UDK 616.853-053-07-08+613.24+615.874+616-037
DOI: 10.56871/CmN-W.2023.29.19.002

KETOGENIC DIET IS A NON-DRUG METHOD OF TREATING EPILEPSY

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For citation: Bogdanova NM, Kravtsova KA. Ketogenic diet is a non-drug method of treating epilepsy. Children's medicine of the North-West (St. Petersburg). 2023;11(4):15-24. DOI: https://doi.org/10.56871/CmN-W.2023.29.19.002

Received: 07.09.2023 **Revised: 18.10.2023** **Accepted: 11.12.2023**

Abstract. The article presents data on the possibilities of using a ketogenic diet in patients with epilepsy. The relevance of the topic is due to the fact that drug treatment of this disease leads to seizure relief in less than 70% of cases, and therefore there is a need to use alternative therapies. Experimental and clinical data on the results of treatment with the ketogenic diet were analyzed, and the mechanisms underlying its clinical effects were considered.

Key words: *epilepsy; ketogenic diet; ketone bodies; neurotransmitters; paroxysms; microbiota.*

КЕТОГЕННАЯ ДИЕТА — НЕМЕДИКАМЕНТОЗНЫЙ СПОСОБ ЛЕЧЕНИЯ ЭПИЛЕПСИИ

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Для цитирования: Богданова Н.М., Кравцова К.А. Кетогенная диета — немедикаментозный способ лечения эпилепсии // Children's medicine of the North-West. 2023. Т. 11. № 4. С. 15–24. DOI: https://doi.org/10.56871/CmN-W.2023.29.19.002

Поступила: 07.09.2023 **Одобрена: 18.10.2023** **Принята к печати: 11.12.2023**

Резюме. В статье представлены данные о возможностях применения кетогенной диеты у пациентов с эпилепсией. Актуальность темы обусловлена тем, что медикаментозное лечение данного недуга приводит к купированию приступов менее чем в 70% случаев, в связи с чем существует необходимость использования альтернативных методов терапии. Проанализированы экспериментальные и клинические данные о результатах применения кетогенной диеты, а также рассмотрены механизмы, лежащие в основе ее клинических эффектов.

Ключевые слова: *эпилепсия; кетогенная диета; кетоновые тела; нейромедиаторы; пароксизмы; микробиота.*

INTRODUCTION

Epilepsy is a chronic, polyetiological disease of the brain, characterized by repeated unprovoked (or reflex) seizures of disturbances in motor, autonomic, sensory and mental functions resulting from *excessive* electrical *neuronal discharges*. This definition was given by the main regulatory body of the actions of epileptologists - the International League Against Epilepsy (ILAE), created more than 100 years ago. The presented formulation of the disease remains relevant today, although with minor additions [1, 2]. The onset of the disease is observed mainly in childhood (about 75% of all cases) [3]. The mechanisms of development of paroxysms are quite complex, and the etiological factors are multifaceted. Although still in 40–60% of patients, the cause of epilepsy remains unknown [1, 4, 5].

The main clinical manifestations of epilepsy in children are epileptic seizures, occurring in the form of tonic-clonic seizures, absence seizures,

 ISSN 2221-2582

myoclonus with loss of consciousness or with preserved consciousness. Often, epileptic paroxysms occur in an atypical, erased manner. Instrumental and laboratory diagnosis of this disease includes electroencephalogram (EEG), skull radiography, computed tomography (CT), magnetic resonance imaging (MRI) and brain positron emission tomography (PET), biochemical blood test and cerebrospinal fluid analysis.

Classic treatment of epilepsy in children involves the observance of the protective regime, taking anticonvulsants, psychotherapy, and, if necessary, neurosurgical intervention. Despite the therapy, in more than 30% of patients with epilepsy, seizures are not able to be reduced, but have a progressive nature, that is, so-called refractory epilepsy is noted [6]. Even the addition of alternative treatments, such as neurostimulation and surgery, does not always provide a positive effect.

It has been proven that uncontrolled epilepsy has a negative impact on the quality of life of both the patients themselves and their relatives and friends, and this this requires the development of new, more promising treatment areas.

KETOGENIC DIET AS AN ALTERNATIVE METHOD OF TREATING EPILEPSY

The relationship between the central nervous system (CNS) and the ketogenic diet (KD) has been known for over a century. The first KD was developed by Dr. Russell Morse Wilder in 1921 at the Mayo Clinic [7, 8].

