict KD should be initiated as soon as possible, since it provides ketone bodies as alternative sources of acetyl-CoA. In particular, KD was seen to positively affect the epileptogenesis in PDHD, which is caused by energy failure and abnormal neurotransmitter metabolism, progressively altering neuronal excitability. The effectiveness of KD in the
PDHD has been documented in some cases [43-47]. In a study conducted among seven boys with E1 deficiency who received KD with varying degrees of carbohydrate restriction, better clinical outcomes in terms of longevity and improved mental development were seen both for patients who had the diet initiated earlier in life or for those who were placed on greater carbohydrate restriction, even among subjects with identical mutations [43]. More recently, a 39-month-old male with a neonatal onset of PDHD, who failed to adhere to the standard KD, once put on a less restrictive dietary regimen continued to show clinical progress. He was a child who developed early in life hypotonia, hyporeflexia, growth and motor delay, and sporadic episodes of seizure-like activity; when the diagnosis of PDHD was made, Thiamine was started and, at the age of 15 months, KD was introduced resulting in the achievement of seizure and hyperventilation cessation. Unfortunately, after 6 months, he was no longer able to tolerate the diet and a less restrictive dietary regimen was initiated; despite this “modified diet” the child gained weight and continued to show cognitive-behavioural development progress [46]. In another study, a 3-year-old boy with PDHD was put on KD and obtained considerable results; the patient, presenting with generalized hypotonia, severe psychomotor development delay, and refractory epilepsy, within 6 months from the beginning of KD, showed reduction in seizure frequency and improvement in psychomotor development. Unfortunately, the diet was maintained just for a period of 6 months, when complications occurred (hypercholesterolemia and hypertriglyceridemia in association with viral respiratory infections) and the child was forced to interrupt KD [47]. (All case studies are reported in Table 1).

Nevertheless, available data to promote its use are still based on a few uncontrolled case reports; analysing dietary regimens of proven cases of PDHD over the last decades, a great variability of the percentage of daily caloric intake from fat and carbohydrate, within and among patients, and a lack of specificity in fatty acid composition, emerged [48]. In particular, the quantity and the quality of dietary fatty acid composition could deeply affect the long term safety and efficacy of KD, since tissue insulin sensitivity and plasma clearance of low density lipoproteins have been correlated inversely with the saturation degree of long chain fatty acid [49,50]. Moreover, among polyunsaturated acids, omega 3 fatty acid are reported to improve insulin sensitivity of peripheral tissues, decrease serum levels of circulating lipoproteins by inhibiting their
hepatic synthesis and secretion, and turn around the upregulation of piruvate dehydrogenase kinase activities in heart and skeletal muscle [51]. In addition, long-term complications in children on KD for a period longer than 2 years have not been systematically reviewed.

2.4 Ketogenic diet and Respiratory Chain Complex defects

Although in the past the use of KD has been avoided in patients with RCC defects [52], more recent studies have reported good outcomes in terms of seizure rate for individuals with RCC defects treated with KD [53]. In particular, a retrospective study was conducted to investigate the clinical efficacy and safety of KD in 14 refractory epileptic children diagnosed with RCC defects (9 with Complex I defects, 1 with Complex II defect, 3 with Complex IV defects, and 1 with combined Complex I and IV defects). All patients have been monitored for at least 6 months from the initiation of KD. Seven individuals achieved seizure freedom with the introduction of the diet, 3 of whom were able to successfully complete the dietary period without relapse; 4 patients, including two diagnosed with Leigh disease, did not respond to the diet or were forced to discontinue KD because of complications [11]. KD had a favorable effect in the treatment of ophthalmoplegia of a young male aged 7 years with Complex I deficiency; the boy had an early-onset ophthalmoplegia with a progressive development of cerebellar ataxia, dystonia and spasticity. KD led to an improvement in ocular palsy, without affecting other neurological findings [54]. Recently, a case of a female infant with Ohtahara Syndrome, associated with mitochondrial RCC I defect was reported; the baby, affected by NADH dehydrogenase deficiency, showed epileptic seizures refractory to antiepileptic drugs (AEDs)-polytherapy. The baby achieved seizures control and cessation of suppression-burst-patterns within 3 months from the beginning of KD; unfortunately, she experimented seizures relapse 2 months after KD cessation due to maintenance problems [55]. (These data are reported in Table 1).

2.5 Ketogenic diet and other mitochondrial diseases

Favorable outcomes in terms of seizure frequency after KD were reported also for a young girl affected by Alpers-Huttenlocher Syndrome. At the age of 55 months, while on AEDs polytherapy, the patient presented epilepsy partialis continua; after the initiation of KD, clinical improvement including increased alertness,
memory function, a return of bladder and bowel control, ability to speak in 3–4-word sentences and to walk with assistance were reported, in addition to a remarkable EEG improvement. She remained seizure free for seven months, when an intercurrent infection occurred and she was no longer able to reinitiate dietary regimen [56].

KD was also reported to improve mitochondrial dysfunction in Mitochondrial Encephalopathy with lactic acidosis and stroke-like episodes (MELAS), as reported in a case of a 22-year-old Chinese girl. She suffered from MELAS due to mutation in the MT-TL1 gene, showing recurrent episodes of status epilepticus, multiple cortical stroke-like episodes, normal development and recurrent headaches. From the introduction of KD and magnesium supplementation, the patient achieved seizure freedom, a decrease in the frequency of stroke-like episodes and cortical lesions; she was maintained successfully on KD for 1 year [37]. (All cases described above are included in Table 1).

