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Attention Deficit Hyperactivity Disorder and Omega-3 Fatty Acid Supplementation: A Systematic Review

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ABSTRACT

Objective: Attention deficit hyperactivity disorder (ADHD) is a chronic multifactorial disorder mainly affecting school-aged children and resulting in inattention, hyperactivity and impulsivity symptoms. While exact underlying cause remains unknown, observations regarding the low plasma levels of omega-3 fatty acids in ADHD patients leads to a new treatment approach, omega-3 fatty acid supplementation.

Method: Literature search is performed about the relation between omega-3 fatty acid supplementation and ADHD treatment by using 3 databases. Nineteen studies met the inclusion criteria and further analyzed.

Results: Studies performed with higher number of participants and for longer trial period demonstrate beneficial effects of omega-3 fatty acids in ADHD treatment while no significant additional adverse effects are recorded compared to regular treatment options.

Discussion: Omega-3 fatty acid supplementation approach in ADHD treatment is one of the highly investigated issues while there is a lack of comprehensive literature review regarding that issue. In this literature review, we conclude beneficial effects of omega-3 fatty acids in ADHD treatment while it is important to emphasize the need for additional and more comprehensive clinical trials about this issue.

Key words: Fatty acids, omega-3, attention deficit disorder with hyperactivity, methylphenidate

ÖZ

Dikkat Eksikliği Hiperaktivite Bozukluğu ve Omega-3 Yağ Asidi Takviyesi: Sistematik Bir Derleme

Amaç: Dikkat eksikliği hiperaktivite bozukluğu başlıca okul çapındaki çocukları etkileyerek dikkat eksikliği, hiperaktivite ve dürtüselliğe yol açan kronik ve çok etkenli bir hastalıktır. Asıl nedeni bilinmemekle birlikte dikkat eksikliği hiperaktivite bozukluğu hastalarında gözlemlenen düşük plasma omega-3 yağ asidi seviyeleri omega-3 yağ asidi takviyesini şeklinde yeni bir tedavi yaklaşımını ortaya çıkarmıştır.

Yöntem: Omega-3 yağ asidi takviyesi ve dikkat eksikliği hiperaktivite bozukluğu tedavisi arasındaki ilişkiyi incelediğimiz literatür taraması 3 farklı veritabanı kullanılarak yapılmıştır. Dahil edilme kriterlerini karşılayan on dokuz çalışma detaylıca incelenmiştir.

Bulgular: Daha fazla katılımcıyla ve daha uzun süreli yapılan çalışmalar omega-3 yağ asidi takviyesinin dikkat eksikliği hiperaktivite bozukluğunun tedavisinde yararlı etkilerini ortaya koymuştur. Aynı zamanda güncel tedavi yöntemlerine kıyasla daha ciddi yan etkiler gözlemlenmemiştir.

Tartışma: Dikkat eksikliği hiperaktivite bozukluğunun omega-3 yağ asidi takviyesiyle tedavisi yaklaşımı sıklıkla incelenen bir konu olmasına ragmen konuya ilişkin kapsamlı bir literatur taramasının eksikliği görülmüştür. Bu literatür taramasında, ek ve daha kapsamlı klinik araştırmalara ihtiyaç duyulduğunu vurgulamakla beraber omega-3 yağ asidi takviyesinin dikkat eksikliği hiperaktivite bozukluğu tedavisinde faydalı olduğu sonucuna ulaşmış bulunmaktayız.

Anahtar sözcükler: Yağ asidi, omega-3, dikkat eksikliği hiperaktivite bozukluğu, metilfenidat.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a chronic condition characterized by hyperactivity, inattention and commonly impulsivity[1,2] Even though exact underlying cause of ADHD remains unknown, there are strong evidences that suggest both genetics and environmental factors such as complications or smoking during pregnancy are involved.[1,2] 11% of the school aged population and 4.4% of the adult population of United States are diagnosed with ADHD which is traditionally treated with 5 main types of drugs: Methylphenidate, dexamphetamine, lisdexamfetamine, atomoxetine, and guanfacine.[1-3] Methylphenidate is the most commonly used medication in the treatment of ADHD and licensed for use in children and teenagers.[3,4] However, methylphenidate utilization is associated with severe adverse effects including elevated blood pressure and heart rate, headache, mood swings, loss of appetite and sleep disorders.[3,4] Dexamphetamine is licensed for use in children over the age of 3 and not for adults.[4] Usage of dexamphetamine is related to similar side effects with methylphenidate.[3,4] Atomoxetine functions as selective noradrenaline (NE) reuptake inhibitor in order to increase its' concentration in CNS that enhances and prolongs action of NE as neurotransmitter.[5] Children over the age of six and adults are eligible to use atomoxetine, nevertheless, it is associated with nausea, dizziness, headache, sleep disorders and stomach ache.[5] In general, other two medications are relatively less commonly preferred options for ADHD treatment and have similar side effects.[1-3] In addition to drug treatment options for the management of ADHD diet, therapy and nutritional supplement options are available, though, no consensus has been reached about the efficiency of these options.[1,2]