KD can be successfully used to compensate for a group of severe neurological diseases [9, 10] and is recommended for children as an alternative treatment for any form of epilepsy when traditionally used antiepileptic drugs are ineffective (recommendation level A, evidence level 1) [11].

By definition, a traditional KD is a low-carbohydrate, high-fat, moderate-protein diet that aims to replace glucose with ketone bodies (KBs) [7–10, 12]. The so-called *VLCKD model* is very-low-carbohydrate KD.

For constant mental work, the brain needs glucose as the fastest and most reliable way to obtain energy. Once in the bloodstream, glucose crosses the blood-brain barrier (BBB) with the help of carrier proteins and provides neurons with fuel.

When glucose reserves in the hepatocyte mitochondria are depleted as a result of β-oxidation, KBs (acetoacetate, β-hydroxybutyrate (β-HB), acetone) are formed from fatty acids, which, thanks to special monocarboxylate transporters, enter the blood from the liver and then pass through the BBB and provide energy to brain cells. Although it is known that the brain cannot exist solely due to KBs [12–14].

Thus, during glucose deficiency, KBs (mainly β-hydroxybutyrate) become the energy substrate for the production of adenosine triphosphate (ATP), a universal energy molecule, in cells throughout the body, including the brain. This metabolic shift causes many neurobiochemical, neuroplastic and hormonal changes, resulting in a decrease in neuronal excitability and, accordingly, the frequency of seizures.

The positive therapeutic effect of KD for the reduce seizures is confirmed by many clinical studies.

First, for glucose transporter type 1 deficiency syndrome (GLUT-1 is the main transporter that removes glucose from the luminal membrane of the BBB capillaries), VLCKD is the main and only treatment method.

GLUT-1 deficiency syndrome is a genetic metabolic encephalopathy with various focal and multifocal types of seizures (classic epileptic variant, occurs in 90% of patients). Mutations in the SLC2A1 gene, encoding the GLUT-1 synthesis, disrupt glucose transport to the brain. Transferring a patient with this pathology to KD provides neurons with "fuel" due to the fact that CBs pass through the BBB using other transport proteins (MCT1).

The work of foreign and native-born scientists has proven that early initiation and lifelong adherence to VLCKD guarantees children with GLUT-1 deficiency syndrome, a normal level of psychomotor, speech, motor, cognitive development and the absence of epileptic paroxysms [15, 16].

Secondly, the results of two meta-analyses confirmed the positive therapeutic effect of KD in epilepsy.

The first, including 7 studies involving 427 children and adolescents with epilepsy, demonstrated a reliable decrease in seizure frequency by an average of 85% after 3 months of adherence to VLCKD [17].

The second meta-analysis, presenting the results of 12 studies (270 patients) of the use of various variants of KD in drug-resistant epilepsy, showed its overall effectiveness in 42% of patients [18]. Similar data were obtained from the analysis of single works of the period from 1946 to 2019: 13 studies involving 932 participants, of which 711 were children from 4 months to 18 years [19–22]. The authors noted that VLCKD is most effective in patients with generalized epilepsy [23].

Thirdly, the experience of Moscow neurologists, dietitians and nutritionists using VLCKD both

in combination with anticonvulsant therapy and other non-drug methods in the treatment of refractory epilepsy in children from 1 to 18 years of age indicates a reduction in the number of seizures by more than 50% in 50–85% of children. It has been noted that an integrated approach, involving a differentiated choice of one or another treatment method, can achieve significant positive results [24–26].

However, recent experimental work reveals that KD, which has been established since 1921, has a large number of side effects. Thus, scientists at the University of California in an in *vivo study* obtained data on the negative effect of such VLCKD on the cognitive abilities of mice under hypoxic conditions [27].

Currently, for the treatment of refractory epilepsy in both children and adults, it has been proposed to use a modified Atkins diet, in which the body obtains about 45% of its energy from substituted medium-chain fatty acid residues of triglycerides (MCTs), and not by the metabolism of long-chain fatty acids (LCFA), as in the classic version of KD. To maintain daily energy balance in the diet, the carbohydrate component of the diet is slightly increased, mainly due to sugars with a low glycemic index, as stable glucose levels are shown to be related to seizure control [28].

