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The role of fatty acids in attention deficit hyperactivity disorder

Dikkat Eksikliği ve Hiperaktivite Bozukluğunda Yağ Asitlerinin Rolü

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset disorder that affects 5% to 12% of children worldwide. Etiological factors, including nutrition, contribute to this disease, which is characterized by inattention, impulsivity and hyperactivity symptoms. Fats, which form an important part of the daily diet, can have effects on ADHD and its symptoms. In the literature, it is stated that omega-3 fatty acids are low in children with ADHD, and supplementation studies may be effective in improving symptoms. In addition, high omega-6/omega-3 fatty acids ratio in the diet and diets rich in saturated and trans fatty acids are associated with ADHD. In this review, the relationship between ADHD and dietary fatty acids was evaluated.

Keywords: ADHD, saturated fatty acids, trans-fatty acids, omega-3 fatty acids, omega-6/omega-3 ratio

ÖZ

Dikkat eksikliği hiperaktivite bozukluğu (DEHB), çocukluk çağında başlayan ve dünya çapındaki çocukların %5 ile %12'sini etkileyen bir hastalıktır. Dikkatsizlik, dürtüsellik ve hiperaktivite semptomları bozukluklarıyla seyreden DEHB'de beslenmenin de içerisinde bulunduğu etiyolojik faktörler yer almaktadır. Günlük diyetin önemli bir parçasını oluşturan yağlar, DEHB ve semptomları üzerine etkileri olabilmektedir. Literatürde DEHB tanılı çocuklarda omega-3 yağ asitlerinin düşük olduğu ve takviye araştırmalarının semptomları iyileştirmede etkili olabileceği belirtilmektedir. Ayrıca diyetteki yüksek omega-6/omega-3 yağ asitleri oranı ile doymuş ve trans yağ asitlerinden zengin beslenme düzenleri DEHB ile ilişkilendirilmektedir. Bu derlemede DEHB ile diyetle alınan yağ asitleri arasındaki ilişki değerlendirilecektir.

Anahtar kelimeler: DEHB, doymuş yağ asitleri, trans yağ asitleri, omega-3 yağ asitleri, omega-6/omega-3 oranı

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children. It affects between 5% and 12% of all children globally and is a syndrome characterized by inattention, lack of focus, restless overactivity, impulsivity and deficiencies in executive functions [1]. ADHD is an illness with a complex etiology, influenced by genetic and environmental components. Genetic predisposition has an essential place in the etiology of ADHD and pathogenic processes for gene expression are linked to a variety of environmental factors, including physical, chemical, dietary, familial and social impacts [1]. ADHD is thought to be a multifactorial disorder, but its pathophysiology has not yet been fully demonstrated [2].

Fatty acids, one of the nutritional factors, play an essential role in maintaining the normal function of the brain and nervous system. The nervous system is the second organ with lipid concentration after adipose tissue: nearly 35% consists of long-chain polyunsaturated fatty acids (LC-PUFAs) [3]. Humans cannot produce linoleic acid, an omega-6 fatty acid, nor alpha-linolenic acid which is an omega-3 fatty acid,and must consume both with nutrition. Linoleic acid and alpha linolenic acid undergo desaturation and elongation by several enzymes; LC-PUFAs are then formed, which are involved in neurodevelopmental processes [4]. Studies have shown that LC-PUFA, Eicosapentaenoic (EPA, n-3) and docosahexaenoic acids (DHA, n-3), may play a role in ADHD. Insufficient omega-3 fatty acid consumption can disrupt serotonin pathway function and impact impulse control, sensory gating and behaviour, resulting in ADHD [5]. Trans fatty acids, in addition to inadequate dietary omega-3 fatty acid intake, can disrupt the body's omega-3 balance [6]. Aside from fatty acid types, the link between a high-fat diet and ADHD has also been investigated: evidence from animal experiments reports that high-fat and saturated-fat diet models may increase to the risk of ADHD through neuroinflammation [7,8].

According to other studies, children with ADHD have atypical fatty acid profiles and these changes may be linked to symptoms [9,10]. In addition, there are cohort studies showing that maternal fatty acid consumption during pregnancy may also have an effect on children's behavior. [11–13]. For this reason, studies on fatty acid supplementation in both pregnancy and childhood continue to be the subject of current study in the literature.

In this review, the properties of dietary fatty acids, the effects of fatty acid intake during pregnancy on children's behavior, the status of fatty acids in children with ADHD and the end points of supplementation studies in the literature, was evaluated.

