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THE ROLE OF MILK NUTRITION IN CHILDHOOD EPILEPSY

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Some studies have found that the supplementation with individual nutrients reduced seizure frequency leading to the hypothesis that diet may be fundamental in patients with epilepsy. In human newborn milk fulfils the nutritional needs and ensures safe development and growth during the first stages of life. Milk protein is a very heterogeneous nutritional component involved both in the liberation of bioactive peptides and in adverse immune reactions. Milk lipids play a role in the brain development especially through the supply of polyunsaturated fatty acids and sphingolipids. Dietary pattern modulate gut microbioma and the concept of microbiome-gut-brain axis has been developed. Few studies provide adequate clinical and laboratory data to document the possibility that certain foods or allergens may induce convulsion in children with epilepsy. The role of diet in childhood epilepsy and its implication on the modulation of gut-brain axis, brain inflammatory reactions, and dietary allergic disorders are reviewed. In particular, a focus on milk from different lactating species as a future dietary strategy to alleviate the negative impact of epilepsy in infants has been reported.

Keywords: Dairy species, Childhood epilepsy, Seizures, Cytokines, Proteins, Lipids

INTRODUCTION

Diet is a fundamental aspect of human life and patients with epilepsy often request if foods are related to their illness. There are several reports suggesting that certain foods might trigger seizures; studies on animal model reported the reduction of seizure threshold in rats administered with excess dietary amino acids and induction of convulsions by monosodium glutamate (Asadi-Pooya *et al.*, 2008). Dietary therapies are often perceived as natural treatments for disease. Prior to the advent of medication, in particular antiepileptic drug medication, alternative forms of treatment were sought for treatment of epilepsies. The first report of the effects of starvation on epilepsy date back to the fifth century when Hippocrates described a man whose seizures were cured by abstaining from all food and drink (Cross, 2010). First report in the medical literature described the effect of complete fasting on the cessation of seizures (Guelpa, 1911). Subsequently Geyelin *et al.* (1921) described that epilepsy could be cured by diet based on the work of Conklin, who believed that epilepsy was caused by intoxication from the payers patches of the intestine and therefore advocated complete rest of the gut. Geyelin fasted his patients for up to 25 days, reporting a 90% success rate in children under the age of 10 years, decreasing with age to 50% in adults. Wilder (1921) proposed the use of a maintained diet to mimic starvation suggesting diet high in fat and low in carbohydrate to mimic the ketotic effects; driving the body to utilize the fat in the diet, so generating ketosis. Subsequently, the diet was shown to have benefits in epilepsy by several other authors and it was widely used up until the 1950, probably coming out of favour in the late 1930 with the introduction of phenytoin and other

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antiepileptic drug made the diet seem outdated and unnecessary. For many decades, the ketogenic diet was used only at a few academic centers until public interest was rekindled (Kinsman *et al.*, 1992). Renewed publicity was enhanced by the successful use of the diet in key individuals, most notably "Charlie" treated for intractable epilepsy that have failed to respond to multiple drugs and even surgery. The creation in 1994 of "The Charlie Foundation" today named "The Charlie Foundation for Ketogenic Therapies" has led to resurgence in the diet's popularity and an increase in research.

Furthermore, in recent study, at least 30% of children with intractable epilepsy had intakes below the recommended dietary allowance for vitamins D, E, and K, folate, calcium, and linoleic acid (Volpe *et al.*, 2007). Gordon and Dooley (2015) approached a cross-sectional survey on food insecurity and health status concluding that the experience of food insecurity appears to be more frequent among persons living with epilepsy. Recently, Albenzio *et al.* (2016a) reported the effects of protein fractions from different animal species such as bovine, ovine, and caprine milk in infants with generalized epilepsy.

