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The Role of Milk Nutrition and Ketogenic Diet in Epileptic Disorders

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Abstract: This chapter explores the role of the gut-brain axis, ketogenic diet, and cow's milk allergy on epileptic seizures, with a special focus on childhood. Milk nutrition is particularly relevant for normal growth and health in childhood; however, some studies report an association between cow's milk allergy and epileptic events. It is necessary to clarify the role of protein polymorphisms in these events and the influence of milk protein fractions on gut microbiota in the pathophysiology of epilepsy. The rationale for the discussion assumes that appropriate nutrition in infants offers the possibility of minimizing diet-induced proinflammatory mediators in the brain, and at the peripheral level. The putative role of diet on inflammation and intestinal microbiome in infants with generalized epilepsy are presented. Furthermore, the potential benefits of ketogenic diet along with non-bovine milk alternatives to manage epilepsy in children are discussed.

Keywords: childhood epilepsy; cow's milk allergy; gut-brain-axis in epilepsy; ketogenic diet for epilepsy; nutrition and epilepsy

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INTRODUCTION

Epilepsy is defined as a condition of chronic seizure disorders with sudden and transient episodes of seizures with loss or disturbance of consciousness in which recurrent spontaneous seizures are not directly related to a specific triggering event. However, seizures are at times provoked by external or internal stimuli. A plethora of precipitating factors such as sleep deprivation, excess alcohol intake, premature awakening, menstruation, psychological stress, and photic stimulation, as well as reading, thinking, writing, calculating, and playing musical instruments have been identified (1). Knowledge of seizure precipitants is potentially helpful because this can lead to behavioral modification and, perhaps, a reduction in seizure frequency. Although the perception of food as a seizure precipitant is linked to cultural beliefs and differs greatly between Middle Eastern and Western countries (2), the real weight of food and food allergies on seizure remains undetermined and offers a stimulating debate about the mechanisms underlining the relationship between foods-mediated allergic disease and seizures. Nutrients appear able to modulate the inflammatory status of humans, and inflammation has consequently emerged as an important research topic in food and nutritional sciences (3). In a recent review on the clinical evidence of dairy products and inflammation, Bordoni et al. (4) reported that while dairy products exert a general anti-inflammatory activity in humans, they can also exert a pro-inflammatory activity in subjects allergic to bovine milk. This event is of particular interest in infants because it may affect the development of the immune system and the gut microbiota. Gut microbiota is considered a key regulator of immunity especially in infants. This chapter discusses the relationship between the gut-brain axis, ketogenic diet, and milk consumption on epileptic disorder.

THE GUT-BRAIN AXIS IN CHILDHOOD EPILEPSY DISORDER

The communication network between the intestinal microbiome, the central nervous system (CNS) such as the vagal afferent nerves and the hypothalamic–pituitary–adrenal cortical axis, the immune system, and certain active metabolites has been established (5–8). Gut microbiota comprises a large number of intestinal microbial communities mainly characterized by anaerobic bacteria and other microorganisms such as Archaea, Eukarya, viruses, and fungi (9), which are recognized as important for individual health. Gut microbiota can communicate with other parts of the body, including the brain (10). The complex interplay between the gut microbiota and the brain, the "microbiota-gut-brain axis", is activated through the work of various signaling networks. This axis can be considered a dynamic multidirectional neuroendocrine system which includes direct nerve connections, immune factors, and endocrine signals (11–13). During gut dysfunction/dysbiosis, inflammation, alteration of neuromodulators, and the disruption of the blood brain barrier can occur (14). An alteration of microbial population generates unhealthy signals which are transferred to the brain, activating cellular degeneration, unbalanced energy homeostasis, and increased oxidative stress (15). Due to the central role of this "microbiota-gut-brain axis", experimental and clinical studies have discussed about the modulatory role of gut microbiota in

several pathologies such as cancer (16), obesity (17), diabetes (18), and neurological diseases such as Alzheimer's disease (19), Parkinson's disease (20) and epilepsy (21–24). Notably, in the development and maintenance of some of these pathologies, the loss of microbial diversity in the intestine represents a crucial factor (21, 23, 24). Diet can influence the composition of the gut microbiota (25, 26) and as a result, the outcome of a dietary intervention depends on the composition of the gut microbiota at the time of the intervention (27).