This research was a literature review of peer-reviewed journal articles that study long-chain fatty acids, saturated fatty acids and trans fatty acids' role in ADHD. The journal articles were found using the following search engines: Google Scholar, National Library of Medicine (Pubmed.gov). Most of the searches were narrowed only to include studies from the past ten years, 2012-2022. The following search keywords were used for relevant articles: “ADHD and fatty acids” and “ADHD and diet.” "Maternal nutrition and ADHD", "ADHD fatty acids RCT", "DHA and ADHD", "EPA and ADHD", "trans fatty acids and ADHD". Articles were also found by reviewing the references of previous literature reviews.

2. Dietary fatty acids

The most important class of dietary fats is triglycerides. The triglycerides' properties are determined by the double bonds, the number and location of the double bonds and their cis-trans forms [14].

Saturated fatty acids (SFA): Fatty acids without double bonds in their side chains. Dairy products, meat, coconut and palm oil are foods rich in SFAs [14] (Figure 1).

Monounsaturated fatty acids (MUFA): Fatty acids with one double bond in their side chains. Olive oil is one of the foods rich in MUFAs [14] (Figure 1).

Polyunsaturated fatty acids (PUFAs): Fatty acids with more than one double bond in their side chains [14]. This fatty acid is referred to as a long-chain acids polyunsaturated fatty acid (LC PUFA) if it is made up of more than 20 carbon atoms. Omega-3 (n-3) and omega-6 are the most common forms

of PUFA (n-6). These include alpha-linolenic acid (ALA: n-3) and linoleic acid (LA: n-6), which are essential nutrients to humans and thus must be obtained via nutrition. Humans are capable of synthesizing arachidonic acid (AA: LC-n-6 fatty acids) from LA and eicosapentaenoic (EPA: long-chain n-3 fatty acids) and docosahexaenoic acid (DHA: long-chain n-3 fatty acids) from AL. Fish and flaxseed oil are rich in n-3 fatty acids, and sunflower, corn and soybean oil are rich in n-6 fatty acids [14] (Figure 1).

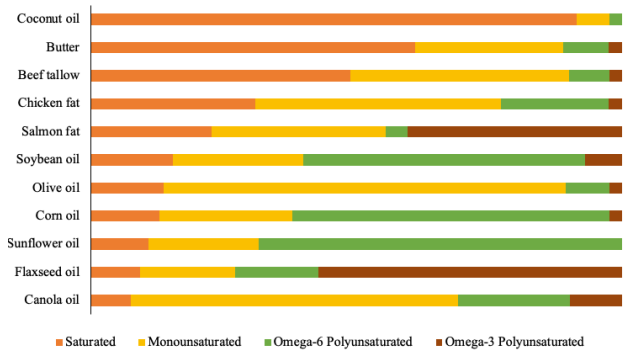

Figure 1: Composition of dietary fats [14]

Trans fatty acids (TFA): Chemically, these are classified as an unsaturated fatty acid but show a saturated fatty acid role in the human metabolism. Trans fatty acids are found in animal fats, milk and dairy products, and vegetable oils saturated with hydrogenation [6]. In vegetable oils, conversion to trans bonds is used to boost oil stability [15].

Dietary cholesterol: It is exclusively found in food of animal origin, such as meat and dairy products [14].

Plant sterols/ Phytosterols: Phytosterols are naturally occurring chemicals found in vegetable oils and nuts [16]. It is commercially added to margarine, mayonnaise, yogurt, cheese and some sauces [17,18].

Dietary fats are macronutrients, one of the main components (35 to 40%) of daily energy [19]. Fatty acids differ according to dietary patterns: while the Mediterranean diet, which is shown as the healthiest diet [20], is rich in PUFAs, SFAs are consumed in excess in the Western diet, which is associated with the increased disease [21] (Figure 2) [14]. Studies investigating the dietary patterns of patients with ADHD show that the Western diet is more readily espoused whereas compliance with the Mediterranean diet is low [22,23]. It has also been reported that the mother's diet contributes to the child's ADHD symptoms [24,25].