2.6 Contraindications to the use of Ketogenic diet

Conversely, KD is not recommended in some specific disorders: in particular, an absolute contraindication to the use of KD exists for fatty acid transport and β-oxidation disorders, including carnitine deficiency, carnitine palmitoyltransferase (CPT) I or II deficiency, carnitine translocase deficiency, β-oxidation defects, pyruvate carboxylase deficiency and porphyria [4]. In fact, carnitine, thanks to the facilitating action of CPT and carnitine translocase, is responsible for long-chain fatty acid transport across the mitochondrial membrane. Once in the mitochondria, fatty acid are β-oxidized leading to the formation of two carbon units of acetyl-CoA which can feed the Krebs cycle and serve for ATP production or ketones generation. Thus, congenital alteration at any step along this pathway could cause severe catabolic crisis in patients that are fasting or on KD [57,58]. Similarly, in the pyruvate carboxylase deficiency, a mitochondrial enzyme catalyzing the conversion of pyruvate to oxaloacetate, KD should be avoided since it would further impair the tricarboxylic acid cycle activity and energy production, which are already damaged by the lack of the enzyme. Also in porphyria, a low carbohydrate dietary intake would worsen the course of the disease [59].

2.7 Conclusions
In conclusion, KD is worldwide considered particularly beneficial in PDHD; although the last knowledges confirm the efficacy of KD in reducing epilepsy frequency, it seems not to deeply modify the progressive course of mitochondrial disease [60]. Recently, encouraging data about the usefulness of KD in various mitochondriopathies are emerging; in particular, in RCC defects. (Data from literature are reported in Table 1).

3. Ketogenic diet and Alternating Hemiplegia of Childhood

AHC is a rare neurologic condition. It is characterized by episodes of hemiplegia starting in the first months of life, various non-epileptic paroxysmal and non-paroxysmal manifestations which lead to a progressive global neurological impairment [61,62]. Recently, heterozygous mutations in the ATP1A3, the gene encoding the neuron-specific Na+/K+-ATPase α3 subunit, have been identified as the causal mechanism of AHC [63-65]; although the disease has also been associated with rare mutations in other genes, such as CACNA1A, ATP1A2, SCN1A, SLC2A1 and SLC1A3, showing a great genetic heterogeneity. Flunarizine can reduce severity, duration and frequency of the attacks in some cases [62-66], but no curative treatment exists. KD and one of its variants, the MAD, have shown efficacy in the treatment of paroxysmal movement disorders related to GLUT1-DS [67]. GLUT1-DS is a neurological disorder characterized by an impaired transport of glucose across the blood-brain barrier due to SLC2A1 gene mutation [68]. In GLUT1-DS, KD provides an alternative fuel source and its efficacy might be enhanced by its anticonvulsant action. Moreover, in these patients, KD also has a positive effect on movement disorders such as hypotonia, ataxia, dystonia, and paroxysmal exertion-induced Dystonia (PED); seizure and movement disorders control can be achieved by a 2:1 or 3:1 ketogenic ratio [69]. GLUT1-DS and AHC share several paroxystic and nonparoxystic features so that it has been hypothesized that AHC could benefit from KD, too. According to this, in a cohort of ten unrelated patients from Spain and Greece, who were diagnosed with AHC, three of them showed remarkable improvement in the frequency and the severity of the attacks from the institution of KD [12]. More in detail, one girl who showed no clinical benefits while on flunarizine, at the age of 11 years started KD and continued the diet for 1 year, reporting notable advances in behavioral and
sociability context. Similarly, in other two patients who showed a poor response to the administration of flunarizine or benzodiazepines, KD led to a complete cessation of hemiplegic attacks and improvement in cognitive functions. In another paper, a case of a female child with a diagnosis of familial AHC due to ATP1A3 p.Asp923Asn maternally inherited mutation was reported. The young girl, presenting tonic/dystonic and plegic attacks (mostly triggered by exercise), was started on MAD at the age of 3 and 5 months, with a complete disappearing of the attacks for a period of 15 months [13]. Similarly, a 10-year-old girl (with AHC harboring a de novo mutation in the ATP1A3 gene, together with a duplication and insertion in the SLC2A1 gene), showed a great clinical improvement while on KD. After an ineffective flunarizine therapy, KD led to a marked decrease in frequency, length and intensity of paroxysmal events, in addition to changes in hemiplegic attacks, which became less frequent [14]. (The three case studies are included in table 2).

In the reported cases of AHC, the decision to start KD has been generally made empirically, before molecular diagnosis was established. It was found to be more effective in patients with frequent paroxysmal attacks who poorly responded to other conventional treatments. The successful use of KD was reported especially for patients carrying mutations in ATP1A3, sharing clinical features with GLUT1-DS, one of them harboring a SLC2A1 rare variant.

The rationale for the use of KD therapy in AHC has not been yet clarified; nevertheless, reasons to encourage its use are based on findings of impaired cerebral glucose metabolism as detected by FDG-PET studies in a cohort of Japanese AHC patients [70] and the potential role of KD in reducing neuronal excitability. In fact, this is altered in AHC, due to ATP1A3 dysfunction; hence, the stabilizing effect on neuronal membrane would lead to less frequent and severe paroxysmal activity in AHC.

