REVIEW ARTICLE

CONTENTS

Long-chain polyunsaturated fatty acids and brain functions – literature review

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ABSTRACT

Long-chain ω-3 PUFAs such as DHA and EPA are often present in high amounts in algae and fish. DHA in particular is crucial for the proper development and functioning of the brain because it is the main structural component of ω-3 PUFA in the brain. This makes it an indispensable element of the phospholipids of the nervous membrane. The purpose of this article is to present the benefits of Omega-3 acids in the functioning of the nervous system. The text discusses a literature review focusing on the impact of omega-3 fatty acids. Polyunsaturated fatty acids (PUFAs) are essential for overall health and have been extensively studied for their contributions to human well-being and disease management. Recent research indicates their effectiveness in preventing and treating various diseases. Omega-3 PUFAs have been identified as therapeutic agents, particularly in combating inflammatory conditions like cardiovascular and neurodegenerative diseases. The aim of this article is to present the benefits of omega-3 fatty acids supplementation. Publications outlining properties of polyunsaturated fatty acids on the brain and articles presenting the effects of polyunsaturated fatty acids were reviewed using the Pubmed platform. The review included the keywords "Omega-3 fatty acids""DHA""EPA""PUFA

KEY WORDS: Alzheimer's disease, EPA, DHA, Brain, Omega-3, ω-3 PUFAs

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INTRODUCTION

Omega-3 fatty acids are fatty acids that in their chemical structure have a double bond between the third and fourth carbon atoms from the methyl end. The most important compounds belonging to this group include, first of all, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), given their influence on the proper functioning of the brain [1].

It is estimated that about 60% of the brain is made up of fats, with DHA accounting for 40% of the total, while EPA accounts for less than 1%. It is assumed that these are essential compounds for the proper functioning of the nervous system. DHA has many functions in the central and peripheral nervous system, functional in the transmission of signals between neurons, as well as structural, ensuring the maintenance of cell membrane integrity by being one of the main components of phospholipids [2]. Studies confirm their antioxidant, anti-inflammatory and endothelial protective properties.

Man is unable to synthesize them, only a small amount (0.5%) can be formed from alpha-linolenic acid (ALA), which also belongs to the group of polyunsaturated fatty acids [3]. The main sources of EPA and DHA acids are oily marine fish such as salmon, sprat, mackerel, among others. While vegetable oils do not contain DHA and EPA, they can be a source of ALA, which is found in many plant products such as flaxseed, chia seeds or walnuts. Transport of omega-3 fatty acids is possible via albumin in free or esterified form.

AIM

Long-chain ω-3 PUFAs such as DHA and EPA are often present in high amounts in algae and fish. DHA in particular is crucial for the proper progress and functioning of the cerebrum because it is the main structural component of ω-3 PUFA in the brain. This makes it an indispensable element of the phospholipids of the nervous membrane. The purpose of this article is to present the assistance of Omega-3 acids in the functioning of the nervous system.

MATERIALS AND METHODS

Analytical methods were used for the research. The source data comes from scientific sources from around the world regarding the effects of omega-3 acids on the human nervous system. The articles presenting the

effects of polyunsaturated fatty acids were reviewed using the Pubmed platform. The review included the keywords "Omega-3 fatty acids""DHA""EPA""PUFA.

REVIEW AND DISCUSSION

OMEGA 3 AND FETAL AND CHILD BRAIN DEVELOPMENT

Arachidonic acid (AA) and docosahexaenoic acid (DHA) are crucial for normal brain growth and cognitive development. They rapidly accumulate in the brain and retina during the later stages of pregnancy and early postnatal period [4]. The omega-3 fatty acids necessary for normal fetus development are provided by transfer from the mother's circulation. DHA is transported across the placenta by fatty acid-binding proteins, which are then released into the fetal circulation, then transferred to the liver where they are esterified and re-secreted in lipoproteins [5].