With respect to epilepsy, there have been relatively few studies on the composition of gut microbiome (28). A recent retrospective study confirms that gut microbiota can affect children's neurodevelopment and this, in turn, can be dramatically affected by diet (29). It has been reported that gut microbiome composition in infants with refractory epilepsy differed significantly from that of healthy controls, with lower alpha diversity and especially increased representation of *Firmicutes* and *Proteobacteria*. The authors concluded that administration of ketogenic diet could significantly reshape the gut microbiota of epileptic infants (29). Manipulation of diet can alter microbiome to achieve a therapeutic effect in epilepsy, such as supplementation of diet with probiotics and/or prebiotics. This can be achieved by the administration of yogurt and fermented milk that contains health-promoting microorganisms such as *Lactobacillus*, *Bifidobacterium,* and *Streptococcus*. Interestingly, probiotics have also been reported to alter gamma aminobutyric acid (GABA) subunits in the brain, an effect that has promise for affecting hyperexcitable brain conditions, such as epilepsy (30).

THE ROLE OF KETOGENIC DIET IN EPILEPSY TREATMENT

An adequate nutrition is essential for the prevention and control of many diseases. Nutrition has a direct influence on metabolic and inflammatory processes (31). The pharmacological agents that are currently used to treat epilepsy cause many adverse events including decreased cognitive functions, psychiatric complications, hepatic toxicity, and cutaneous reactions. In this scenario, diet represents a valid strategy in the treatment of epilepsy. Nutritional therapy could be an economical and promising option to treat epilepsy. Adverse effects associated with nutritional therapy are not so severe, and minimal most of time. Nutritional treatment includes treatment with amino acids, antioxidants, vitamins, minerals, and ketogenic diet (32). A typical ketogenic diet is characterized by a higher percentage of fat and a lower percentage of carbohydrates, mimicking the metabolic state of fasting in which the metabolism of glucose is replaced by the metabolism of ketone bodies. The diet includes the consumption of mostly fats instead of carbohydrates, producing ketones (acetoacetate, acetone, beta-hydroxybutyrate) (33). Ketogenic diet has various beneficial effects on numerous organs and tissues, inducing weight loss, reducing blood insulin levels and cardiovascular risk factors, increasing mitochondriogenesis, and modulating neurotransmitter activity, as well as improving vascular density in the brain (34). Ketogenic diet also has an important role as a signalling mediator, driver of protein post-translational modification, and modulator of inflammation and oxidative stress (34–36). Mild dietary ketosis is a normal physiological mechanism, and the protective role of ketone bodies has been proposed (37).

Ketogenic diet can reduce epileptic seizures, for example, of drug-resistant epilepsy in children (31, 32, 35). The mechanism of action of ketogenic diet in the control of epilepsy is still unclear because epilepsy is thought to have multifactorial etiopathogenesis. Ketone bodies likely have a positive interaction on GABA receptors, enhancing the GABA system (33, 38). Another hypothesis analyses the influence on neuronal uncoupling proteins implicated in the upregulation of numerous energy metabolism genes and mitochondrial biogenesis with reactive oxygen species (ROS) generation and energy production (39). Another pathogenic mechanism considers the limited glucose and glycolytic flux that increase K_{ATP} channels with hyperpolarization of neurons and glia (38). In infants, an association between milk allergies and epileptic events has been reported. Ketogenic diet is indicated in treatment of refractory epilepsy in infants and can also be given as a first-line treatment in GLUT1 and pyruvate dehydrogenase complex deficiency, another mitochondrial disorder associated with lactic acidosis and progressive neuromuscular degeneration in childhood (40). Ketogenic diet has been shown to treat the clinical symptoms of these disorders without adverse reactions for up to two years of treatment (41). Ketogenic diet for infants affected by these diseases has a lower fat content (lipid: non-lipid ratio 3: 1 compared to the traditional 4: 1 ratio). Diet can vary based on weight gain. Adequate hydration and integration of micronutrients must be ensured. GLUT1-Disease (GLUT1-DS) represents an elective disease for which classical ketogenic diet is a resolutive therapy. Glucose transporter 1 deficiency syndrome is caused by heterozygous mutations, mostly de novo, in the SLC2A1 gene on chromosome 1p34.2, which codes for GLUT1 (42). Mutations in this gene limit the availability of glucose in the brain, causing a shortage of energy in the brain. The severe "classic" phenotype is characterized by a chronic childhood-onset encephalopathy with drug-resistant epilepsy, usually presenting within the first months of life with psychomotor retardation, microcephaly, spasticity, ataxia, and mixed movement disorders. Ketogenic diet is considered the gold standard therapy for GLUT1-DS; in fact, since the glucose supply is insufficient, the ketone bodies, which penetrate the blood brain barrier, are the only relevant alternative brain fuel source. Most of the clinical cases of epilepsy and GLUT1-DS reported in the literature reveal an important gap between the clinical onset and the time of diagnosis of the syndrome. The most important factor for predictive outcome is age at diagnosis because the effectiveness of the diet decreases when it is started in late childhood (33, 35, 41, 42).