4. Ketogenic diet and brain tumors
Brain tumors are the most frequent solid-type tumors and have the highest mortality rate amongst all forms of pediatric malignant tumors. The main tumor types described are glial tumors followed by Primitive Neuroectodermal tumors or PNET, Plexus Choroid tumors and Craniopharyngiomas.

Medulloblastoma is the most common form of brain tumors in children, comprising almost 25% of all central nervous system (CNS) malignant tumors before the age of 15 years. This tumor may have the onset at any age (birth up until adulthood), but the majority is diagnosed between 5 and 10, with a male predominance of 2:1.

Half of all CNS tumors are glial tumors. The overall 5-year survival for malignant gliomas, which infiltrate the brain stem, is approximately 0% and for optical pathway low-grade gliomas is approximately 90%. Survival for CNS tumors improved significantly from 57% to 65% [71]. However, brain tumors represent the first cause of death from disease in children and adolescents; malignant tumors in general being the second cause of death in this age group after accidents [72,73].

Beyond the classical treatment options for brain tumors including extensive surgical resections, chemotherapy, radiotherapy and surgical treatment of tumor complications (raised intracranial pressure and obstructive hydrocephalus), in the last years, there is a growing evidence for the anticancer, antiangiogenic and proapoptotic effect of disrupting glycolytic metabolism through dietary intervention [74].

There may be a possible link between some pediatric brain tumors and mitochondriopathies. Recent studies have reported that mitochondrial genome and tumor proteome are important factors contributing to brain tumor risk in children. Indeed, findings from these studies [75] on pediatric tumor brain samples including protein expression, mtDNA sequence variation, mtDNA copy number variation and oxidative damage, have shown that these factors may have a significant contribution in the development of pediatric brain tumors.

4.1 Ketogenic diet and brain tumors: animal based studies
KD has been suggested as adjunctive or alternative option for the treatment of brain tumors, such as gliomas. Experimental studies on the effect of ketogenesis in animal models of brain tumors seem to support the potential efficacy in humans [76-80]. In a study [76], a calorie restricted KD supplemented with a low dose of 2-deoxy-D-glucose (25 mg/kg) reduced the CT-2A malignant mouse astrocytoma more than a dietary restriction or 2-DG alone, indicating a synergistic interaction between the drug and the diet. Overall, in these animal models, a calorie restricted diet showed to be effective as an alternative therapeutic option for malignant brain cancer. In other three studies of glioma models [77,78,80], effects of KD were assessed in immunocompetent, syngeneic GL261-Luc2 mouse model of malignant glioma. In the first study [77] patterns of gene expression were compared in tumors vs normal brain from animals fed either with KD or with a standard diet. Animals received intracranial injections of bioluminescent GL261-luc cells and tumor growth was monitored in vivo. KD treatment significantly reduced the rate of tumor growth and was associated with prolonged survival. Moreover, KD decreased ROS production in tumor cells, altered also the gene expression involved in modulating ROS levels, including those as cyclooxygenase 2, glutathione peroxidases 3 and 7, and pyroredoxin 4. In the second study [78] KD decreased tumor microvasculature and expression of vascular endothelial growth factor receptor 2 and other tumor growth markers. In the third study [80], KD significantly enhanced the anti-tumor effect of radiation, suggesting a potential use as an adjuvant to the current standard of care for the treatment of human malignant gliomas. More recently, KD has not been able to suppress tumor growth in a genetically engineered mouse model of medulloblastoma [79]; indeed, serum insulin was significantly decreased in mice fed with KD, with no effect on PI3 kinase activity.

4.2 Ketogenic diet and brain tumors: human based studies

Clinical studies found their rationale and support on pre-clinical studies in mouse models of brain tumors; in fact, heightened glycolysis, even in the presence of oxygen and reduced use of ketone bodies, are specific features of tumoral cells [79]. Few evidences in small series or single cases in human population (especially in adults, more rarely in children) are available [17-21]. Of five patients with advanced brain tumors and favorable response [17,18], 3 were children affected, respectively, by anaplastic astrocytoma
stage IV, cerebellar low-grade astrocytoma grade III, and juvenile pilocytic astrocytoma. All three children aged three and half, five, and eight responded to the diet, showing remission of five, four and one year, respectively. One child, aged 3 and half, received KD as monotherapy, while the other two were on simultaneous multimodal therapy. The duration of response in the remaining two adult patients with malignant glioblastoma lasted about 4 months. It is noteworthy that in one patient a rapid tumor regression was observed two months after starting a KD (600 kcal/day) associated with a mean blood glucose of less than 60 mg/dl, whereas MRI evidence of tumor recurrence was found 10 weeks after the diet discontinuation. In further 20 adult patients with recurrent glioblastoma treated with a not-rigidly calculated and not supervised KD [19], three patients discontinued the diet for poor tolerability, two had a stable disease and one had a minor response after 6 weeks. Median progression-free survival of all patients was 5 weeks (range, 3-13) and median overall survival from the start of the diet was 32 weeks. A trend towards an increase in progression-free survival was reported in patients with stable ketosis compared to others. Globally, KD was demonstrated to be feasible and safe.