One of the highly dwelled on nutritional supplementation approach for the treatment of ADHD is omega-3 fatty acids.[6] Omega-3-fatty acids, comprise of alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), are polyunsaturated fatty acids particularly found in soybean, fish, canola oil and walnuts.[6] In human body omega-3-fatty acids are highly concentrated in brain and though to be significant in several physiological events such as inflow and outflow of calcium ions in cells, muscle contraction, blood clotting, prevention of inflammation and retardation of some tumor types.[6] The basis of omega-3 fatty acid supplementation approach is the studies demonstrating lower levels of omega-3 fatty acids in the plasma of ADHD patients compared to non-ADHD individuals.[7,8] A study conducted with 29 ADHD patients and 43 non-ADHD individuals illustrates negative correlation between plasma omega-3 fatty acid levels and various indicators of ADHD including anti-social and unemotional traits.[7] In addition, a meta-analysis reveals that ADHD patients composed of children and youth have higher plasma omega-6/omega-3 fatty acid levels in correlation with higher arachidonic acid/eicosapentaenoic acid levels compared to controls.[8] Also, there are few studies indicating the beneficial effects of omega-3 supplementation in prisoners to diminish aggressiveness.[9] Furthermore, a study performed on rats shows hyperactivity symptoms are associated with perinatal omega-3 fatty acid deficiency and improvement in hyperactivity symptoms after the implementation of omega-3 fatty acid supplementation.[10]

Besides the studies aiming to test the efficiency of omega-3 fatty acid supplementation in the treatment of ADHD, there are other studies testing possible benefits and side-effects of omega-3 supplementation.[6,11] It has been reported that omega-3 fatty acids are beneficial for bone strength by elevating calcium levels, lower blood pressure, protection against cardiovascular diseases including atherosclerosis, and relief of asthma symptoms.[6,11] On the other hand, adverse effects of omega-3 supplementation include higher risk of bleeding (increase in bleeding time) and effects related to its' interaction with other medications such as cyclosporine, diabetes drugs and blood-thinning drugs.[6,11]

MATERIALS AND METHOD

Literature Search

In order to perform literature search about the association between omega-3-fatty acids and ADHD 3 electronic databases are utilized (PubMed, Embase and the Cochrane Library). During literature search Medical Subject Headings (MHS) related to our topic of interest are used including "attention deficit hyperactivity disorder", "ADHD", "omega-3 fatty acid", "omega-3", "nutrition" and their combinations. Studies that are published in English between 2005 and January 2018 are selected. References of the selected studies are looked for additional studies that might have been overlooked during literature search. Procedure of literature search and study selection can be seen from Figure 1.