There is no contraindication for breastfeeding during ketogenic diet. Although breast milk is high in sugar (6.9–7.2 g/dl), several studies have shown that ketogenic diet can be started safely and effectively in infants while continuing to breastfeed, and infants can achieve and maintain ketosis in a similar way to non-breastfed babies (43). Nowadays, most researchers recommend following mothers' wishes to include breast milk and combining breast milk with a highly specialized ketogenic formula based on the calculated carbohydrate in breastmilk (43). Ketogenic diet also plays an important role in the homeostasis of the intestinal microbiome: ketone bodies selectively inhibit the growth of bifidobacteria and the reduction of intestinal proinflammatory Th17 cell levels, the imbalance of which has recently been found in children with intractable epilepsy (41). In this respect, the positive effect on the immune system resulting from breastfeeding and ketogenic diet seems to go beyond the "pH-mediated" metabolic reduction

of the seizure threshold, opening the horizon for new anti-inflammatory effects on nerve cells. In addition, it has been reported that metabolic disorders such as insulin resistance, metabolic syndrome, and obesity may be risk factors for epilepsy in children (38, 41, 42). In the light of these evidence, ketogenic diet represents a valid strategy in the treatment of epilepsy on two fronts: controlling body weight and related disorders via regulating metabolic profile, and the production of ketone bodies modulating brain transmission. However, further studies are needed to clarify the molecular mechanism behind the beneficial effect of ketogenic diet on epilepsy.

COW'S MILK ALLERGY AND EPILEPTIC EVENTS

Some researchers suggest that peripheral inflammation of the gastrointestinal (GI) tract could trigger the GI immune system and cause disruption of the blood brain barrier (44, 45). In particular, food allergen-mediated activation of local antigen-presenting cells could cause a shift toward Type-II helper T-lymphocytes (Th2) and subsequent secretion of pro-inflammatory cytokines. These pro-inflammatory agents can cross the blood brain barrier thereby sustaining CNS inflammation and triggering seizures. Abnormalities in the expression of cytokines and immune cells have been observed both in patients with epilepsy and in animal models (46, 47). Cow's milk proteins may trigger inflammation of infant's GI tract. At a very young age, seizures may be the first clinical manifestation of cow's milk allergy. In this regard, literature supports the fragility of the CNS to seizure susceptibility in children <12 months of age (44). Indeed, the occurrence of simple febrile seizures in this age group has been associated with a statistically significant increase in the risk of subsequent epilepsy (48, 49). Moreover, the vulnerability of the blood brain barrier in very early childhood is a predisposing factor for the abnormal development of the CNS, and severe and complex epileptic syndromes (50). Therefore, as a therapeutic strategy to improve the treatment efficacy of neurologic disorders, food allergy must be considered. In clinical cases of epilepsy in which a food allergy is diagnosed, exclusion of certain foods can be prescribed. For example, cow milk-free diet resulted in complete clinical and electroencephalography remission with no side effects in epileptic children who were allergic to cow's milk (51). In newborns, however, milk fulfils nutritional needs and ensures healthy growth and development by delivering macronutrients as well as numerous bioactive compounds and interactive elements. Therefore, a conservative approach with respect to the milk diet of infants is the evaluation of the proteome composition of alternative milks to cow's milk for their potential contribution of elements capable of mucosal immune diseases.