A retrospective review [20] of 53 patients with high-grade glioma, revealed that 6 of them were additionally fed with a KD during treatment, including radiotherapy and chemotherapy. Four of six patients were alive at a median follow-up of 14 months. No major side effects due to KD have been reported in any of these patients. In another retrospective small study [81], which included five children with Tuberous Sclerosis Complex, three of them had progression of a known tumor or tumors or the development of a new tumor while on KD. More recently, in two adult patients, aged 55 and 52 years, with malignant glioblastoma [21] treated with KD after therapeutic failure with standard treatments (including tumor excision, radiotherapy and chemotherapy), clinical and radiological evidence of tumor progression has been reported after 4 and 12 weeks, respectively. Possible explanations of KD failure were the difficulty in keeping low blood sugar levels, a positive expression of ketolytic mitochondrial enzymes such as BDH-1 and OXCT-1 in tumor tissue with persisting ability of cancer cells to metabolize ketones and deriving energy for subsequent growth. (All data are reported in Table 3).
5. Ketogenic diet and migraine.

Headache is the most frequently reported somatic disorder in children and adolescents. Headache prevalence in pediatric age is highly variable, ranging between 5.9% and 82%. The primary headaches are the most common, and include migraine with and without aura, tension-type headache and, exceptionally, cluster headache. Migraine headache [82] typically lasts from hours to several days with prominence of nausea and/or vomiting, photophobia and phonophobia. In children, however, migraine headache is commonly localized bifrontally or bitemporally and is usually of shorter duration if compared to adults. A waxing and waning dull pain, distributed as a “hat band”, usually allowing the child to continue his daily activities, characterizes the tension-type headache. The international headache society classification differentiates a sporadic (<12 attacks a year), a frequent (1-15 days a month) and a chronic (>15 days a month) form of tension-type headache [83,84].

Management of primary headache disorder in children is based on acute therapy of migraine attacks and on a pharmacological prophylaxis to be started when migraine attacks are more than 4/month and if non-pharmacological measures have failed. The latter have usually significant success rates in juvenile headache disorders, comprising general measures like lifestyle modification, measures of behavioural medicine, relaxation techniques, biofeedback programs, cognitive-behavioural therapy (extended also to parents), and avoidance of trigger factors. A potential role of dietary treatment (i.e. KD) in migraine disorder has been supposed. In fact, recent studies have suggested that at least some subtypes of migraine may be related to mitochondrial defect. Such a relationship between mitochondria and migraine relay upon deficient OXPHOS, mitochondrial morphological abnormalities and genetic evidence including specific mtDNA mutations and polymorphisms [85]. Furthermore, it has been hypothesized that there may be a different epigenetic status including mitochondrial methylation between healthy controls and individuals with migraine [86].

5.1 Ketogenic diet and migraine: clinical studies
Recently, few reports are available on the potential role of KD in patients with overweight/obesity and recurrent headache, in whom several prophylactic treatments had failed. The rationale may be linked to the modulation of cortical excitability by ketone bodies [87], dampening of inflammation, neuroinflammatory phenomena [88], inhibition of oxidative stress (leading to a reduced free radical formation) in neurons [89] and to cortical spreading depression phenomena [90]. More in detail, KD was found to be effective in improving high-frequency migraine without aura in two 47-year-old twin sisters who were taking the diet in order to lose weight [22]. Before starting the diet, both patients experienced an average of 5-6 attacks/month of severe headache with related symptoms, including phono-photophobia, nausea and occasional vomiting. Several prophylactic treatments had failed in the past. According to the dietary protocol, a ketogenic regimen was adopted for repeated 4-week cycles separated by two-month interval during which patients followed a transitional low-calorie, non-ketogenic low-carbohydrate diet. Both sisters, using headache diaries, experimented the disappearance of migraine concomitantly with each ketogenic period. Migraine improvement seemed to be more linked to ketogenesis and less probably to the weight loss itself. Following this observation, the same Authors recruited from a diet clinic 96 overweight females suffering from recurrent migraine attacks [23]. Patients were randomized to a KD (n=45) or a standard diet (n= 51) prescription. At baseline and at 6-month follow-up, the following variables were taken into consideration: baseline attack frequency, number of days with headache, and tablet intake per month. In the KD group, all these variables were significantly reduced after the first month of diet. After a slight worsening of each variable in the second month, there was a sustained improvement up to month 6, as compared to standard diet group. KD efficacy in migraine disorder could be related to its ability to enhance mitochondrial energy metabolism and counteract neural inflammation. In a previous prospective, open-label study [24], 8 adolescents, aged 12-19 years, with chronic daily headaches (minimum of 15 headaches per week) for at least 3 months’ duration, were treated with MAD. All patients had failed at least two pharmacological preventative drugs prior to enrollment. Adolescents were restricted to 15 g/day of carbohydrates. Three patients (38%) completed the 3-month period study, while the other five discontinued because of lack of efficacy and restrictiveness. None had any reduction in headache frequency. These results could be due to the difficulty of carrying on such a restrictive dietary regimen in
teenagers, who are probably poorly motivated by being normal weight at baseline. Anyway, also this conclusion can not be firmly drawn, since the efficacy of KD in migraine has not yet been proven and is currently not supported by consistent data. (All data are reported in Table 4). Furthermore, no data are available so far for headache in mitochondriopathies treated by KD.

6. Ketogenic diet and Autism

ASD, according to the latest version of the DSM-5, includes all syndromes and clinical conditions defined previously as pervasive developmental disorders in DSM-IV-TR. New diagnostic criteria for ASD are: a) persistent deficits in social communication and social interaction across contexts; b) restricted, repetitive patterns of behaviour, interests, or activities; c) symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities; d) symptoms limit and impair everyday functioning [91].