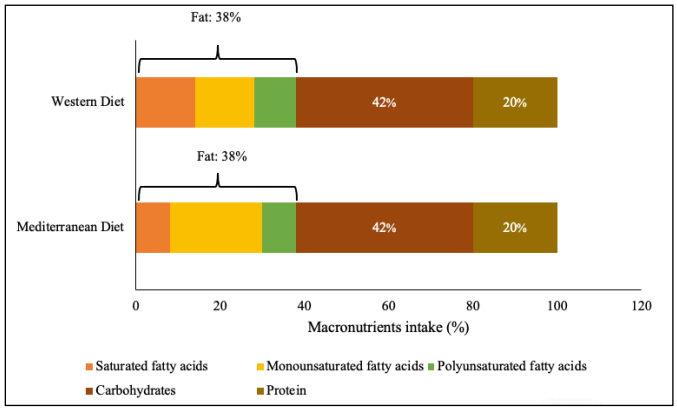

Figure 2: Contribution of fatty acid intake to total energy intake in Mediterranean and Western diets [14]

3. The function of fatty acids in ADHD

Omega-3 and omega-6 fatty acids are abundant in the central nervous system. DHA regulates the synthesis, release and transport of neurotransmitters and plays an important function in neuron development, membrane permeability, endothelial activity, neuronal survival and neurodegeneration prevention [9]. The function of the serotonin receptor, a neurotransmitter, depends on cell fluidity. DHA regulates the serotonin receptor by increasing cell fluidity. EPA and DHA levels regulate serotonin synthesis, storage, release and receptor function during neurodevelopment in the maternal period [26]. The decrease in brain serotonin levels can lead to disorders in social behaviours, such as learning and memory disorders and impulsive behaviours. Therefore, low serotonin levels are one of the underlying mechanisms of ADHD [24]. It has been shown in animal experiments that deprivation of omega-3 fatty acids causes behavioural abnormalities, but behavior returns to normal when DHA supplementation is administered [27].

The brain signalling system is mediated by highly unsaturated fatty acids (HUFAs) along with dopaminergic and serotonergic pathways [28]. N-6 fatty acids are required in the structure of the membrane and the synthesis of eicosanoids [14]. Eicosanoids involve several physiological processes in the brain with the inclusion of

synaptic plasticity, release of neurotransmitters, temporal summation, membrane excitability and apoptosis [29].

Nowadays, the intake of n-3 fatty acids in diets has declined and in western diets, the n-6/n-3 ratios have risen from 1:1 in conventional diets, to around 16:1 [30]. This changed rate can lead to inflammation, vasoconstriction and thrombosis [9]. A low n-6/n-3 ratio is desirable because it reduces the risk of a high prevalence of chronic diseases [30]. Furthermore, a high n-6/n-3 ratio can affect the activity of neurons by limiting the supply of LC n-3 in the brain [31].

4. Maternal diet and ADHD

The placenta delivers long-chain fatty acids to the fetus, and breast milk delivers them to the newborn [32]. According to the examined studies, decreased DHA levels in newborns can lead to mental and behavioural dysfunction, such as poor reading ability, low memory performance, opposing behaviours and emotional disturbances [32]. Hibbel et al. conducted observational cohort research on the seafood intake of 11.875 pregnant women. In the regression analysis, it was seen that the risk of low verbal intelligence scores was approximately 1.5 times higher in the children of those who consumed below 340 grams of seafood each week. They were also shown to be at risk in terms of social behavior, fine motor abilities, communication and social development [11]. DHA, a fatty acid present in seafood, helps to sustain the structure and function of the growing brain. DHA deficiency can impair attention by affecting monoaminergic systems [33]. An Italian cohort study investigated the effect of mothers' seafood consumption during early pregnancy on their children. High seafood consumption has been linked to greater child attentiveness: analyses were made when children reached 8 years of age and were examined independently of seafood consumption and cognitive functions [12]. In another randomized controlled experiment including 1 094 pregnant women, DHA supplementation was administered. Children were assessed when they were 5 years old and improved attention scores were observed in those given the supplement over the placebo [13].

5. Fatty acids status of patients with ADHD

Wang et al., in their study on 216 ADHD and 216 controls, found that serum SFA and n-6/n-3 ratio were higher and MUFA were lower than the control [34]. A cross-sectional study by Montgomery et al., related low DHA levels to decreased reading and memory performance, increased opposing behaviours and emotional disturbances [35]. Parletta et al. showed that children with autism and ADHD have low degrees of EPA, DHA and AA in the blood, and a high n-6/n-3 fatty acids ratio, and these values are associated with ADHD symptoms [9]. However, while omega-3 supplementation trials for ADHD have been successful in the literature, no effect has been observed for autism [36]. Similar to Parletta et al. study, in the Italian sample, it was found that children with ADHD had low DHA levels, n-3 index, and MUFA, and these findings were associated with behaviours but not with cognition [10]. Hawkey et al. published a meta-analysis including 9 studies evaluating blood fatty acid levels in patients with ADHD [37]. In these cross-sectional studies, the levels of fatty acids analyzed from plasma or erythrocyte and dietary intake of fatty acids were evaluated. According to the meta-analysis results, fatty acid levels were found to be low in ADHD patients.