In addition to the Atkins ketogenic diet, it is possible to prescribe a modified Mediterranean-ketogenic diet (MMKD) with different ratios of fats, proteins and carbohydrates. MMKD includes olive oil as the main source of polyphenols and monounsaturated fatty acids (MUFAs), which have an antioxidant profile [29, 30].

Such "relatively" gentle diets are more accessible and more physiological for both brain activity and the intestines, despite the fact that discussions about their therapeutic effectiveness continue [31].

A large randomized controlled trial (RCT) conducted by V. Sondhi et al. (2020) with the participation of children (n=158), compared the effectiveness of classical KD, Atkins KD and MMKD in preventing seizures in patients. The researchers found that while all dietary interventions showed improvement compared to the control group, traditional KD was most effective in reducing episodes and severity of seizures [32].

These days, most ketogenic diets are customized, modified KDs that balance ketogenic effects with palatability.

As scientists study the practicality of modified KD, they are seeking to determine the molecular mechanisms of anticonvulsant action and identify whether the responsiveness of treatment depends on the length of the carbon skeleton [31].

MECHANISMS OF KETOGENIC DIET ACTION

The main pathogenetic action of KD, aimed at suppressing excitability in brain cells, has not been fully studied, but a number of hypotheses are being considered about the direct influence of ketones, which are [31, 33]:

- reduce ATP production from glucose oxidation and the opening of ATP-sensitive potassium channels, and also enhance GABA-mediated inhibition;
- change the mitochondrial permeability of mitochondrial membranes, reducing the severity of mitochondrial dysfunction, oxidative stress and cell death;
- inhibit adenosine kinases with a subsequent increase in adenosine levels and activation of adenosine A1 receptors.

In addition, a series of scientific studies have found that ketones affect the metabolism of amino acids in neurons, and, accordingly, the metabolism of neurotransmitters. It has been noted that when following a modified Atkins KD, the concentration of glutamate in brain tissue decreases and the level of γ-aminobutyric acid (GABA) increases [31, 34].

In vitro experiments with neuronal cell cultures assessing the effects of all amino acids demonstrated that CTs sharply reduce the concentrations of three amino acids: leucine, arginine and glutamine, resulting in inhibition of mTOR, a DEPDC5-dependent signaling pathway, and a decrease in the anticonvulsant activity of neuronal cells [21].

The intracellular signaling peptide mTOR is one of the universal signaling pathways characteristic of most human cells and is involved in many neurological disorders. Excessive induction of this molecule increases the susceptibility of neurons to seizures. *The signaling* by a *protein* called DEPDC5 acts as a brake on the mTOR pathway. Many people with epilepsy have mutations in the *DEPDC5* gene, which are associated with focal epilepsy, infantile spasms, and even sudden infant death syndrome [35].

Animal studies have shown that high concentrations of acetone and β-HB stimulate GABA and glycine receptors, and brain cell saturation with β-hydroxybutyrate is inversely related to seizure severity [36–38]. Accumulation of acetoacetate inhibits voltage-gated calcium channels in hippocampal pyramidal cells, thereby inhibiting neuronal excitability. In addition, ketones can compete with chlorine in the vesicular glutamate

transport, inhibiting glutamatergic transmission and, consequently, seizure activity [38].

Thus, the increased content of ketones and, above all, β-HB is the main anticonvulsant mechanism of KD in people with epilepsy, especially when it is not amenable to drug treatment [39].

It is believed that the energy profile of brain cells is influenced not only by ketones, but also by the fatty acids themselves. Once in brain cells, they undergo β-oxidation directly in astrocytes, thereby increasing the production of CBs directly in glial cells.

It has been noted that the shorter the chain length of fatty acids, the easier it penetrates into the mitochondrial matrix, where it binds to a high-energy bond with coenzyme A and provides the synthesis of CBs and ATP [31, 34].

The anticonvulsant effect of decanoic (capric — $CH_3(CH_2)_8COOH$) and octanoic (caprylic — $CH_3(CH_2)_6COOH$) fatty acids (FAs) is dynamically studied in animal models. The main food source of these FAs is coconut oil.

The anticonvulsant effect of decane FA is predetermined by its ability in micromolar concentrations to selectively block AMPA receptors (an ionotropic glutamate receptor that transmits fast excitatory signals at synapses of the nervous system) [38] and induce peroxisome proliferator activated receptor γ (PPARγ), which leads to increased mitochondrial function, increases the mitochondrial complex I activity and stimulates mitochondrial biogenesis in neurons [18, 34].