In order to improve social interaction and communication, the most effective intervention program is worldwide considered the applied behavioural analysis; while among the evolutionary approaches, the Denver model has given promising results. As for the pharmacological intervention, literature is unanimous in recognizing that no specific drugs for ASD treatment are so far available [92]. Therefore, antipsychotics are among the most widely used drugs for treating challenging behaviours in these subjects (hyperactivity, inattention, compulsions and rituals, mood swings, irritability, self- and hetero- aggressiveness, sleep disorders). However, such drugs are often disappointing and ineffective, also resulting in not negligible side effects [93].

For this reason, KD has been recently introduced, with the aim of decreasing severity of challenging behaviours and improving mood stability in these patients. The rationale is, basically, the same of headache disorder. Indeed, as for the relationship between KD and ASD, we need to distinguish the role of KD in the treatment of seizures associated with ASD, the use of the KD in the treatment of the core symptoms of ASD and, the KD in animal models of autism.
6.1 Ketogenic diet and animal models of autism

Clinical data about the potential role of KD in autistic disorder are substantiated by experimental mouse models of autism. In mouse models of ASD, i.e., Rett syndrome [94], BTBR model [95], and prenatal valproic acid (VPA) model of ASD [96], the use of the KD has improved behavioural abnormalities (increased sociability and decreased self-directed repetitive behavior) and/or decreased the number of seizures, normalized ataxia, and increased life span of mutant mice. However, while KD was originally designed to be administered under controlled caloric intake, most of the mouse studies have been performed under ad libitum conditions and/or for a relatively short period [95]. In another study, pregnant animals received a single-intraperitoneal injection of 600 mg/kg VPA. In the offspring group fed with KD, there were improvements in social behaviour. In fact, these mice displayed higher scores in sociability index and social novelty index when compared with the VPA mice fed with a standard diet [96].

6.2 Ketogenic diet and seizure associated with autism spectrum disorder

It is well established that individuals with ASD have higher prevalence of epilepsy and/or subclinical epileptic discharges (SEDs), compared to healthy individuals [97]. Although the exact relationship to the etiology of ASD remains to be further defined in many cases, epilepsy is associated with higher rates of intellectual disability [98], more severe ASD symptoms [99], and higher rates of mortality [100], especially if it continues into adulthood. The underlying causes of epilepsy are often related to genetic [101] and/or metabolic abnormalities found in ASD individuals.

Among ASD population, it is then necessary to distinguish two subgroups: ASD children with SEDs and those with ASD and epilepsy. Both groups share similar features including more frequent regression, neurological and brain MRI abnormalities. Indeed, children with ASD and epilepsy have more severe intellectual disability and more severe socialization and hyperactivity disorders, compared to those with SEDs only.

Furthermore, two neuropathological findings are shared by ASD and epilepsy: abnormalities in minicolumn architecture and GABA neurotransmission [102], as reported in medical conditions associated with both
epilepsy and ASD, including specific genetic syndromes, specific metabolic disorders and immune dysfunctions.

On the other hand, KD has a long and successful history for treating refractory epilepsy, showing an effect comparable to AEDs [103]. In a retrospective case-control survey study [104], based on parental perceptions of effectiveness, KD was rated as being the most favorable non-AEDs treatment in improving seizures, and was also rated as providing favorable effects on other important clinical factors related to ASD. More in detail, responses were obtained in 733 children with seizures. In general, AEDs (mainly VPA, levetiracetam, lamotrigine and ethosuximide) were perceived to decrease seizure frequency, but worsened other clinical factors. Conversely, some non-AEDs treatments such as KD, were reported to have favorable effects both on seizures and on other clinical features as behaviour disorders. In particular, a single case study [105] reports the administration of a gluten-free casein-free modified KD (1.5:1 lipid: non-lipid ratio; medium-chain and polyunsaturated fatty acids) for a period of 14 months to a 12-year-old child with ASD, seizures, medical comorbidities associated with a family history of metabolic and immune disturbances. Because of improvements in seizure activity, electroencephalogram pattern, cognitive and social skills, language function, and complete resolution of stereotypies, anticonvulsant medication doses were reduced without worsening of seizures. Notably, the administration of the diet was accompanied by a wealth of medications, a significant weight loss, and transitioning to puberty; for all these reasons, it is difficult to evaluate the role of KD.