Epilepsy is a fairly common chronic, complex neurological disease that comprises a group of neurological disorders characterized by the periodic occurrence of spontaneous seizures (Vezzani *et al.*, 2008). It is estimated by the World Health Organization to affect 0.8% of the world's population (Li *et al.*, 2011) although more recent data reported that epilepsy affects 1-3% of the general population (Guler *et al.*, 2016). Epilepsy is classified as partial, referred to a specific location; generalized with respect to the type of seizure and electroencephalographic findings; idiopathic, normally hereditary or with age-related onset; symptomatic, due to organic causes, with regard to aetiology. The term cryptogenetic is used rather than idiophatic or primary for certain serious aged-related syndromes and assumed to be symptomatic despite the fact that no precise cause has yet been discovered (Pelliccia *et al.*, 1999). Rolandic epilepsy is the best known and described form of idiopathic epilepsy (Lucarelli *et al.*, 2012).

THE ROLE OF MICROBIOMA IN CENTRAL NERVOUS SYSTEM DISORDER

Dietary patterns may modulate gut microbiome via alteration of nutrients availability. Recent developments have suggested that dietary intervention can impact gut microbial gene richness. Lower microbiome richness was identified as less healthy and associated with metabolic dysfunction and low-grade inflammation. Animal studies have provided the proof of concept that perturbation of the microbial composition of the gut alters functions not only in the intestine, but also in the brain (Collins, 2015). The gut microbiome has played a crucial role in the bidirectional gut-brain axis that integrates the gut and Central Nervous System (CNS) activities, and thus the concept of microbiome-gut-brain axis is emerging. The term gut-brain axis describes an integrative physiology concept that incorporates all, including afferent-efferent neural, endocrine, nutrient, and immunological signals between the CNS and the gastrointestinal system (Romijin *et al.*, 2008). Changes of dietary pattern as a result of CNS control of food intake can impact nutrient availability to gut microbiota and consequently their composition. Studies are revealing how diverse forms of neuro-immune and neuro-psychiatric disorders are correlated with or modulated by variations of microbiome, microbiota-derived products and exogenous antibiotics and probiotics. The microbiome poises the peripheral immune homeostasis and predisposes host susceptibility to CNS autoimmune diseases such as multiple sclerosis. Neural, endocrine and metabolic mechanisms are also critical mediators of the microbiome-CNS signalling, which are more involved in neuro-psychiatric disorders such as autism, depression, anxiety, stress (Wang and Kasper, 2014). Epilepsy occurs in 10-30% of individuals with autism; the association between autism and specific epileptic electroencephalography (EEG) abnormalities is not firmly established, neither is the prevalence of epileptiform abnormalities in the broader range of Pervasive Developmental Disorders (PDDs). The use of neurological investigative techniques such as electroencephalography should be routinely considered in children with autistic spectrum disorder (Gabis *et al.*, 2005). The possibility that autism is the consequence of an imperfect development of gut flora is supported by a number of observations like: the frequent coexistence of gastrointestinal symptoms in autistic children; the appearance of the disease after an incidental antimicrobic therapy and the increased levels of urinary biomarkers of specific pathogens of *Clostridium* spp. in the urine of autistic children (Grossi and Terruzzi, 2014).

Upward regulation of the CNS by microbiome can be achieved through neural, endocrine, metabolic and immunological mechanisms. The neural pathway is operational through the Enteric Nervous System (ENS), a