The anticonvulsant activity of octane FA is associated with a non-selective effect on adenosine receptors. Moreover, its derivatives (5-methyloctanoic acid) demonstrate AMPA-dependent control of seizures both *in vitro* and *in vivo* [31].

A number of experimental and clinical studies have found that polyunsaturated fatty acids (PUFAs) are also capable of providing anticonvulsant protection, especially docosahexaenoic acid (DHA, 22:6n-3), a derivative of α-linolenic PUFA (the omega-3 class) [40]. PUFAs can stimulate peroxisome proliferator-activated receptors (PPARs—a group of nuclear receptors that function as transcription factors), which regulate anti-inflammatory, antioxidant, and mitochondrial genes, leading to increased energy reserves, stabilization of synaptic function, and restriction of increased excitability [41].

DHA regulates neuronal activity through interaction with ion channels and release of neurotransmitters [42]. A study of children (case–control) revealed a lower omega-3/omega-6 ratio in the blood serum of patients with epilepsy compared to healthy [43]. *In vitro* and *in vivo* studies have shown that the DHA-rich diet is useful for controlling epilepsy, but clinical data have been somewhat inconsistent [40]. A meta-analysis of seven clinical studies conducted in 2021 confirmed that dietary omega-3 supplementation significantly reduced seizure frequency and was more effective in adults than in children [44].

In the last decade, the role of the intestinal microbiota in the antiepileptic effect of the ketogenic diet has been actively discussed [45, 46]. The presented hypothesis has several scientific and clinical explanations.

Firstly, no one doubts that food is the main factor determining the gut microbiome. Accordingly, the transformation of the diet in the form of adherence to the classical CD with very low content of carbohydrates (VLCKD), predominantly complex, makes significant changes in the α- and β-diversity of the gut microbiome, both at the level of bacterial types and at the level of species and genera of microorganisms and, therefore, it is involved in the treatment of epilepsy [33, 46].

A study conducted by G. Xie (2017) showed that children with epilepsy have an imbalance of gut microbiome before the onset of VLCKD. Adherence to the diet induces the growth of bacteria of the *Bacterioides* species and significantly reduces the number of pathogenic proteobacteria (*Escherichia, Salmonella* and *Vibrio*), which are in high titer in the basic analysis. The authors noted the association of *Bacteroides* spp. with the digestion and metabolism of high-fat nutrients and the regulation of IL-6 and IL-17 secretion by dendritic cells, due to the consequences of seizures in patients with epilepsy. Researchers have suggested that VLCKD may reduce these symptoms by promoting changes in microbiota diversity [47].

Secondly, the general transformation of the gut microbiome helps to improve the relationship between *Firmicutes* and *Bacteroides* species due to the relative increase in bacteria of the *Bacteroides* species, which have a more favorable effect on the host body and CNS as well. It is important to note the identified two-stage effect of VLCKD: at the beginning of the diet, there is a sharp decrease in bacterial richness and diversity, but after 12 weeks, the concentration of bacteria gradually returns to the baseline level, significantly exceeding it by the 23–24th week of strict adherence to the prescribed diet [48].

And third, gut microbiome secretes a range of chemicals: cytokines, neuroactive molecules (neu-

rotransmitters, neuropeptides), chemokines, endocrine messengers, and microbial metabolites such as short-chain fatty acids (SCFAs), branched-chain amino acids, and peptidoglycans that directly promote communication between the gut and the brain, influencing various neuroendocrine, neuroimmune and metabolic processes. For example, it has been noted that GABA, the main inhibitory neurotransmitter of CNS mammals, including humans, is produced by strains of *Lactobacilli* and *Bifidobacteria*, more precisely *Lactobacillus brevis, Bifidobacterium denteum, Bifidobacterium bifidum*. In hippocampal damage or status epilepticus, GABA synthesized by the microbiome can lead to an imbalance between the GABA and glutamate systems, causing seizures. The gut also produce 90% of serotonin thanks to microorganisms such as *Enterococcus* spp., *Streptococcus* spp. and *Escherichia* spp. [49]. Serotonin binding to 5-HT receptors in microglia in the white or gray matter of the brain activates the release of cytokine-carrying exosomes, providing a mechanism for gut-induced modulation of neuroinflammation [50]. Another microbial metabolite that influences the microglia activity is tryptophan, a serotonin precursor [51]. Bacterial metabolites derived from dietary tryptophan may control CNS inflammation through a mechanism mediated by aryl hydrocarbon receptors (Ahr), affecting microglial activation and the transcriptional program of astrocytes [51].