Many studies show that the percentage of long-chain polyunsaturated fatty acids is higher in the fetal circulation than in the maternal circulation, this indicates that the placenta may play a role in the preferential transfer of the aforementioned acids, particularly favouring DHA [6]. The effect of DHA on fetus brain development was demonstrated in an observational study, which found that children born to women who consumed more oily marine fish during pregnancy improved motor skills, showed better social skills, higher verbal intelligence and higher social development scores at eight years of age [7]. Another study using magnetic resonance imaging by Ogundipe et al. found that consuming 300 mg/d of DHA orally during the third trimester of pregnancy correlates positively with brain volume in infants [8].

Available clinical evidence suggests that omega-3 fatty acid supplementation may support optimal neural development in full-term infants. Elevated DHA levels at birth were associated with better child neurodevelopment. Nevertheless, mixed results from prenatal supplementation studies have led to speculation that other factors, such as socioeconomic status and lifestyle, may influence the benefits of DHA. In summary, adequate DHA intake through maternal diet or breastfeeding may offer some neuronal protection in specific groups of children, suggesting that DHA may be a modifiable risk factor for Autism Spectrum Disorders (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) [9].

The mother's role in providing omega-3 fatty acids does not end with childbirth. The intake during infancy through breastfeeding is also important. Maternal milk-derived omega-3 fatty acids may prove essential for better cognitive functioning, speech handling and improved psychosocial behavior [10]. Oddy et al. in their study showed, breastfeeding for less than 6 months was a factor indicating the presence of mental health problems [11]. Three randomized controlled trials conducted showed positive effects on children's cognitive development in women who supplemented with DHA [12-14]. However, it should be noted that in one of these studies, the benefits of supplementation during pregnancy and lactation were not sustained over the long term [14].

A mother's diet enriched with n-3 fatty acids protects newborns from stroke compared to children of mothers on a standard diet. Studies suggest that a diet enriched with omega-3 fatty acids affects the composition of fats that make up the newborn brain. With n-3 supplementation, there were no changes in the levels of inflammatory markers in the brain, and the accumulation of cytokines and chemokines induced by transient occlusion of the middle cerebral artery was reduced in young children on a diet supplemented with n-3 fatty acids, which shows that under basal conditions the effect of a diet supplemented with fatty acids from marine fish is not present under basal conditions, while their anti-inflammatory and homeostatic effects are reflected in reduced susceptibility to neonatal stroke [15]

OMEGA-3 AND BRAIN AGING

The process of brain aging is complex, consisting of several levels, starting from the subcellular level to the organ level. We can look for the beginning early in life, which accelerates as the years go by. This process can be divided into morphological and pathophysiological character. Morphologically, the brain volume decreases, the cortex thins, the white matter degrades, and the ventricular system dilates. . In pathophysiology, on the other hand, nerve cells shrink, dendrites degrade and demyelinate, and metabolism slows down [15]. Studies have shown that environmental factors affect brain plasticity, synapse formation and dendrite formation [16].

Diet is one of the main factors that affect brain plasticity. Currently, although somewhat contradictory, a growing number of human and animal studies suggest that omega-3 polyunsaturated acids may exhibit beneficial effects on the brain, which is subject to aging [17]. As we age, the ability to learn and remember information becomes impaired. This is associated with a significant decline in the production of new nerve cells. Omega-3 fatty acids have beneficial effects on neurogenesis in adults. A study performed on old rats that received a diet enriched with EPA and DHA acids for 12 weeks showed that these compounds can positively act on

processes related to the loss of neural tissue and the reduction of transcription factors associated with learning and memory – retinoic acid receptors and retinoid X receptors [18].

Another reason that may speak to the deterioration of brain function with age is inflammatory processes arising in neural tissue. A number of studies have shown useful effects of omega-3 fatty acids on age-related cognitive decline associated with their anti-inflammatory properties [19]. One study was conducted on old rats that had elevated concentrations of the markers of nervous system inflammation – interferon-γ and interleukin-1β, the use of polyunsaturated fatty acid supplementation resulted in a decrease in the concentration of the aforementioned markers, which was associated with the restoration of long-term synaptic potentiation (LTP), responsible for an increase in the efficiency of synaptic conduction [20].