main division of the Autonomic Nervous System (ANS) that governs the gastrointestinal tract (GI) functions, and Vagal Afferent Nerves (VAN) that convey sensory information from viscera to the CNS (Verdu, 2009). Vagal activation is necessary for a range of effects of gut microbiome or probiotics on brain functions (Cryan and Dinan, 2012). In the endocrinal pathway, the gut microbiome plays a major role in the development and regulation of the Hypothalamus-Pituitary-Adrenal (HPA) axis that is critical to stress response. Studies in gnotobiotic mice showed that postnatal exposure to gut microbiome affected the set point of the HPA axis (Sudo, 2012). Enteroendocrine cells can secrete neurotransmitters and other signaling peptides in response to luminal stimuli that act as transducers for the gut-endocrine-CNS route (Rhee *et al*., 2009). Besides, the Vasoactive Intestinal Peptides (VIP), a peptide hormone sunthesized in the gut but also brain, could mediate immune-modulation during CNS inflammation (Gonzalez-Rey *et al.*, 2006). A metabolic pathway is naturally implicit in the microbiome-gut-CNS signaling. Examples of metabolites associated with microbial metabolism or microbial-host co-metabolism have been reviewed (Holmes *et al.*, 2011). In particular, metabolic pathway represents an important inter-kingdom communication as host signaling molecules that can be fully synthesized or mimicked by microbiota-derived metabolites. Commensal organisms can produce a range of neuroactive molecules such as serotonin, melatonin, gamma-aminobutyric acid (GABA), catecholamines, histamine and acetylcholine (Forsythe *et al.*, 2010; Lyte, 2011; and Barrett *et al*., 2012). Milk proteins are precursors of many different biologically active peptides which are inactive within the sequence of the parent protein and can be released by enzymatic proteolysis during gastrointestinal digestion. Once they are liberated in the body, bioactive peptides may act as regulatory compounds with hormone-like activity (Meisel, 1997). On the contrary, some peptides may be able to cause noxious effects on the CNS by interacting with neurotransmitter (Reichelt *et al.*, 1991).

Dietary lipids play an important role in the brain development; after the adipose tissue, the brain is the organ with the highest concentration of lipids (Soares *et al*., 2012). The brain requirements of polyunsaturated fatty acids (PUFA) must be supplied by the diet (Salvati *et al.*, 2006). In particular, it is known that Conjugated Linoleic Acid (CLA) cross the blood-brain barrier and is incorporated and metabolized in the brain (Fa *et al.*, 2005). Milk lipids have been shown to influence brain development and electrophysiological properties associated to important neurological disturbance like migraine and epilepsy (Soares *et al.*, 2012). Milk sphingolipids play a significant role in neuronal cell function by regulating rates of neuronal growth, differentiation and death as well as have the potential to exert dramatic effects on the activities of the CNS (Mills *et al.*, 2011).

The immunological pathway seems to be an independent mechanism in the microbiome-gut-CNS signaling. The CNS, though viewed as an immune-privileged site, is not devoid of immune cells. Aberrant CNS autoimmunity arises as a consequence of direct immune disruption of neural tissues. Indeed, immune-CNS communication is also mediated by systemic circulation of immune factors, which is implicated in neuro-psychiatric disorders such as depression. Factors that increase peripheral inflammation markers such as C-reactive protein (CRP), IL-1, IL-6 and tumor necrosis factor (TNF-a) are also risk factors for depression (Dantzer *et al.*, 2008; and Rook *et al.*, 2011).

BRAIN INFLAMMATION IN EPILEPSY

Inflammatory reactions occur in the brain in various CNS disease, including autoimmune, neurodegenerative, and epileptic disorders. To defend the host from the invasion of foreign organisms or pathogenic threats, the immune system has evolved into two parts: one responsible for an immediate action against external agents, defined *innate immune system*, and the other that allows antigen recognition via specific Antigen-Presenting Cells (APCs) and antigen receptors, constituting the *adaptive immune system* (Vezzani and Granata, 2005). The innate immune system uses mainly phagocytic cells, including monocytes/macrophages and microgliai, B and T lymphocytes are the pivotal cellular members of the adaptive immune system (Becher *et al.*, 2000; and Nguyen *et al.*, 2002). Communication between cells of the immune system occurs either via direct cell-to-cell contact or via soluble factors called cytokines. Proinflammatory and antiinflammatory cytokines and related molecules have been described in CNS and plasma, both in experimental models of seizures and in clinical cases of epilepsy. The CNS is considered immunoprivileged site because of the presence of a Blood-Brain Barrier (BBB), graft acceptance, lack of a conventional lymphatic drainage, and an apparently low traffic of monocytes and lymphocites. However, it should be defined as an immunological specialized site (Ransohoff *et al.*, 2002) because it is becoming clear that immune and inflammatory reaction do

occur in the CNS constituting part of the innate immunity or in the peripheral tissues and imported by competent immune cells into the CNS (acquired immunity). The transition between innate and adaptative immunity is mediated by a large variety of inflammatory mediators, among which cytokines and Toll-Like Receptors (TLRs) play a key role (Akira *et al.*, 2001).