Extensive investigation of goat milk revealed the presence of a high number of alleles at the four casein loci; the knowledge of milk protein genetic variants is more fragmentary in ovine species and is mainly oriented to αs1-CN and β-LG loci, giving less conclusive results than in goats (52). The casein polymorphism is associated with different casein synthesis levels in goat milk (distinguishing strong, medium, weak, and null alleles) and different rates of phosphorylation of the peptide chain (53, 54). In goat milk, it is suggested that animals with weak or null alleles, especially for CSN1S2 and CSN1S1, could be used in breeding

programs aimed at producing milk with hypoallergenic properties (53, 55). The role of milk from alternative species to bovine, and their protein fractions on the immune status of infants with epilepsy, has been investigated to highlight different responses both at milk source and milk protein fraction using peripheral blood mononuclear cells (PBMC) from young epileptic patients (52, 56). The lyophilized pasteurized bovine, caprine, and ovine bulk milks and the milk protein fractions [αS1-casein (CN), αS2-CN, κ-CN, β-CN, and a mix of α-lactalbumin (α-LA) and β-lactoglobulin (β-LG)] were incubated with PBMC from control children and children with generalized epilepsy to monitor the pro- and anti-inflammatory cytokines and oxidative status. This approach is because of the presence of numerous polymorphic forms known for milk proteins that generate different epitopes able to mediate inflammatory and allergic responses in patients with food allergy. Though the genetic polymorphisms of milk proteins are of importance as they are associated with quantitative and qualitative parameters of milk, they also play an important role in eliciting different degrees of allergic reaction (57).

Due to poor data on cytokine threshold levels in healthy and epileptic children, the authors (52, 56) adopted a classification criterion based on the level of the monitored cytokines. The levels of cytokines found in controls are used as a threshold level to group the response of infants with epilepsy: (i) children with epilepsy having low levels of cytokines not different from those of control children; (ii) children with epilepsy having cytokine levels at least 5-fold higher than those of control children; and (iii) children with epilepsy having cytokine levels at least 10-fold higher than those of control children. Albenzio et al. (52) found that: (i) the levels of tumor necrosis factor-α (TNF-α) detected in cultured PBMCs in presence of caprine milk were lower than bovine and ovine milk; (ii) whey protein fraction induced lower level of TNF-α secretion than casein fractions; and (iii) within milking species, caprine whey protein fraction showed lower levels of TNF-α. The ability of PBMC to secrete cytokines in response to milk and protein fraction stimulation may be a predictor of the secretion of soluble factor TNF-α in the bloodstream of challenged patients. In the same experiment, the authors found that the amount of IL-6 after treatment of PBMCs with cow, ovine, and caprine milk were lower than other pro-inflammatory cytokines probably because this cytokine is not a reliable marker of epilepsy in the bloodstream.

Due to its higher oxygen consumption rate and high level of polyunsaturated fatty acids, the brain is vulnerable to oxidative stress. Brain possesses a relatively weaker antioxidant defense system so that brain injuries caused by oxidative stress play a significant role in the pathogenesis of many cerebral disorders, including stroke, migraine, dementia, and epilepsy (58). It has been reported that oxidative damage occurring during epileptogenesis contributes to acute injury-induced neuronal damage leading to detrimental effects on areas of the brain that control learning and memory functions (59). Excess ROS is increasingly recognized as a key factor in seizure-induced neuronal damage (60). Albenzio et al. (52) found that levels of ROS and reactive nitrogen species (RNS) detected in PBMCs were higher in bovine and ovine milk than caprine milk, and the highest levels of ROS/RNS were found after incubation of PBMC with the β-CN fraction of bovine milk. Taken together, these data further support the use of antioxidants as adjunct to antiepileptic drugs to improve seizure control.