Another important mechanism associated with aging is the progressive accumulation of oxidative damage. Free radicals are responsible for the damage, which, once formed in the body, are not completely destroyed by endogenous defence systems [21]. Lipids are the building blocks of nerve cell membranes, their peroxidation may be a major cause in the pathogenesis of the aging process. Omega-3 fatty acids may promote the maintenance of membrane homeostasis by counteracting the modifications that occur with age, resulting in a reduction in cognitive decline [22]. One study observed improved memory abilities along with reduced lipid peroxidation in the hippocampus by administering DHA for 10 weeks in 25-month-old rats deficient in polyunsaturated fatty acids [23]. Human studies show that erythrocyte membranes from human offspring in their nineties show reduced lipid peroxidation and greater membrane integrity compared to the general population [24].

Another observational study of 1,315 women aged 65 to 80 years who did not have dementia found that participants with higher levels of polyunsaturated fatty acids in their red blood cells had significantly larger white matter and hippocampal volumes. In summary, aging is characterized by the occurrence of low-grade inflammation in nervous tissue. Particular attention should be paid to the activation of microglial cells and increased production of pro-inflammatory factors such as cytokines. The appearance of the inflammatory process is associated with a decline in cognitive functions, which directly translates into a deterioration in the quality of life and has serious socioeconomic consequences. Omega-3 fatty acids may play a significant role in the process of slowing down the development of neurodegenerative changes [25].

OMEGA-3 AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the leading cause of dementia in the elderly, affecting tens of millions of people worldwide. Clinically, it manifests as a gradual deterioration of the brain's cognitive functions, eventually leading to complete memory loss and personality changes. This clinical picture is due to extensive loss of neurons and synapses, especially in areas of the hippocampus and cortex. Macroscopically, Alzheimer's disease is characterized by symmetrical atrophy of the cerebral cortex, mainly in the medial temporal lobes, while sparing the primary motor, sensory and visual cortex. In addition, characteristic neuropathological features of this disease include the presence of amyloid extracellular plaques and intracellular neurofibrillary tangles.

Polyunsaturated fatty acids, which are an important building block of the brain, may show beneficial effects on AD. Several studies have shown reduced EPA and DHA content in postmortem brain tissue and serum samples of AD sufferers [26].

Individuals suffering from mild dementia due to AD show better cognitive performance when EPA and DHA supplementation is added to their diet. Amyloid plaque formation results from abnormal extracellular accumulation and deposition of Aβ peptide, which is thought to be an early toxic event in AD pathogenesis, triggering the disease process. Physiologically, Aβ monomers are derived from amyloid precursor protein (APP) after its cleavage by β- and γ-secretase. DHA affects amyloid-related processes, leading to reduced Aβ production. Modifies the ratio of APP processing by the amyloidogenic and non-amyloidogenic pathway. Inhibits the activity of β- and γ-secretase enzymes, both directly and by regulating the intracellular transport of β-secretase BACE-1 and the connection of presenilin 1 (PS1) to lipid raft membrane microdomains. In addition, DHA and other fatty acids with four or more double bonds, such as EPA, stimulate α-secretase activity, which promotes non-amyloidogenic APP processing [27].

Total brain Aβ levels, as well as amyloid pathology, depend not only on Aβ production, but also on transport and enzymatic degradation processes [28]. The insulin-degrading enzyme (IDE) plays a key role in the elimination of Aβ in brain tissue. Supplementation with DHA or EPA leads to increased IDE-dependent degradation of Aβ40 in immature neuroblastoma cells. In addition, omega-3 fatty acids show beneficial effects on microglia Aβ42 phagocytosis and Aβ clearance in the interstitial tissue, further promoting Aβ elimination. DHA appears to further inhibit Aβ aggregation in vitro and counteract Aβ-induced toxicity in immature neuroblastoma cells. Overall, the beneficial effects of polyunsaturated fatty acids in lowering Aβ levels are

based not only on reducing its production, but also on stimulating elimination processes.