The concept that the immune system plays a role in the epileptogenic process has been sustained by several authors that reported the existence of a variety of immunological alternations in epileptic patients (Billiau *et al.*, 2005). Literature counted numerous studies on the immunological alteration in patients with epilepsy, and on the involvement of the innate immune system in the pathogenesis of epilepsy (Vezzani and Granata, 2005). Many studies focused on immediate postictal changes in cytokines, cytokine-mRNA and leukocyte subsets in animal model revealing a significant increase of inflammatory cytokines production after induced status epilepticus or seizures in hippocampal structures (De Simoni *et al.*, 2000) and upregulation of inflammatory cytokines mRNA within a few hours after generalized seizures (Minami *et al.*, 1990; and Plata-Salamán *et al.*, 2000). In the blood of epileptic patients IL-6 levels were elevated immediately after complex, partial and generalized seizures (Peltola *et al.*, 2000; Kalueff *et al.*, 2004; Lehtimki *et al.*, 2007; and Bauer *et al.*, 2009). Pacifici *et al.* (1995) showed that peripheral blood mononuclear cells from epileptics produced more IL-1β, IL-6, IL-1α than those of controls.

FOOD ALLERGY AND EPILEPSY

The possibility that certain foods or allergens may induce convulsions has been reported in the literature. Periodic convulsive phenotypes may represent a response of the immune system to an allergic metabolic disturbance (Spangler, 1931). There are case reports of the occurrence of generalized convulsion after consumption of larger amount of gingko nuts (Miwa *et al.*, 2001). In animal studies monosodium glutamate (Bhagavan *et al.*, 1971) and aspartame (Camfield *et al.*, 1992) were found to provoke seizure. At least 30% of children with intractable epilepsy had intakes below the recommended dietary allowance for vitamins D, E, and K, folate, calcium, and linoleic acid (Volpe *et al.*, 2007). Gordon and Dooley (2015) approached a cross-sectional survey on food insecurity and health status concluding that the experience of food insecurity appears to be more frequent among persons living with epilepsy.

Some studies have indicated an unusually high incidence of allergenic illnesses in subjected with epilepsy (Frediani *et al.*, 2001). Most of the authors examined the relationship between food allergy and epilepsy by comparing groups of adults patients with healthy control subjects. Few studies provide adequate clinical and laboratory data to document the higher incidence of allergy in children with epilepsy. Convulsion could be caused by allergic sensitization and therefore an elimination diet lead to a decrease in both frequency and intensity of seizures: Wallis *et al.* (1923) obtained a positive response to one or more food allergens from 38% of epileptic patients with respect to 4% in the general control group. The prevalence of celiac disease has been found to be higher in patients with epilepsy than in controls (Cronin *et al.*, 1998). Gluten free diet beneficially affected the course of epilepsy only when started soon after epilepsy onset. High index of suspicion is necessary for the diagnosis of celiac disease and investigation for this disease is recommended in patients with childhood partial epilepsy with occipital paroxysms (Labate *et al.*, 2001).

Pelliccia *et al.* (1999) reported a clinical study on children suffering partial cryptogenetic epilepsy with cow's milk allergy. All cases proved significantly positive prick test for cow milk proteins and absence of IgE specific for cow milk proteins. Children were subjected to one-month elimination diet for cow milk and derivatives; in this period children displayed a marked improvement in both behavioural traits and EEG abnormalities. Subsequently, the diagnosis of allergy to milk was confirmed by means of an orally administered double-blind provocative testing; during milk administration children showed an impairment of the symptoms and underwent seizures analogous to those previously experienced and a reappearance of EEG anomalies. The diet eliminating cow milk and derivatives was resumed and followed by the children for about nine months with the total disappearance of the clinical symptomatology and EEG anomalies in awake and asleep. More recently Lucarelli *et al.* (2012) explored the relationship between cow's milk allergy and rolandic epilepsy by using the same clinical approach on a panel of allergic and non-allergic epileptic children. Non allergic subjects underwent a pharmacological treatment whereas allergic subjects were treated with cow's milk free diet. This study suggested that a cow milk free diet made it possible to obtain complete clinical and EEG remission with no side effects. Also children of non-allergic group displayed complete remission but in

some cases they underwent hypertransaminasemia and slight leucopenia attributable to the pharmacological treatment.