CONCLUSION

In this chapter, the role of the gut-brain axis, ketogenic diet, and cow's milk allergy on epilepsy, particularly in childhood, is presented. Due to the crucial role of diet in regulating the inflammatory status and intestinal microbiota composition, nutritional strategies have gained interest in epilepsy. Ketogenic diet can be considered a valid therapeutic strategy to treat children with intractable epilepsy, reducing inflammation at intestinal level, and preserving the homeostasis of the intestinal microbiome. Milk and dairy products represent fundamental foods in early stages of life, and can reduce inflammation; however, they can also exert a pro-inflammatory activity in subjects allergic to bovine milk. Alternative milk formula for infants needs to be further explored as well as hypoallergenic milk sources.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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REFERENCES

1. Sousa PS, Lin K, Garzon E, Sakamoto AC, Yacubian EMT. Self-perception of factors that precipitate or inhibit seizures in juvenile myoclonic epilepsy. Seizure. 2005;14:340–346. https://doi.org/10.1016/j.seizure.2005.04.007
2. Asadi-Pooya AA, Sperling MR. Do foods precipitate seizures? A cross-cultural comparison. E & B. 2007;11:450–453. https://doi.org/10.1016/j.yebeh.2007.07.004
3. Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, Haller D, et al. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br J Nutr. 2013;109(Suppl 1):S1–34. https://doi.org/10.1017/S0007114512005119
4. Bordoni A, Danesi F, Dardevet D, Dupont D, Fernandez AS, Gille D, et al. Dairy products and inflammation: A review of the clinical evidence. Crit Rev Food. 2017;57(12):2497–2525. https://doi.org/10.1080/10408398.2014.967385
5. Holmes E, Kinross J, Gibson GR, Burcelin R, Jia W, Pettersson S, et al. Therapeutic modulation of microbiota-host metabolic interactions. Sci Transl Med. 2012;4(137):137rv136. https://doi.org/10.1126/scitranslmed.3004244
6. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, et al. Host-gut microbiota metabolic interactions. Science. 2012;336(6086):1262–1267. https://doi.org/10.1126/science.1223813
7. Collins SM, Surette M, Bercik P The interplay between the intestinal microbiota and the brain. Nat Rev Microbiol. 2012;10(11):735–742. https://doi.org/10.1038/nrmicro2876
8. Montiel-Castro AJ, Gonzalez-Cervantes RM, Bravo-Ruiseco G, Pacheco-Lopez G. The microbiota-gut-brain axis: neu- robehavioral correlates, health and sociality. Front Integr Neurosci. 2013;7:70. https://doi.org/10.3389/fnint.2013.00070
9. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59–65. https://doi.org/10.1038/nature08821
10. Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. Cell Mol Life Sci. 2017;74(20):3769–3787. https://doi.org/10.1007/s00018-017-2550-9