6.3 Ketogenic diet and core symptoms of autism spectrum disorder

Concerning the use of KD in the treatment of children with autistic behaviour, the literature remains largely limited to a prospective pilot study [15], with a group of 30 children aged between 4 and 10 years, with autistic behavior. The John Radcliffe diet (a modified medium-chain triglyceride diet with a caloric distribution of 30% in medium-chain triglyceride oil, 30% fresh cream, 11% saturated fat, 19% carbohydrates, and 10% proteins, with a ratio between fat /protein and CHO varying between 3:1 to 4:1) was administered for 6 months, with intervals of 4 weeks interrupted by two diet-free weeks. Of the 30 children, 40% did not comply or did not tolerate the diet. From the remaining 60%, two children with
milder autistic behaviours showed the highest improvement (as judged by total Childhood Autism Rating Scale score) in concentration and learning abilities, social behavior and interactions, while the others showed mild to moderate improvement. Interestingly, the beneficial effects of KD persisted even after termination of the trial. Six of the children enrolled in this study had a higher baseline ketonemia with no apparent PDH and/or RCC deficiencies. Anyway, it is not clear if any of the other patients underwent this screening, in addition to the lack of the inclusion of a control diet before administering the KD to the ASD group or during the trial. Authors, therefore, stated that there was some evidence for KD to be a potential alternative or additional treatment at least in a subset of children with ASD. Currently, no relationship can be drawn between diet type and clinical findings. Another study [16] performed a detailed metabolic screening in a Greek cohort of 187 of ASD patients revealing biomarkers such as urine 3-hydroxiisovaleric acid and serum B-OH-B in 7% of patients for whom biotin supplementation or a KD prescription resulted in mild to significant clinical improvement in autistic features. These preliminary data seem to suggest that at least a subset of patients with ASD may benefit from dietary treatment with KD, showing improved learning abilities and social skills. (All data are reported in Table 5).

7. Expert commentary

The use of KD for childhood neurological disorders other than epilepsy is constantly increasing. In the last years, the particular metabolic state induced by KD has been widely studied; theoretical basis for the efficacy of KD have been provided for many disorders. In particular, KD can be an effective therapeutic tool for several mitochondrial-based diseases; according to this, there is a large evidence for KD to improve mitochondrial functioning and induce mitochondriogenesis.

Mitochondrial dysfunction is nowadays recognized as central in many medical conditions, including neurodegeneration, inflammation, cancer, etc. Among the large and heterogeneous spectrum of mitochondriopathies, KD is still recommended as first line therapy for PDHD, in which the diet shows efficacy in reducing epilepsy rate, but seems not to deeply modify the course of disease; single cases or
small case series support its beneficial employment also in some RCC defects and MELAS. In fact, thanks to its capacity of neuromodulating and its stabilizing effect on neuronal membrane, KD is able to reduce seizure activity in several and different conditions. This could lead to a decrease not only in epilepsy rate in various mitochondriopathies, including RCC defects, but also in children diagnosed with ASD, for whom latest studies suggest that KD could even influence social and cognitive skills, including ASD core symptoms, at least in a subset of patients.

Nonetheless, it should be emphasized that the few available studies are mostly experimental or based on questionnaires to parents, while the effects of KD should be more properly evaluated, for example, by means of semi-structured tests (eg. ADOS) for a more accurate assessment of changes on autism’s core symptoms.

Data supporting any potential role of KD in improving migraine are available, but still based on small case series. In this field, there is a strong need for KD to be further assessed in randomized controlled trials (RCT).

Moreover, thanks to its anticancer, antiangiogenic and proapoptotic properties, KD could represent an adjunctive or alternative option for the treatment of malignant brain tumors. In this topic, we probably are at a very early stage; more accurate data on the potential benefit of KD can only come from RCT studies (not easy for ethical reasons) in homogeneous populations by age, type of cancer, timing at diet onset (eg. as early as diagnosis has been made), in addition to conventional treatments.

Finally, recent data suggest the potential role of KD in children diagnosed with AHC; in some of these patients, KD seems to improve the clinical course of disease, especially thanks to its emerging capacity of reducing paroxysmal activity. Anyway, at present, these data are still based on a few reported cases.

8. Five-year view

Among mitochondrial disease, KD is currently considered as first line therapy in PDHD. Nevertheless, its use is based on reports of a few children affected by PDHD, who improved dramatically while on KD; in
addition, these reports did not provide detailed information about the caloric distribution of nutrient components. For all these reasons, more detailed systematic studies are requested, in order to achieve a better compliance of the patients to the diet, and to investigate the effect of both standard and less restrictive KD on long-term outcomes. Also concerning the emerging role of KD in other mitochondriopathies, including RCC defects, although some studies have suggested its efficacy as a therapeutic tool, we believe that more clinical trials are needed in order to clarify pathophysiological mechanisms underlying these kinds of diseases and thus to determine which individuals are more likely to benefit from KD. Actually, KD could be proposed cautiously with regard to its side effects and in the absence of definitive evidence for its real efficacy. For some mitochondriopathies, the use of KD is still based on animal models or in vitro experimental; further studies which would investigate KD efficacy in vivo or among human population, are needed.

At the moment, the use of KD is being investigated with promising results, even in other previously discussed neurological conditions: in patients affected by AHC, KD has shown positive effect in attenuating paroxysmal activity and we expect an expanding use of the diet also in other similar and emerging conditions; for which, further studies, including larger populations, are warranted. With regard to malignant brain tumors, given the multitude of simultaneous variables that must be considered in this field, KD could be proposed as a co-adjuvant-therapy depending on the clinical pattern and the extent of the disease; however, larger case series should be provided. The same for migraine and ASD, for which initial data supporting the potential usefulness of KD, should be confirmed by, at least, well conducted open studies.