Observational studies seem promising in preventing cognitive decline. Providing a diet rich in omega-3 fatty acids in healthy populations without previous Alzheimer's disease or dementia suggests a potential protective effect against Alzheimer's disease. It should also be noted that the results of clinical trials, which mainly concern people with AD, in which polyunsaturated fatty acids do not show any effect. This draws particular attention to the fact that fatty acids from sea fish should be consumed before the first symptoms of AD are observed [29].

OMEGA-3 AND DRUG-RESISTANT EPILEPSY

Epilepsy is a common neurological disease characterized by recurrent episodes of seizures. These episodes result from spontaneous and rhythmic changes in neuronal electrical activity, unrelated to toxic, metabolic or infectious factors. It is estimated that between 1 and 3 percent of the population may receive a diagnosis of epilepsy during their lifetime, accounting for approximately 50 million people affected worldwide [30]. In developed countries, 50 new cases of epilepsy per 100,000 people are diagnosed each year, while in developing countries the number is between 100 and 190 new cases per 100,000 people per year [31].

Although the majority of epilepsy patients effectively control their condition with medication, about 25% to 30% of people with epilepsy do not respond positively to drug treatment [32]. Refractory epilepsy is defined as the lack of satisfactory seizure control despite the use of at least two tolerable antiepileptic drugs at appropriate doses for a sufficiently long period of time in both monotherapy and combination therapy [33].

Refractory epilepsy, also known as drug-resistant, pharmacoresistant, incurable, incapacitating or severe epilepsy [34], can be a source of concern and negatively affect the quality of life of affected individuals and their families [30] Moreover, drug-resistant epilepsy is associated with an increased risk of sudden death. The phenomenon of sudden unexpected death due to epilepsy (SUDEP) is as much as five times more common in the population of people with seizures who do not respond to medical treatment, compared to those with well-controlled epilepsy [35].

Over the past decade, researchers have conducted studies on the use of PUFA supplements in the treatment of epilepsy refractory to standard treatment, but the results have been inconsistent. Although some studies have suggested a significant reduction in seizure frequency in people taking omega-3 fatty acids [36], these results have not been confirmed by other research teams [37].

Although high doses of eicosapentaenoic acid and docosahexaenoic acid appear to be relatively safe, omega-3 PUFA compounds may at the same time reduce the tendency for platelet aggregation, which could theoretically lead to a risk of bleeding [38].

The beneficial effects of omega-3 fatty acids (n-3 PUFAs) in the treatment of epilepsy are due to their anti-stimulant and neuroprotective properties [39]. Studies in the 1980s and 1990s that showed PUFA n-3 to be effective in controlling arrhythmias prompted the hypothesis that they may also contribute to reducing seizure activity [40]. Experiments in animal models have confirmed that PUFA n-3 reduce the electrical activity of neurons, inhibit the repetitive stimulatory activity of these cells and affect the regulation of the spread of epileptic seizures [41].

The inhibitory effects of polyunsaturated fatty acids are thought to be related to partial blocking of ion channels in cell membranes, resulting in a reduced influx of positive ions, such as sodium and calcium, into the cell [39]. There is evidence supporting the hypothesis that elevated levels of omega-3 fatty acids may influence the anticonvulsant effects of a ketogenic diet [41]. The concept of this diet stems from historical observations that indicated that epileptic seizures subsided during fasting. This phenomenon was attributed to ketosis, prompting the development of a high-fat, low-carbohydrate diet, usually in a 4:1 ratio, to achieve a similar one. Although the exact mechanisms of action are not yet fully understood, the increased production of ketone bodies and changes in energy metabolism induced by this diet may have potential neuroprotective effects [42].

Omega-3 fatty acids reduce the production of reactive oxygen species, which are bio-products of energy metabolism. These substances can induce oxidative damage to membrane phospholipids, contributing to the inflammation and neurodegeneration process observed in epilepsy patients [41]. In addition, they inhibit the synthesis of cyclooxygenase-2 (COX-2), an enzyme involved in the production of pro-inflammatory substances [43].