11. Burokas A, Moloney RD, Dinan TG, Cryan JF. Microbiota regulation of the Mammalian gut-brain axis. Adv Appl Micro-biol. 2015;91:1–62. https://doi.org/10.1016/bs.aambs.2015.02.001
12. Forsythe P, Bienenstock J, Kunze WA. Vagal pathways for microbiome-brain-gut axis communication. Adv Exp Med Biol. 2014;817:115–133. https://doi.org/10.1007/978-1-4939-0897-4_5
13. Bauer KC, Huus KE, Finlay BB. Microbes and the mind: emerging hallmarks of the gut microbiota-brain axis. Cell Microbiol. 2016;18(5):632–644. https://doi.org/10.1111/cmi.12585
14. Holmes M, Flaminio Z, Vardhan M, Xu F, Li X, Devinsky O, et al. Cross talk between drug-resistant epilepsy and the gut microbiome. Epilepsia. 2020;61(12):2619–2628. https://doi.org/10.1111/epi.16744
15. Noble EE, Hsu TM, Kanoski SE. Gut to brain dysbiosis: mechanisms linking Western diet consumption, the microbiome, and cognitive impairment. Front Behav Neurosci. 2017;11:9. https://doi.org/10.3389/fnbeh.2017.00009
16. Ianiro G, Rossi E, Thomas AM, Schinzari G, Masucci L, Quaranta G, et al. Faecal microbiota transplantation for the treatment of diarrhoea induced by tyrosine- kinase inhibitors in patients with metastatic renal cell carcinoma. Nat Commun. 2020;11(1):8–13. https://doi.org/10.1038/s41467-020-18127-y
17. Lu JF, Zhu MQ, Zhang H, Liu H, Xia B, Wang YL, et al. Neohesperidin attenuates obesity by altering the composition of the gut microbiota in high-fat diet-fed mice. FASEB J 2020;34(9):12053–12071. https://doi.org/10.1096/fj.201903102RR
18. Lecronier M, Tashk P, Tamzali Y, Tenaillon O, Denamur E, Barrou B, et al. Gut microbiota composition alterations are associated with the onset of diabetes in kidney transplant recipients. PLoS One 2020;15(1):1–18. https://doi.org/10.1371/journal.pone.0227373
19. Sun J, Xu J, Ling Y, Wang F, Gong T, Yang C, et al. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. Transl Psychiatry. 2019;9(1):1–13. https://doi.org/10.1038/s41398-019-0525-3
20. Xue LJ, Yang XZ, Tong Q, Shen P, Ma SJ, Wu SN, et al. Fecal microbiota transplantation therapy for Parkinson's disease: a preliminary study. Medicine (Baltimore) 2020;99(35):e22035. https://doi.org/10.1097/MD.0000000000022035
21. Cryan JF, O'riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. Physiol Rev. 2019;99(4):1877–2013. https://doi.org/10.1152/physrev.00018.2018
22. De Caro C, Iannone LF, Citraro R, Striano P, De Sarro G., Constanti A, et al. Can we 'seize' the gut microbiota to treat epilepsy? Neurosci Biobehav Rev.2019;107:750–64. https://doi.org/10.1016/j.neubiorev.2019.10.002
23. Iannone LF, Preda A, Blottière HM, Clarke G, Albani D, Belcastro V, et al. Microbiota-gut brain axis involvement in neuropsychiatric disorders. Expert Rev Neurother. 2019;19(10):1037–50. https://doi.org/10.1080/14737175.2019.1638763
24. Mörkl S, Butler MI, Holl A, Cryan JF, Dinan TG. Probiotics and the microbiota- gut-brain axis: focus on psychiatry. Curr Nutr Rep 2020;9(3):171–82. https://doi.org/10.1007/s13668-020-00313-5
25. Falony G, Joossens M, Vieira-Silva S, Wang J, Darzi Y, Faust K, et al. Population-level analysis of gut microbiome variation. Science; 2016;352(6285):560–564. https://doi.org/10.1126/science.aad3503
26. Makki K, Deehan EC, Walter J, Bäckhed F. The impact of dietary fiber on gut micro-biota in host health and disease. Cell Host Microbe. 2018;23(6):705–715. https://doi.org/10.1016/j.chom.2018.05.012
27. Griffin NW, Ahern PP, Cheng J, Heath AC, Ilkayeva O, Newgard CB, et al. Prior dietary practices and connections to a human gut microbial metacommunity alter responses to diet interventions. Cell Host Microbe. 2017;21(1):84–96. https://doi.org/10.1016/j.chom.2016.12.006
28. Dahlin M, Prast-Nielsen S. The gut microbiome and epilepsy. EBioMedicine. 2019;44:741–746. https://doi.org/10.1016/j.ebiom.2019.05.024
29. Xie G, Zhou Q, Qiu CZ, Dai WK, Wang HP, Li YH, et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. World J Gastroenterol. 2017;23(33):6164–6171. https://doi.org/10.3748/wjg.v23.i33.6164
30. Pittman Q J. A gut feeling about the ketogenic diet in epilepsy. Epilepsy Res. 2020;166:106409. https://doi.org/10.1016/j.eplepsyres.2020.106409
31. Falsaperla R, D'Angelo G, Praticò A D, Mauceri L, Barbagallo M, Pavone P, et al. Ketogenic diet for infants with epilepsy: a literature review. Epilepsy Behav. 2020;112:107361. https://doi.org/10.1016/j.yebeh.2020.107361

