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GUT MICROBIOTA, KETOGENIC DIET AND EPILEPSY: NEW SCIENTIFIC EVIDENCE

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Abstract

Diet has an important role to play in many neurological diseases and the ketogenic diet is the most important non-pharmacologic treatment strategy in pediatric patients affected by refractory epilepsy. This diet is recommended because it is the first line intervention for glucose transporter 1 deficiency syndrome.

It is a normo-caloric, high-fat, adequate-protein, and low-carbohydrate diet aimed at switching the brain metabolism from glucose dependence to the utilization of ketone bodies. No one knows exactly why, but some evidence suggests that ketone bodies might protect against seizures. The ketogenic diet has also an impact on the intestinal microbiota and several studies have shown that gut microbiota can affect epilepsy. Moreover, patients with epilepsy and in treatment with ketogenic diet could take probiotics and prebiotics.

The purpose of this review is to highlight the most recent studies about the relationship between ketogenic diet, epilepsy and gut microbiota.

Keywords: *epilepsy, ketogenic diet, microbiota, children.*

Introduction

Around 1-2 % of population worldwide is affected by epilepsy, one of the most invasive neurological disorders. (1) This disease of the brain is defined by the propensity for an individual to have recurrent unprovoked epileptic seizures (2). Seizures involve abnormal paroxysmal changes in the electrical activity of neurons and are linked to an imbalance of excitatory and inhibitory brain networks (3). Glial cells also play a role in seizure generation as they modulate neural function by restoring homeostasis of ions as well as neurotransmitters glutamate and gamma-aminobutyric acid (GABA) (4). Many underlying causes of brain dysfunction can lead to epilepsy among which cerebral malformations, tumors, CNS infection, trauma, stroke and genetic mutations in epilepsy genes are common. In many patients the cause of epilepsy remains unidentified. This neurological disease can be also evaluated by a large extent of other resources (5): as a matter of fact, cognitive and behavioral impairments (e. g. cerebral palsy, intellectual disability, attention deficit hyperactivity disorder and autism spectrum disorder) are associated with epilepsy.

Commonly, seizures are treated with one anticonvulsant drug or with a combination of more drugs. When a decision for treatment is made an antiepileptic drug (AED) is started in monotherapy. Epilepsy is often controlled in many patients using with one or more AEDs, but when trials of two of these medicines (tolerated, appropriately chosen and used) fail, we could identify it as refractory (6). Despite more than 20 different available antiseizure drugs (ASDs), approximately 30% of patients with epilepsy have refractory epilepsy (7). In fact, despite the pharmacological progress leading to the development of new anticonvulsant drugs in the last fifteen years, 25% of children continue to be subject to uncontrolled seizures.

Some of these patients are not surgery candidates, so it is necessary to search for alternative treatments for epilepsy such as palliative surgery, neuromodulation and a ketogenic diet (KD) (8).

Although ASDs and surgical interventions have been the mainstays of treatment for epilepsy, recent studies have found a significantly positive outcome with the use of the KD for treatment of refractory epilepsy in children and adults (9, 10, 11, 12).

The ketogenic diet as an alternative treatment of epilepsy

Since 1920s the use of ketogenic diet in pediatric patients affected by drug-resistant epilepsy (DRE) (13,14,8) has been showing in which way it is possible to reduce convulsive seizures without a pharmacologic treatment and more specifically as a long-term therapy in different epileptic syndromes, such as Dravet syndrome, epilepsy with myoclonic-atonic seizures, Lennox-Gastaut syndrome (15, 16, 17).

The classic ketogenic diet (cKD) is an isocaloric, hyperlipidic, normoproteic and very low-carbohydrate diet, with caloric and liquids restriction and induction of ketosis with fasting. This diet requires all foods and beverages to be carefully calculated and precisely weighed on a gram scale in order to obtain a specific ratio between fats (gr) and carbohydrates (gr) plus proteins (gr), generally equal to 3:1 or 4:1 (18). The ratio 4:1 contains four times as many grams of fat for every gram of protein and carbohydrate together. Here, 70–90% of the energy intake will be derived from fat (6). KDT includes different diet regimens that have in common the production of ketone bodies for energetic purposes.

In the last two decades, experts developed different models of KD that have similar efficacy to the cKD, as highlighted by several scientific proofs. Among the new variants, it is important to mention the Modified Atkins diet (MAD), a low-glycemic-index and high-fat diet, which allows more protein and does not restrict calories and fluids (19, 20, 21, 22, 23). This kind of diet can be taken as an example of the modern KDs: these are more appetizing and less restrictive in order to increase adherence to the diet (24).

Pediatric epilepsy specialists and dieticians have published their consensus to the ketogenic diet report agreeing that ketogenic diet should be strongly considered in the children who failed two to three anticonvulsivant therapies (25) two randomized controlled prospective studies evaluated the efficacy of KD in medically refractory epilepsy in children. The responder rate, i. e. patients with a decrease in the number of seizures by ≥50%, was 38% and 50% respectively for the two trials (10, 26). It is not known why some patients respond well to the diet while others do not. Dahlin et al. have analyzed the effects of amino acid levels in the cerebrospinal fluid in epileptic children: they found out that GABA levels were higher in responders (>50% seizure reduction) than in nonresponders during the diet (27).