CONCLUSIONS

Available scientific evidence suggests that supplementation or increased intake of fats from marine fish significantly improves brain function, and plays an important role in prenatal and early childhood brain development. The results also show the significant potential of polyunsaturated fatty acids as a natural

therapeutic agent in the treatment of epilepsy, Alzheimer's disease and other diseases that cause progressive dementia. It should be noted, however, that additional research is needed, with the main goal of determining the optimal dosage and confirming the safety profile of omega-3 fatty acids in the long term.

REFERENCES

1. Cholewski M, Tomczykowa M, Tomczyk M. A Comprehensive Review of Chemistry, Sources and Bioavailability of Omega-3 Fatty Acids. Nutrients. 2018 Nov 4;10(11):1662. doi: 10.3390/nu10111662. DOI
2. Cao D, Xue R, Xu J, Liu Z. Effects of docosahexaenoic acid on the survival and neurite outgrowth of rat cortical neurons in primary cultures. J Nutr Biochem. 2005 Sep;16(9):538-46. doi: 10.1016/j.jnutbio.2005.02.002. DOI
3. Cao D, Xue R, Xu J, Liu Z. Effects of docosahexaenoic acid on the survival and neurite outgrowth of rat cortical neurons in primary cultures. J Nutr Biochem. 2005 Sep;16(9):538-46. doi: 10.1016/j.jnutbio.2005.02.002. DOI
4. Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Extrauterine fatty acid accretion in infant brain: implications for fatty acid requirements. Early Hum Dev. 1980 Jun;4(2):131-8. doi: 10.1016/0378-3782(80)90016-x. DOI
5. Innis SM. Dietary omega 3 fatty acids and the developing brain. Brain Res. 2008 Oct 27;1237:35-43. doi: 10.1016/j.brainres.2008.08.078. DOI
6. Innis SM. Essential fatty acid transfer and fetal development. Placenta. 2005 Apr;26 Suppl A:S70-5. doi: 10.1016/j.placenta.2005.01.005. DOI
7. Ostadrahimi A, Salehi-Pourmehr H, Mohammad-Alizadeh-Charandabi S, Heidarabady S, Farshbaf-Khalili A. The effect of perinatal fish oil supplementation on neurodevelopment and growth of infants: a randomized controlled trial. Eur J Nutr. 2018 Oct;57(7):2387-2397. doi: 10.1007/s00394-017-1512-1. Epub 2017 Jul 27. DOI
8. Ogundipe E, Tusor N, Wang Y, Johnson MR, Edwards AD, Crawford MA. Randomized controlled trial of brain specific fatty acid supplementation in pregnant women increases brain volumes on MRI scans of their newborn infants. Prostaglandins Leukot Essent Fatty Acids. 2018 Nov;138:6-13. doi: 10.1016/j.plefa.2018.09.001. DOI
9. Martins BP, Bandarra NM, Figueiredo-Braga M. The role of marine omega-3 in human neurodevelopment, including Autism Spectrum Disorders and Attention-Deficit/Hyperactivity Disorder – a review. Crit Rev Food Sci Nutr. 2020;60(9):1431-1446. doi: 10.1080/10408398.2019.1573800. DOI