32. Dabek A, Wojtala M., Pirola L, Balcerczyk, A. modulation of cellular biochemistry, epigenetics and metabolomics by ketone bodies. implications of the ketogenic diet in the physiology of the organism and pathological states. Nutrients. 2020;12:788. https://doi.org/10.3390/nu12030788
33. Sancheti J, Shaikh MF, Akhade M, Shaikh FA, Sathaye S. Nutritional therapy for epilepsy. J Pharm BioSci. 2013;4:149–156.
34. Monda V, Polito R, Lovino A, Finaldi A, Valenzano A, Nigro E, et al. Short-term physiological effects of a very low-calorie ketogenic diet: effects on adiponectin levels and inflammatory states. Int J Mol Sci. 2020;21(9):3228. https://doi.org/10.3390/ijms21093228
35. Kong J, Nam SO, Ko A, Byun SY, Lim TJ, Kim YM, et al. Longitudinal changes in insulin resistance in children with epilepsy on ketogenic diet: Prevalence and risk factors. Epilepsy Behav. 2020;112:107393. https://doi.org/10.1016/j.yebeh.2020.107393
36. Valenzano A, Polito R, Trimigno V, Di Palma A, Moscatelli F, Corso G, et al. Effects of very low calorie ketogenic diet on the orexinergic system, visceral adipose tissue, and ROS production. Antioxidants. 2019;8(12):643. https://doi.org/10.3390/antiox8120643
37. Puchalska P, Crawford PA. Multi-dimensional Roles of ketone bodies in fuel metabolism,signaling, and therapeutics. Cell metab. 2017;25(2):262–284. https://doi.org/10.1016/j.cmet.2016.12.022
38. Mohammadi M, Meysamie A, Jahanian. A How do parents think about the effect of food and alternative medicine on their epileptic children? Iran J Pediatr. 2010; 20(2):193.
39. Jensen NJ, Wodschow HZ, Nilsson M, Rungby J. Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. Int. J. Mol. Sci. 2020;21(22):8767. https://doi.org/10.3390/ijms21228767
40. Le Pichon JB, Thompson L, Gustafson M, Abdelmoity A. Initiating the ketogenic diet in infants with treatment refractory epilepsy while maintaining a breast milk diet. Seizure. 2019;69:41–43. https://doi.org/10.1016/j.seizure.2019.03.017
41. Verrotti A, Iapadre G, Di Francesco L, Zagaroli L, Farello G. Diet in the treatment of epilepsy: what we know so far. Nutrients 2020;12, 2645. https://doi.org/10.3390/nu12092645
42. Rodríguez-Hernández AI, Pelayo-González ME. Description and evaluation of the effects of the cetogenic diet in children with refractory epilepsy. J Selva Andina Res Soc, 2020;11(2):142–152. https://doi.org/10.36610/j.jsars.2020.110200142x
43. Dressler A, Häfele C, Giordano V, Benninger F, Trimmel-Schwahofer P, Gröppel G, et al. The ketogenic diet including breast milk for treatment of infants with severe childhood epilepsy: feasibility, safety, and effectiveness. Breastfeed Med. 2020;15(2):72–78. https://doi.org/10.1089/bfm.2019.0190
44. Falsaperla R, Romano C, Pavone P, Vitaliti G, Yuan Q, Motamed-Gorji N, et al. The gut-brain axis: a new pathogenic view of neurologic symptoms-description of a pediatric case. J Pediatr Neurosci; 2017;12(1):105–108. https://doi.org/10.4103/jpn.JPN_190_16
45. Vitaliti G, Tabatabaie O, Matin N, Giugno GR, Pavone P, Lubrano R, et al. Nervous system involvement in clinical peripheral inflammation: A description of three pediatric cases. J Pediatr Neurosci. 2016;11(3):277. https://doi.org/10.4103/1817-1745.193359
46. Plata-Salamán CR, Ilyin SE, Turrin NP, Gayle D, Flynn MC, Romanovitch AE, et al. Kindling modulates the IL-1beta system, TNFalpha, TGF-beta1 and neuropeptide mRNAs in specific brain regions. Brain Res Mol Brain Res. 2000;75:248–258. https://doi.org/10.1016/S0169-328X(99)00306-X
47. Ravizza T, Vezzani A. Status epilepticus induces timedependent and astrocytic expression of Il-1-receptor type-1 in the rat limbic system. Neuroscience. 2006;137:301–308. https://doi.org/10.1016/j.neuroscience.2005.07.063
48. Verity CM, Golding J. Risk of epilepsy after febrile convulsions: A national cohort study. BMJ. 1991;303:1373–6. https://doi.org/10.1136/bmj.303.6814.1373
49. Berg AT, Shinnar S. Complex febrile seizures. Epilepsia. 1996;37:126–33. https://doi.org/10.1111/j.1528-1157.1996.tb00003.x
50. Yeghiazaryan NS, Zara F, Capovilla G, Brigati G, Falsaperla R, Striano P. Pyridoxine-dependent epilepsy: An under-recognised cause of intractable seizures. J Paediatr Child Health. 2012;48:E113–E115. https://doi.org/10.1111/j.1440-1754.2010.01866.x
51. Lucarelli S, Spalice A, D'Alfonso Y, Lastrucci G, Sodano S, Topazio L, et al. Cow's milk allergy and rolandic epilepsy: A close relationship? Arch Dis Child. 2012;97:481. https://doi.org/10.1136/archdischild-2011-301424