On another viewpoint, there are studies evaluating the effect of excessive consumption of saturated and trans fatty acids on ADHD. The principal part of the Western diet is SFAs, and the Western diet is linked with ADHD and its symptoms [7,8]. Evidence from experimental animal studies reports that a maternal high-fat diet has structural and functional effects on offspring brain development. A high-fat diet may lead to increased proliferation in the hypothalamus, decreased apoptosis in brain regions and neural differentiation. It can also cause neuroinflammation in the serotonergic nervous system, which increases the probability of behavioural problems like ADHD [38].

The omega-3 level in the body can also be regulated by the intake of trans fatty acids [6]. Trans fats are known to raise the risk of cardiovascular disease [39]. In addition, studies are showing that it can affect brain functions [40]. Trans fatty acids may have an impact on ADHD by lowering DHA levels or by inhibiting the conversion of linolenic acid

to DHA [41,42]. Studies in experimental animals have shown that trans fatty acid reduces DHA levels in plasma, liver and brain [43,44]. Few studies, however, have examined the effect of trans fatty acid intake in patients with ADHD. Kim et al. showed that female adolescents with ADHD consumed more dietary trans fatty acids than controls [45]. Similarly, Colter et al. found that people with ADHD consumed more trans-fatty acids than healthy controls [46]. In a study in which fatty acids from erythrocytes of children with ADHD were examined, it was observed that there was a high level of trans fatty acids, and a lower level of DHA compared to the control group. Furthermore, trans fatty acids have been linked to ADHD symptoms. This study had some limitations, as it has was not examined whether dietary fatty acid intake affects blood levels. Children with ADHD who receive treatment are not excluded, so treatment improves the disease and this may be reflected in their fatty acid levels [47].

6. PUFA's supplementation effect on ADHD

Because of PUFAs on the brain and nervous system, n-3/6 supplementation studies in the treatment of ADHD have been the area of research. Children with ADHD received EPA and DHA for seventeen weeks in a randomized controlled trial. In children with learning difficulties that may progress with ADHD, with the increase in DHA level, progress in reading and spelling, a decrease in oppositional behavior, hyperactivity and anxiety symptoms have occurred [48]. Similarly, Gustafsson et al. showed improvement in behavior and oppositional symptoms in a randomized, placebo-controlled study with ADHD who were given EPA supplements for fifteen weeks [49]. A randomized, placebo-controlled supplement of n-3 fatty acids containing EPA and DHA was administered to children with ADHD in a study by Widenhorn-Müller et al. for sixteen weeks. The memory function of children with ADHD has improved, but no impact on other mental measures [50].

However, in another randomized, placebo-controlled study carried out by Matsudaira et al., adolescents with ADHD were given LC-PUFA supplements for twelve weeks, and it was observed that the treated group did not have any superiority over the placebo [27]. In this study, a power analysis was not performed while determining the number of participants and for this reason, the expected effect may not have been observed. Methylphenidate is a drug that is frequently used in the treatment of ADHD [1]. In a double-blinded randomized controlled study of 40 children, the administration of methylphenidate in combination with PUFA supplements resulted in a further reduction in the severity of symptoms than placebo [51].

Chang et al. revealed in a comprehensive review and meta-analysis that supplementation might enhance clinical symptoms and cognitive function in ADHD individuals with low n-3 fatty acid levels [52]. However, it is controversial whether n-3 supplements should be used in children with normal blood levels [7]. Studies must be methodologically consistent for n-3 supplements to be recommended in the treatment of ADHD. For this, accurate ADHD diagnosis criteria, measuring fatty acid levels of patients before supplementing, a double-blind controlled design, consistency of symptom scales and nonpharmacological intervention studies are required [28].

Limitations: There is a limitation in this review. There are studies in the literature in which teacher scales are lacking in assessments for ADHD symptoms. This prevents establishing an exact symptomatic connection. Therefore, a complete relationship could not be established.

Conclusion: Children with ADHD have low levels of n-3 fatty acids, and when children with low n-3 fatty acid levels took the n-3 supplement, improvements in clinical symptoms were seen. Moreover, dietary patterns with a high n-6/n-3 ratio, rich in saturated and trans-fatty acids, may worsen ADHD symptoms. However, long-term randomized controlled double-blind studies are needed to demonstrate the effect of supplementation. In addition, it is not clear how fatty acids affect ADHD.

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