10. Belfort MB, Rifas-Shiman SL, Kleinman KP, et al. Infant feeding and childhood cognition at ages 3 and 7 years: Effects of breastfeeding duration and exclusivity. JAMA Pediatr. 2013 Sep;167(9):836-44. doi: 10.1001/jamapediatrics.2013.455. DOI
11. Oddy WH, Kendall GE, Li J, et al. The long-term effects of breastfeeding on child and adolescent mental health: a pregnancy cohort study followed for 14 years. J Pediatr. 2010 Apr;156(4):568-74. doi: 10.1016/j.jpeds.2009.10.020. DOI
12. Gibson RA, Neumann MA, Makrides M. Effect of increasing breast milk docosahexaenoic acid on plasma and erythrocyte phospholipid fatty acids and neural indices of exclusively breast fed infants. Eur J Clin Nutr. 1997 Sep;51(9):578-84. doi: 10.1038/sj.ejcn.1600446. DOI
13. Jensen CL, Voigt RG, Prager TC, et al. Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. Am J Clin Nutr. 2005 Jul;82(1):125-32. doi: 10.1093/ajcn.82.1.125. DOI
14. Helland IB, Smith L, Blomén B, Saarem K, Saugstad OD, Drevon CA. Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. Pediatrics. 2008 Aug;122(2):e472-9. doi: 10.1542/peds.2007-2762. DOI
15. Blinkouskaya Y, Caçoilo A, Gollamudi T, Jalalian S, Weickenmeier J. Brain aging mechanisms with mechanical manifestations. Mech Ageing Dev. 2021 Dec;200:111575. doi: 10.1016/j.mad.2021.111575. DOI
16. Ambrogini P, Lattanzi D, Ciuffoli S, Betti M, Fanelli M, Cuppini R. Physical exercise and environment exploration affect synaptogenesis in adult-generated neurons in the rat dentate gyrus: possible role of BDNF. Brain Res. 2013 Oct 9;1534:1-12. doi: 10.1016/j.brainres.2013.08.023. DOI
17. Denis I, Potier B, Vancassel S, Heberden C, Lavialle M. Omega-3 fatty acids and brain resistance to ageing and stress: body of evidence and possible mechanisms. Ageing Res Rev. 2013 Mar;12(2):579-94. doi: 10.1016/j.arr.2013.01.007. DOI
18. Dyall SC, Michael GJ, Michael-Titus AT. Omega-3 fatty acids reverse age-related decreases in nuclear receptors and increase neurogenesis in old rats. J Neurosci Res. 2010 Aug 1;88(10):2091-102. doi: 10.1002/jnr.22390. DOI
19. Orr SK, Trépanier MO, Bazinet RP. n-3 Polyunsaturated fatty acids in animal models with neuroinflammation. Prostaglandins Leukot Essent Fatty Acids. 2013 Jan;88(1):97-103. doi: 10.1016/j.plefa.2012.05.008. DOI
20. Lynch AM, Loane DJ, Minogue AM, et al. Eicosapentaenoic acid confers neuroprotection in the amyloid-beta challenged aged hippocampus. Neurobiol Aging. 2007 Jun;28(6):845-55. doi: 10.1016/j.neurobiolaging.2006.04.006. DOI
21. Gómez-Pinilla F. Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci. 2008 Jul;9(7):568-78. doi: 10.1038/nrn2421. DOI