FOCUS ON THE ROLE OF MILK FROM DIFFERENT SPECIES ON GENERALIZED EPILEPSY

In human newborn milk fulfils the nutritional needs and ensures safe development and growth during the first stages of life. However, the complex immunological mechanism that regulates the allergic reaction to cow milk allergy may play a role in the onset of epileptic manifestation.

Milk protein is a very heterogeneous component in cow, sheep and goat mainly influenced by genetic variants. The genetic polymorphisms of milk proteins are of importance as they are associated to quantitative and qualitative parameters in milk. In particular, genetic polymorphism was associated with different levels of protein synthesis in milk, different rate of phosphorylation and glycosilation of the peptide chain and amino acids sequences of the protein (Albenzio *et al.*, 2011). Genetic polymorphisms of milk proteins also play an important role in eliciting different degrees of allergic reaction (Saini and Gill, 1991; Park, 1994; and El-Agamy, 2007). Caseins and especially α-CN are among the most important milk allergens (Restani *et al.*, 1999; and Ballabio *et al.*, 2011). Some studies revealed that goat milk (Bevilacqua *et al.*, 2001; Slaèanac *et al.*, 2010) can be considered as a proper alternative to human milk due to hypoallergenic properties of its proteins. Extensive investigation in goat milk revealed the presence of high numbers of alleles at the four casein loci as recently reviewed by Albenzio *et al.* (2016b). Milk from other species alternative to cow has been investigated for its role in children with Cow Milk Allergy (CMA); higher TNF-α levels were indeed found after exposure to cow milk casein and β-Lg than after exposure to the same fractions from goat milk (Albenzio *et al.*, 2012). TNF-α is one of the mediators involved in adverse reactions to cow milk proteins as gastrointestinal manifestations, and respiratory and cutaneus symptoms (Motrich *et al.*, 2003). Results on TNF-α evidenced that it is important to test the immune reactivity against each protein fraction before considering milk alternative to cow as a safe substitute for feeding infant with CMA.

IL-10 is one of the major cytokines produced by regulatory T-cells (Reuss *et al.*, 2002). IL-10 has broad anti-inflammatory properties by its inhibition of antigen-presenting cell function and suppression of production of pro-inflammatory cytokines (O'Garra *et al.*, 2008). Secretion of IL-10 after Peripheral Blood Mononuclear Cell (PBMC) stimulation was influenced by milk protein source being higher in goat's than cow's milk. Within cow milk protein fractions, casein induced higher levels of regulatory cytokine than β-Lg and milk protein mixture. Tiemessen *et al.* (2003) investigated the role of IL-10 in T-cells reactivity of children with CMA suggesting that activated allergen-specific T-cells might contribute to an active form of immune suppression *in vivo* through the production of IL-10 and thereby prevent aberrant reactions towards antigens such as cow's milk.

In a subsequent study, Albenzio *et al.* (2012) evaluated the effect of protein fractions from different animal species such as bovine, ovine, and caprine milk, on pro- and anti-inflammatory cytokines and reactive oxygen species production by PBMCs from infants with a mean age of 35 months with generalized epilepsy. PBMCs' ability 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 blood stream of the challenged patients. Several studies reported that TNF-α possibly acts in a concentration-dependent manner; TNF-α has been shown to play a proconvulsive role in *Shigella*--mediated seizures at low concentration, but exerted an anticonvulsive effect at higher concentration (Yuhas *et al.*, 2003). In the CNS, TNF-α can activate its two receptors, p55 and p75, and may modulate cell-signaling pathways: low concentration of TNF-α may predominantly activate proconvulsive effects via p55 while high concentration of TNF-α can play anticonvulsive role trough p75 pathway (Li et al., 2011). Albenzio *et al.* (2016a) found that the levels of TNF-α detected in cultured PBMCs stimulated against caprine milk reached lower levels than bovine and ovine milk. Whey-protein fraction induced lower level of TNF-α secretion than casein fractions and, within milking species, caprine whey protein fraction showed lower levels.