Various neurotransmitters produced by the microbiota can pass through the intestinal mucosa, but rarely through the BBB, with the exception of GABA. However, they have the potential to influence microbiota-gut-brain (MGB or BGM) signaling, regulating enteric vagal afferent activity and inflammatory reactions. Moreover, bidirectional transmission of biochemical signals takes place [52–55]. However, the exact mechanism behind these phenomena still needs to be studied.

Experimental studies examining the relationship of VLCKD with antiepileptic effects in mice noted significant changes in the structure of intestinal taxonomic units over 4 days of the diet. Two species of bacteria, Akkermansia and Parabacteroides, increased significantly in mice fed a ketogenic diet. Subsequent colonization of gnotobiotic mice by these microorganisms provided them with anticonvulsant protection, which was associated with a decrease in the subpopulation of ketogenic (leucine) and glutamylated (glutamine) (GG) amino acids both in the gut and in the bloodstream, as well as inhibition of the production of the microsomal enzyme — γ-glutamyl transpeptidase (GGTP) by the gut microbiome [56]. It is assumed that GG amino acids have transport properties through the BBB that are different from non-glutamylated forms. This feature of glutamylated amino acids increases the ratio of GABA to glutamate in the mouse brain. It has been suggested that VLCKD-associated limitation of microbiota and GG amino acids plays a key role in the antiepileptic effect.

It has been noted that KD causes diversification of the gut microbiota, namely a decrease in the number of pro-inflammatory microbes such as Desulfovibrio and Turicibacter, as well as an increase in the number of beneficial bacteria *Akkermansia muciniphila* and *Lactobacillus plantarum*, capable of produsing SCFAs that can modulate neurotransmitters such as glutamate, glutamine, GABA and neurotrophic factors [57].

Some SCFAs (propionate and butyrate) have an anticonvulsant effect because they provide maturation of brain microglia and reduce the permeability of the BBB. Butyrate improves mitochondrial dysfunction and protects brain tissue from oxidative stress and apoptosis through the Keap/Nrf2/HO-1 pathway, thereby increasing the seizure threshold and reducing seizure intensity [58]. In addition, propionate and butyrate influence the cellular signaling system by modifying intracellular potassium levels [59], which, in turn, regulate the expression levels of tryptophan 5-hydroxylase 1, involved in the synthesis of serotonin, and tyrosine hydroxylase. The latter enzyme is necessary in the biosynthesis of dopamine, adrenaline and norepinephrine [60]. It has been established that SCFAs are able to indirectly affect the MGB axis by inducing the release of several gastrointestinal hormones, such as glucagon-like peptide-1 (GLP-1) and leptin, through the enteroendocrine cells. These gastrointestinal hormones can interact with the vagus nerve and even brain receptors [61–64].

Despite the growing body of evidence, a number of questions still remain about the mechanisms by which KD may protect patients with epilepsy from seizures. For example, how does modulation of bacterial species influence changes in the membrane potential of hippocampal neurons? Is modulation of GABA/glutamate levels a major pathway? How might changes in bacterial species modulate GABA/glutamate levels [33]?

Therefore, specialized and restricted diets adopted for the treatment of certain diseases need to be studied for their effect on the human microbiota (for example, FODMAP control for irritable bowel syndrome and the ketogenic diet for re-

fractory epilepsy). These patterns, by reducing or eliminating a particular food type, can positively or negatively influence the composition of the microbiota and the associated effect on host physiology. This refers to the very-low-carbohydrate ketogenic diet (VLCKD), a nutritional approach that is gaining popularity not only for treating neurological disorders but also for rapid weight loss.

CONCLUSION

Currently, about 25–30% of patients diagnosed with epilepsy are refractory to treatment with antiepileptic drugs (AEDs). Uncontrolled seizures can lead to cognitive disorders, such as memory and learning impairment, as well as varying degrees of permanent brain dysfunction and even death. Side effects of AEDs may limit their use in some patients. Such people need improved alternative treatments, one of which is the ketogenic diet.

For people with refractory epilepsy who are unable to undergo neurosurgical intervention, the ketogenic diet remains the main and only method of therapy. However, further research is needed to confirm this position.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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