22. Agrawal R, Gomez-Pinilla F. 'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition. J Physiol. 2012 May 15;590(10):2485-99. doi: 10.1113/jphysiol.2012.230078. DOI
23. Gamoh S, Hashimoto M, Hossain S, Masumura S. Chronic administration of docosahexaenoic acid improves the performance of radial arm maze task in aged rats. Clin Exp Pharmacol Physiol. 2001 Apr;28(4):266-70. doi: 10.1046/j.1440-1681.2001.03437.x. DOI
24. Lee LK, Shahar S, Rajab N, Yusoff NA, Jamal RA, Then SM. The role of long chain omega-3 polyunsaturated fatty acids in reducing lipid peroxidation among elderly patients with mild cognitive impairment: a case-control study. J Nutr Biochem. 2013 May;24(5):803-8. doi: 10.1016/j.jnutbio.2012.04.014. DOI
25. Chen C, Xun P, Kaufman JD, et al. Erythrocyte omega-3 index, ambient fine particle exposure, and brain aging. Neurology. 2020 Aug 25;95(8):e995-e1007. doi: 10.1212/WNL.0000000000010074. DOI
26. Chiu CC, Su KP, Cheng TC, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Aug 1;32(6):1538-44. doi: 10.1016/j.pnpbp.2008.05.015. DOI
27. Grimm MO, Haupenthal VJ, Rothhaar TL, et al. Effect of Different Phospholipids on α-Secretase Activity in the Non-Amyloidogenic Pathway of Alzheimer's Disease. Int J Mol Sci. 2013 Mar 13;14(3):5879-98. doi: 10.3390/ijms14035879. DOI
28. Nalivaeva NN, Turner AJ. Targeting amyloid clearance in Alzheimer's disease as a therapeutic strategy. Br J Pharmacol. 2019 Sep;176(18):3447-3463. doi: 10.1111/bph.14593. DOI
29. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010 Apr;51(4):676-85. doi: 10.1111/j.1528-1167.2010.02522.x. DOI
30. Nalivaeva NN, Turner AJ. Targeting amyloid clearance in Alzheimer's disease as a therapeutic strategy. Br J Pharmacol. 2019 Sep;176(18):3447-3463. doi: 10.1111/bph.14593. DOI
31. Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol. 2003 Apr;16(2):165-70. doi: 10.1097/01.wco.0000063766.15877.8e. DOI
32. Cardenas-Rodriguez N, Huerta-Gertrudis B, Rivera-Espinosa L, et al. Role of oxidative stress in refractory epilepsy: evidence in patients and experimental models. Int J Mol Sci. 2013 Jan 14;14(1):1455-76. doi: 10.3390/ijms14011455. DOI
33. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77. doi: 10.1111/j.1528-1167.2009.02397.x. Erratum in: Epilepsia. 2010 Sep;51(9):1922.
34. Cardenas-Rodriguez N, Huerta-Gertrudis B, Rivera-Espinosa L, et al. Role of oxidative stress in refractory epilepsy: evidence in patients and experimental models. Int J Mol Sci. 2013 Jan 14;14(1):1455-76. doi: 10.3390/ijms14011455. DOI
35. Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. Nat Rev Neurol. 2009 Sep;5(9):492-504. doi: 10.1038/nrneurol.2009.118. DOI
36. Yuen AW, Sander JW, Fluegel D, Patsalos PN, Bell GS, Johnson T, Koepp MJ. Omega-3 fatty acid supplementation in patients with chronic epilepsy: a randomized trial. Epilepsy Behav. 2005 Sep;7(2):253-8. doi: 10.1016/j.yebeh.2005.04.014. DOI
37. Bromfield E, Dworetzky B, Hurwitz S, Eluri Z, Lane L, Replansky S, Mostofsky D. A randomized trial of polyunsaturated fatty acids for refractory epilepsy. Epilepsy Behav. 2008 Jan;12(1):187-90. doi: 10.1016/j.yebeh.2007.09.011 DOI
38. Phang M, Lincz LF, Garg ML. Eicosapentaenoic and docosahexaenoic acid supplementations reduce platelet aggregation and hemostatic markers differentially in men and women. J Nutr. 2013 Apr;143(4):457-63. doi: 10.3945/jn.112.171249. DOI
39. Taha AY, Burnham WM, Auvin S. Polyunsaturated fatty acids and epilepsy. Epilepsia. 2010 Aug;51(8):1348-58. doi: 10.1111/j.1528-1167.2010.02654.x. DOI
40. Schlanger S, Shinitzky M, Yam D. Diet enriched with omega-3 fatty acids alleviates convulsion symptoms in epilepsy patients. Epilepsia. 2002 Jan;43(1):103-4. doi: 10.1046/j.1528-1157.2002.13601.x. DOI
41. Freeman J, Veggiotti P, Lanzi G, Tagliabue A, Perucca E; Institute of Neurology IRCCS C. Mondino Foundation. The ketogenic diet: from molecular mechanisms to clinical effects. Epilepsy Res. 2006 Feb;68(2):145-80. doi: 10.1016/j.eplepsyres.2005.10.003. DOI
42. Levy RG, Cooper PN, Giri P. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev. 2012 Mar 14;(3):CD001903. doi: 10.1002/14651858.CD001903.pub2. Update in: Cochrane Database Syst Rev. 2016;2:CD001903.
43. Dahlin M, Hjelte L, Nilsson S, Amark P. Plasma phospholipid fatty acids are influenced by a ketogenic diet enriched with n-3 fatty acids in children with epilepsy. Epilepsy Res. 2007 Feb;73(2):199-207. doi: 10.1016/j.eplepsyres.2006.10.005. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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