Benefits and adverse effects on epilepsy therapy

The antiepileptic effects of these KD-type diets are presently used in the treatment of drug-resistant adult and child patients. In addition to their benefit for certain forms of epilepsy, the KD appears to have some positive effects on other neurological conditions, such as migraine, glaucoma, multiple sclerosis, Parkinson's disease, and Alzheimer's disease (28, 29, 30, 31).

There is no agreement on how a ketogenic diet can help control epileptic seizures. But the higher efficacy seems to be obtainable in generalized symptomatic forms of epilepsy, especially in the congenital glucose transporter GLUT1 deficiency (GLUT1 deficiency syndrome, GLUT1-DS).

KD induces ketosis, the biochemical principle from which the diet gets its name. In conditions of restricted carbohydrate and high-fat availability, the brain metabolism shifts from glucose dependence to the utilization of ketone bodies, principally β-hydroxybutyrate (BHB) and acetoacetate (ACA), converted in the liver by the oxidation of fatty acids (32). These ketones are used as an alternative energy substrate for ATP production in the cells of the body including the brain. This metabolic shift induces many biochemical, metabolic and hormonal changes that may in part contribute to decreased neuronal excitability and reduced number of seizures (6). The main goal of KD is to mimic the metabolic condition that occurs during starvation (25, 33). In the brain, the ketone bodies act as an alternative fuel to glucose. GLUT1-DS is caused by a defect in the protein responsible for the transfer of glucose across the blood-brain barrier and is manifested in seizures early in life and impairment of brain growth with developmental delay and other neurological problems, including a complex movement disorder. Patients with GLUT-1 deficiency use ketone bodies in the brain instead of glucose. In fact, these bodies can cross the blood-brain barrier via facilitated diffusion through the MCT_1 transporter (34).

Even though the positive effects of the KD in reducing epileptic seizures are well proven, the underlying mechanisms of action of KD are not fully explained. Nevertheless, the recent studies indicate some advances in this topic and propose several potential mechanisms. These include enhanced GABA-mediated inhibition, direct inhibitory actions of polyunsaturated fatty acids on ion channels, elevated levels of ATP which is converted to the inhibitory mediator adenosine as well as increased mitochondrial biogenesis and reduced oxidative stress (35). Many KD studies have demonstrated an elevated antioxidant activity, diminished reactive oxygen species' (ROS) production, and decreased ROS-induced damage (32, 36, 37) due to NADH oxidation, upregulation of the mitochondrial uncoupling protein (UCP) activity, and the biosynthesis of glutathione (38).

KD can also exert a neuroprotective effect. It is known that the epileptogenic state involves complex molecular pathways in which oxidative stress and mitochondrial dysfunction can play important roles in neuronal cell death (39).

Furthermore, KD has been shown to enhance energy reserves, ATP levels, the expression of many enzymes involved in multiple metabolic pathways in the mitochondria and it increases mitochondrial biogenesis in the hippocampus (36, 40).

In addition, there is also emerging evidence that ketone bodies exhibit systemic and neuroprotective anti-inflammatory effects, as KD treatment reduces the expression of pro-inflammatory cytokines, microglial activation, pain and inflammation. (41, 42, 43)

The KD is also implicated in several mechanisms linked to biochemical alterations, such as cellular substrates and mediators responsible for neuronal hyperexcitability. However, there are no evidence that the success of KD used in the treatment of epilepsy is due to one or more of these mechanisms (43, 45, 46, 47). Therefore, this shows that this neurological disease can be also identified as a metabolic one. (48)

KDs are not free from contraindications. They may cause short- term side effects such as constipation, diarrhea (particularly in patient with MCT supplementation), nausea, vomiting and longer term side effects include pancreatitis, the risk of nephrolithiasis, mineral and vitamin deficiencies, growth retardation, and hyperlipidemia. So that, all ketogenic diet's patients should receive a daily multi-vitamin as well as calcium supplementation. Carnitine, found in milk and red meats, has also been found deficient in patients placed on these diets so it also needs to be supplemented. (49)

Gut microbiota, ketogenic diet and neurological disorders

Scientists think the microbiota varies according to its surrounding environment. The term gut microbiota refers to the community of microorganism presents in the intestinal tract. Recently, it has been proposed the implication of the gut microbiota alongside changes in the functioning of the mitochondria, alteration of neurotransmitter release and neuron function by ketone bodies, and antiepileptic effects of glucose stabilization and/or fatty acids. (50, 51)

So that it plays a fundamental role in human health, stimulating the immune system and providing resistance to the colonization of potential pathogens.