Next years will probably witness an expanding investigation of KD role in emerging various medical conditions, through more structured, human based studies.
9. Key issues

- KD represents the treatment of choice for PDHD.
- Emerging data from literature suggest its potential role on reducing seizure activity and achieving better clinical outcomes in various mitochondrial diseases, including RCC defects.
- Alternating hemiplegia could benefit from KD, especially concerning paroxysmal activity.
- In addition to its efficacy in decreasing epilepsy rate in children with ASD, KD could improve cognitive and social skills in children being affected.
- Thanks to anticancer, antiangiogenic and proapoptotic properties, KD could represent an adjunctive or alternative option for the treatment of brain tumors.
- KD could be effective in reducing intensity and frequency of migraine attacks in selected cases, although available data are still few.
- In addition to its potential efficacy in decreasing seizure frequency in children with ASD, KD looks promising in improving cognitive and social skills in autistic children, though well-conducted clinical studies are currently missing.
- Before starting KD, inborn errors of metabolism should be carefully investigated and excluded.

Funding

This paper was not funded.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Table 1. Effect of Ketogenic diet in the treatment of mitochondriopathies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Mithochondriopahies</th>
<th>Type of KD</th>
<th>Patients enrolled (n)</th>
<th>KD duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wexler et al. (1997)</td>
<td>PDHD</td>
<td>KD with different degrees of CHO restriction (3:1, 2:1, 1:1)</td>
<td>7 boys</td>
<td>variable (ranging from 4 months to 14)</td>
<td>favorable (increased longevity and improved mental development)</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Condition</td>
<td>Treatment</td>
<td>Age Cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------</td>
<td>--------------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falk et al. (1976)</td>
<td>PDHD</td>
<td>Less restrictive KD (&lt;1:1 ratio)</td>
<td>2 boys</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>not well defined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable (increased rate of growth, development, strength, endurance)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wijburg et al. (1992)</td>
<td>Leigh disease associated with PDHD</td>
<td>KD (1:1 ratio)</td>
<td>1 boy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable (clinical and biochemical amelioration, striking improvement of cerebral lesions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El-Gharbawy et al. (2011)</td>
<td>PDHD</td>
<td>Classic KD (3:1 ratio) and less restrictive KD</td>
<td>1 boy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months on classic KD, 1 year on less restrictive KD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable (seizures cessation, cognitive and behavioural progress)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Pisa et al. (2012)</td>
<td>PDHD</td>
<td>Classic KD</td>
<td>1 boy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable (reduced seizure frequency, improvement in psychomotor development)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kang et al. (2007)</td>
<td>RCC defects</td>
<td>Classic KD (4:1 ratio)</td>
<td>14 children</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable (7 patients: seizures free, 2 patients: reduction of seizures frequency)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>not favorable (4 patients: not response to KD or not able to complete KD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laugel et al. (2007)</td>
<td>RCC I defect</td>
<td>KD (3:1 ratio)</td>
<td>1 boy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable (improvement in ocular palsy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seo et al. (2010)</td>
<td>Ohtahara Syndrome associated with RCC I defect</td>
<td>KD (2:1 ratio)</td>
<td>1 female infant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not specified (at least 3 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable (partial seizure control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joshi et al. (2009)</td>
<td>Alpers-Huttenlocher Syndrome</td>
<td>Classic KD (4:1 ratio)</td>
<td>1 girl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable (seizure control, improvement in psychomotor development)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steriade et al. (2014)</td>
<td>MELAS</td>
<td>Modified KD not well defined</td>
<td>1 girl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>favorable (seizure cessation, decreased frequency of stroke-like episodes)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Effect of Ketogenic diet in the treatment of alternating hemiplegia of childhood.

<table>
<thead>
<tr>
<th>Study</th>
<th>Mutations involved</th>
<th>Type of KD</th>
<th>Patients enrolled (n)</th>
<th>KD duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vila-Pueyo et al. (2014)</td>
<td>ATP1A3 (patients 1 and 2)</td>
<td>Not available</td>
<td>3 patients</td>
<td>Variable (1-2 years)</td>
<td>Favorable (reduction in the frequency and severity of the attacks, improvement in cognitive functions)</td>
</tr>
<tr>
<td></td>
<td>ATP1A3 + CACNA1A (patient 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roubergue A et al. (2015)</td>
<td>ATP1A3</td>
<td>MAD</td>
<td>1 girl</td>
<td>15 months</td>
<td>Excellent (complete disappearing of the attacks)</td>
</tr>
<tr>
<td>Ulate-Campos et al. (2014)</td>
<td>de novo mutation in the ATP1A3 gene with a duplication and insertion in SLC2A1 gene</td>
<td>KD (ratio 4:1)</td>
<td>1 girl</td>
<td>4 years</td>
<td>Favorable (reduction in the frequency and severity of the attacks, improvement in motor function)</td>
</tr>
</tbody>
</table>

AHC: alternating hemiplegia of childhood; KD: ketogenic diet; MAD: modified Atkins diet;
Table 3. Effect of ketogenic diet in the treatment of brain tumors.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of tumor</th>
<th>Type of KD</th>
<th>Patients enrolled (n)</th>
<th>KD duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebeling et al. (1995)</td>
<td>Advanced stage malignant Astrocytoma tumors</td>
<td>Classic KD</td>
<td>2 pediatric females</td>
<td>8 weeks</td>
<td>Favorable in 1 patient, free of disease progression up to 12 months</td>
</tr>
<tr>
<td>Rieger J (2014)</td>
<td>Recurrent glioblastoma</td>
<td>carbohydrate intake to 60 g/day, highly fermented yoghurt drinks (500 ml per day) and two different plant oils (basic oil and addition oil)</td>
<td>20 adults (13 F, 7 M)</td>
<td>6 weeks</td>
<td>Moderate at best: 3 patients, stable disease up to 11, 12, 13 weeks, possible synergistic effect with other therapies</td>
</tr>
<tr>
<td>Champ CE et al. (2014)</td>
<td>Glioblastoma multiforme</td>
<td>Classic KD</td>
<td>Retrospective analyses of 53 patients, 6 of whom received KD</td>
<td>Not available</td>
<td>Favorable: 4 patients alive at a median follow up of 14 months</td>
</tr>
</tbody>
</table>
Schwartz K et al. (2015) Glioma Classic KD 2 12 weeks Unfavorable: both patients progressed their tumor (one after 4 weeks, one after 12 weeks)

KD: ketogenic diet.