Several animal studies and clinical observations suggest an anticonvulsant effects of IL-10; one report showed protective effects of IL-10 against the development of epileptic form activity evoked by transient episodes of hypoxia in rat hippocampal slices (Levin *et al.*, 2007). Youn *et al.* (2013) reported that IL-10 was significantly elevated in plasma 48-72 hours after seizure onset leading to the hypothesis that IL-10 may have anticonvulsive effect in neonatal seizure patients by suppressing pro-inflammatory

cytokines production. Bovine, caprine and ovine bulk milk induced low level of IL-10 by cultured PBMC from children with generalized epilepsy in at least 50% of cases (Albenzio *et al.*, 2016a).

Chronic expression of IL-1β during epileptogenesis highlighted the possibility that this cytokine might be involved in the mechanisms underlying the onset of spontaneous seizures (Vezzani *et al.*, 2008). Cultured PBMCs of children with generalized epilepsy induced different levels of IL-1β after exposure to milk and milk protein fractions from different milking species. In particular, caprine milk and its casein fraction induced the highest levels of IL-1β (Albenzio *et al.*, 2016a).

The complexity of the PBMCs response against milk protein fractions stimulation relies on the ambiguous nature of IL-6 that is necessary for the normal development of the nervous system but has neurotoxic and proconvulsive effects when increased levels are detected in the brain (Samland *et al.*, 2003). The increase of IL-6 levels in CNS after generalized seizure was found to be more pronounced than the increase in plasma (Li *et al.*, 2011). Albenzio *et al.* (2016a) found that the amount of IL-6 after stimulation of PBMCs with cow, ovine and caprine milk were lower than other proinflammatory cytokines probably because this cytokine is not a reliable marker of epilepsy in the blood stream.

Due to its higher oxygen consumption rate and high level of PUFA the brain is vulnerable to oxidative stress. It 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 (Guler *et al.*, 2016). Recently, it was reported that oxidative damage occurring during epileptogenesis contributes to acute injury-induced neuronal damage leading to detrimental effects on areas of the brain controlling region associated to learning and memory function (Pearson *et al.*, 2015). Excess of reactive oxygen species (ROS) is increasingly recognized as a key factor in seizure-induced neuronal damage (Kovac *et al.*, 2016). Albenzio *et al.* (2016a) found that levels of ROS/RNS detected in PBMCs were higher in bovine and ovine milk than caprine milk. Devi *et al.* (2008) suggested the possible use of antioxidants as adjunct to antiepileptic drugs to improve seizure control. The production of ROS is not only part of the killing strategy of effector cells within the Th1-type immune response, it is also involved to further amplify the release of pro-inflammatory cytokines. An oxidizing mileau is also relevant trigger of redox-sensitive signal transduction pathway in cells including the induction of pro-inflammatory cytokines like TNF-α (Murr *et al.*, 2005).

CONCLUSION

Many studies have addressed the role of diet in triggering epileptic disorders. In childhood milk nutrition is particularly relevant, therefore the role of milk nutrition in childhood epilepsy need to be explored. The implications of the diet on the modulation of gut-brain axis, brain inflammatory reactions, and dietary allergic disorders in epilepsy have been reviewed although studies on childhood epilepsy are still lacking. The study of the effects of milk components from different dairy species could offer a future dietary strategy to alleviate the negative impact of epilepsy in infants. In particular, monitoring the level of the pro-inflammatory and anti-inflammatory cytokines and ROS might be useful to discriminate the effects of foods on the inflammatory response in epileptic children.

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