52. Albenzio M, Santillo A, Ciliberti MG, Figliola L, Caroprese M, Marino R, et al. Milk from different species: Relationship between protein fractions and inflammatory response in infant affected by generalized epilepsy. J Dairy Sci. 2016;99:5032–5038. https://doi.org/10.3168/jds.2015-10704
53. Albenzio M, Santillo A, d'Angelo F, Sevi A. Focusing on casein gene cluster and protein profile in Garganica goat milk. J Dairy Res. 2009;76:83–89. https://doi.org/10.1017/S0022029908003853
54. Park YW, Juárez M, Ramos M, Haenlein GFW. Physico-chemical characteristics of goat and sheep milk, Small Rumin Res. 2007;68:88–113. https://doi.org/10.1016/j.smallrumres.2006.09.013
55. Roncada P, Gaviraghi A, Liberatori S, Canas B, Bini L, Greppi GF. Identification of caseins in goat milk. Proteomics. 2002;2:723–726. https://doi.org/10.1002/1615-9861(200206)2:6<723::AID-PROT723>3.0.CO;2-I
56. Albenzio M, Santillo A, Ciliberti MG, Figliola L, Caroprese M, Polito AN, Messina G. Milk Nutrition and childhood epilepsy: an ex vivo study on cytokines and oxidative stress in response to milk protein fractions. J Dairy Sci. 2018;101(6):4842–4852. https://doi.org/10.3168/jds.2017-13104
57. El-Agamy EI. The challenge of cow milk protein allergy. Small Rum. Res. 2007;68:64–72. https://doi.org/10.1016/j.smallrumres.2006.09.016
58. Guler SK, Aytac B, Durak ZE, Cokal BG, Gunes N, Durak I, et al. Antioxidative-oxidative balance in epilepsy patients on antiepileptic therapy: a prospective case-control study. Neurol. Sci. 2016;37(5):763–767. https://doi.org/10.1007/s10072-016-2494-0
59. Pearson JN, Rowley S, Liang LO, White AM, Day BJ, Patel M, Reactive oxygen species mediate cognitive deficits in experimental temporal lobe epilepsy. Neurobiol. Disease. 2015;85:289–297. https://doi.org/10.1016/j.nbd.2015.07.005
60. Kovac S, Dinkova-Kostova AT, Abromov AY. The role of reactive oxygen species in epilepsy. React Oxyg Specis. 2016;1:38–52. https://doi.org/10.20455/ros.2016.807