Table 4. Effect of Ketogenic diet in the treatment of migraine.

<table>
<thead>
<tr>
<th>Study</th>
<th>Severity of migraine</th>
<th>Type of KD</th>
<th>Patients enrolled (n)</th>
<th>KD duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Lorenzo et al. (2013)</td>
<td>5-6 attacks per month (up to 72 hours of duration)</td>
<td>weight-loss KD</td>
<td>47 years old twin sisters</td>
<td>4-week cycles separated by two-month intervals</td>
<td>Favorable: migraine disappeared during each KD period (from day 3 of KD start) and returned during the transitional diet periods, albeit with reduced frequency, duration and intensity.</td>
</tr>
<tr>
<td>Di Lorenzo et al (2015)</td>
<td>Not specified</td>
<td>very-low-calorie KD</td>
<td>45 (KD group), 51 (SD)</td>
<td>4 weeks followed by 5 months of SD</td>
<td>Favorable: migraine improved in the KD group (attack frequency, days with headache, tablet intake) during the KD period and worsened after the transition to SD</td>
</tr>
</tbody>
</table>
Kossof et al. (2010) 15 headaches per week for 3 months MAD 8 adolescents 12 weeks Indifferent: no effect on headache frequency

KD: ketogenic diet; MAD: Modified Atkins Diet; SD: standard diet.

Table 5. Effect of ketogenic diet in the treatment of Autism Spectrum Disorder.

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment</th>
<th>Patients enrolled (n)</th>
<th>Type of KD</th>
<th>KD duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frye et al. (2011)</td>
<td>Seizures associated to ASD</td>
<td>Survay of 733 parents of subjects with ASD</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Favorable: KD was perceived to improve seizures as well as other symptoms</td>
</tr>
<tr>
<td>Herbert et al. (2013)</td>
<td>Seizures associated to ASD</td>
<td>1 patient</td>
<td>gluten-free casein-free ketogenic diet</td>
<td>14 months</td>
<td>Favorable: seizure free, improvement in mood and behaviour, stereotyped behaviours, social skills and language function</td>
</tr>
<tr>
<td>Evangeliou et al. (2003)</td>
<td>ASD symptoms</td>
<td>30 children</td>
<td>John Radcliffe diet</td>
<td>6 months, with intervals of 4 weeks interrupted by two diet-free</td>
<td>Significant improvement (assessed with CARS) in 2 patients, average improvement in 8 patients, minor improvement in 8</td>
</tr>
<tr>
<td>Name</td>
<td>ASD symptoms</td>
<td>Classic KD</td>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spilioti et al. (2013)</td>
<td>6 children with pathologically increased beta-hydroxybutyrate and lactate following glucose loading test</td>
<td>Not reported</td>
<td>Favorable in 1 patient with remarkable improvement in CARS score; 5 patients: subtle improvement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**KD:** ketogenic diet. **ASD:** Autism Spectrum Disorder; **CARS:** Childhood Autism Rating Scale

**References**

**Reference annotations**

* Of interest  
** Of considerable interest


A paper of great interest: the first attempt to create a consensus statement regarding the clinical management of KD.


A manuscript of high value regarding side effects of KD for intractable epilepsy.


A study of notable interest investigating physiopathological mechanisms beyond anti-seizure effects of ketone bodies.


A study assessing the safety and efficacy of KD in RCC defects, a new field of growing interest.


A manuscript of great interest because of recent knowledges about KD and malignant brain tumors.


A manuscript of notable value for new fields of KD investigation in vitro.
A paper of high interest because providing useful information about the role of KD in the management of PDHD.


A critical analysis of the use of KD in PDHD, of interest.


57. Bastin J. Regulation of mitochondrial fatty acid beta-oxidation in human: what can we learn from inborn fatty acid beta-oxidation deficiencies? Biochimie 2014;96:113-20

58. Bennett MJ. Pathophysiology of fatty acid oxidation disorders. J Inherit Metab Dis 2010;33:533-7


A study of great impact regarding new direction about the usefulness of KD in the management of brain tumors.


82. Hershey AD. Current approaches to the diagnosis and management of paediatric migraine. Lancet Neurol 2010; 9:190-204


88. * Cullingford T. The ketogenic diet; fatty acids, fatty acid-activated receptors and neurological disorders. Prostaglandins Leukot Essent Fatty Acids. 2004;70:253-64
A paper of remarkable value; it provides a detailed analysis of molecular mechanisms involved in the efficacy of KD in neurological disorders.


91. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders; Fifth Edition (DSM-5), 2013


99. El Achkar CM, Spence SJ. Clinical characteristics of children and young adults with co-occurring autism spectrum disorder and epilepsy. Epilepsy Behav. 2015;47:183-90


学霸图书馆
www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，
提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具