The gut microbiota and the brain can communicate bidirectionally through the central and enteric nervous system as well as endocrine, immune and metabolic pathways (52). In fact, it has been demonstrated that the intestinal microbiota influences the psychology of the CNS (53). For this reason, the intestinal dysbiosis has been associated with a variety of neurological disorders: autism (54), multiple sclerosis (55), Parkinson's (56), Alzheimer's (57) and epilepsy. (58)

The composition of the gut microbiota is influenced by several factors. (59)

Gong, et al. have studied the composition of the fecal microbiota of patients with epilepsy by utilizing 16S ribosomal RNA sequencing. Microbiome alterations in patients with refractory-epilepsy included enrichment of bacterial taxa in Actinobacteria, Verrucomicrobia, and Nitrospirae and the genera Blautia, Bifidobacterium, Subdoligranulum, Dialister, and Anaerostipes. They also found out that the structure of the fecal microbiota varies between patients with different clinical prognoses (drug-resistant and drug-sensitive epilepsy). This means that specific gut commensal strains are altered depending on different clinical phenotypes and thus could serve as potential biomarkers for disease diagnosis. (60)

It is probably that dysbiosis is more relevant in some subtypes of epilepsy, such as the one caused by stress. Moreover, epilepsy could be treated by restoring a healthy microbial community, using probiotics, prebiotics and faecal microbiota transpalnt (FMT) from healthy donors. (6)

Diet is one of the main causes of the alteration of gut microbiota (6). Recent research has focused in part on the impact of carbohydrates, where types of dietary fibres, known as microbiota-accessible carbohydrates (MACs), present an essential energy source to a healthy intestinal microbiota. (61)

The ketogenic diet is fiber–deprived and it is usually used in treatments of epileptic patients: in fact, this kind of diet causes a drastic reduction in bacteria that consumed fibers, such as

Bifidobacteria (62), influencing the intestinal microbiota. Zhang, et al. investigated the characteristics of intestinal microbiota in children with refractory epilepsy after ketogenic diet (KD) therapy and explored the bacterial biomarkers related to clinical efficacy. They analyzed 20 patients treated with KD and after 6 months of treatment they found out 2 patients were seizure free, 3 had ≥ 90% seizure reduction, 5 had a reduction of 50–89%, and 10 had < 50% reduction. Compared with baseline, fecal microbial profiles of the first 10 patients showed lower alpha diversity after KD therapy and revealed significantly decreased abundance of Firmicutes and increased levels of Bacteroidetes, while Clostridiales, Ruminococcaceae, Rikenellaceae, Lachnospiraceae, and Alistipes were enriched in the non-responsive group. This means that on one side KD can reduce the species richness and diversity of intestinal microbiota, while on the other side these changes depend on the efficacy after the diet. (63)

In another study, whose aim was to see how KD alters gut microbiota, 14 epileptic and 30 healthy infants were recruited, seizure frequencies were recorded, and stool samples were collected for 16S rDNA sequencing. After one-week KD treatment, 64% of epileptic infants showed an obvious improvement, with a 50% decrease in seizure frequency. Gut microbiota structure in epileptic infants (P1 group) was extremely different from that in healthy patients (Health group), which was more similar to that of epileptic patients treated with diet (P2 group). The level of Proteobacteria (which comprises a variety of pathogens such as Escherichia, Salmonella and Vibrio) was high in the P1 group and decreased after KD treatment. Cronobacter predominated in the P1 group and decreased in P2 group (at a level similar to the healthy patients). Instead, Prevotella (that produce SCFAs which could protect the intestinal mucosa and function as neurotransmitters) and Bacteroidetes was dominant both in the Health and P2 groups. Concerning this, it is known that Bacteroides digest and metabolize high-fat food and regulate the secretion of IL-6 and IL-17 in dendritic cells, a process strongly associated with seizure severity of epileptic patients. Other genera, which may be involved in epilepsy recovery, such as Erysipelatoclostridium, Blautia, Bifidobacterium and Streptococcus, also grew in after-treatment patients (64).

Olson, et al. also found that the KD administrated to a mouse model of epilepsy has caused changes in the microbiome composition and made the mice more resistant to seizures (induced by electrical stimulation). The microbiome is necessary for the beneficial effects of the diet. In fact, antibiotic-treated and germ-free mice fed the KD did not benefit from the protective effects of the diet. Instead the other KD-fed mice are enriched in the bacteria Akkermansia muciniphila, Parabacteroides merdae, and Parabacteroides distasonis, which were shown to be involved in promoting the diet's anti-seizure effects. Manipulation of the gut microbiome through the KD implicated protective benefits against seizures by altering brain neurotransmitter levels, especially GABA (the major inhibitory neurotransmitter in the brain) and glutamate in the hippocampus. In particular reduced levels of GABA are known to exacerbate seizures. (65)

Therefore, it is known that development and function of the immune, metabolic and nervous systems are influenced by the gut microbiome. Recent studies highlight how commensal bacteria could modulate symptoms and pathology in mouse models of neuropsychiatric and neurodevelopmental diseases. More detailed studies about mechanisms used by microbiome gut-brain connections could be essential. In this way, it could be provided new opportunities to target therapies to the gut in order to treat neurologic disorders, such as drug-resistant epilepsy. At the moment it is sure that diet is efficient for manipulating neurotransmitter levels in the brain, with the consequent diet-microbiome interactions mediating the effects of seizures. (66)

In particular, KD could significantly modify symptoms of epilepsy because it reshapes the gut microbiota of epileptic infants (64), but surely further studies are needed.

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