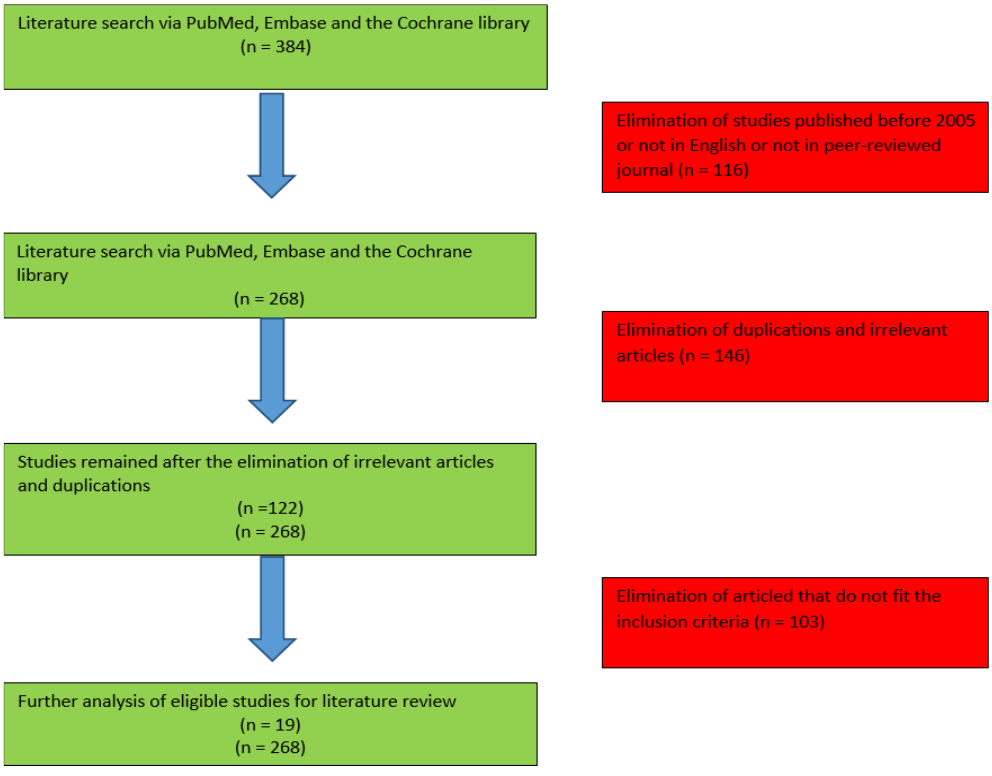

Figure 1: Study selection procedure for literature review

Study selection

Studies that are found in the literature search have been

assessed by two authors independently depending on the abstracts and key words of each study. The studies that do not fit the inclusion criteria are eliminated. Inclusion criteria for the literature review are as follows:

- Studies should be published in a peer-reviewed academic journal between 2005 and 2018 in English. Studies include randomized controlled trials, single or double-blinded studies with or without placebo controls.
- Studies should be conducted with children patients that are diagnosed with ADHD and treated with omega-3-fatty acid supplementation.

Initially, 116 studies which are not published in a peer-reviewed journals or before 2005 or not in English are excluded from the literature search. Then, 146 irrelevant articles or duplications are excluded followed by exclusion of 103 other articles which are either case reports, case series, studies conducted with patients with many co-morbidities or suffering from multiple diagnosis.

RESULTS

Nineteen studies found upon the literature search are further analyzed in terms of the efficiency and possible adverse effects of omega-3 fatty acid supplementation in ADHD patients under the age of 18 compared to either placebo or control groups that are using another medication without any omega-3 fatty acid supplementation (Table 1). Effectiveness of the treatment is assessed mainly by the change in the severity of symptoms including spelling, attention, DSM-IV hyperactivity, oppositional behavior, cognitive problems and DSM-IV inattention in patients using omega-3 supplementation compared to placebo group or patients with regular treatment (mostly methylphenidate). In terms of adverse effects blood pressure, heart rate, weight, unexpected adverse events and the Side Effect Rating Scale are assessed. In general, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and gamma-linolenic acid (GLA) are used as omega-3 fatty acid supplementation source while methylphenidate is used in control groups in some studies for the comparison of efficiency and adverse effects. It is important to note that methylphenidate treatment used commonly in case of ADHD is associated with headache, abdominal pain, sleeplessness, nervousness, growth retardation, reduced appetite, tachycardia, and changes in blood pressure.[3,4]

Even though earlier studies with short trial phase are unable to show any beneficial effects compared to methylphenidate treatment alone, analysis of most studies with longer trial phase or higher number of participants demonstrates effectiveness of omega-3 fatty acid supplementation in the treatment of ADHD without significant additional side-effects.

DISCUSSION

Attention deficit hyperactivity disorders (ADHD) is a common disease of especially childhood affecting 11% of school-aged population in the USA while etiology underlying ADHD remains mostly unknown. Methylphenidate is the most commonly preferred pharmacological intervention for ADHD while other drugs and therapeutic approaches continue to be investigated. One of such therapeutic options is the omega-3 fatty acid supplementation which is based on the studies demonstrating lower plasma levels of omega-3 fatty acids in ADHD patients compared to general population and supportive animal studies. Studies investigating the efficiency and safety of omega-3 fatty acid supplementation are few in number due to being a relatively new treatment approach. Among those limited number of studies most of the trials with longer time period and higher number of participants demonstrate beneficial effects of omega-3 fatty acid supplementation

Table 1. Assessment of studies investigating the effectiveness and safety of omega-3 supplementation in patients with ADHD

Study	Year of Study	Number of Participants	Effectiveness on ADHD	Adverse effects
Voigt et al.[12]	2001	63	Not effective.	No significant adverse effect
Hirayama et al.[13]	2004	40	Not effective.	No significant adverse effect
Johnson et al.[14]	2009	75	Effective in terms of symptoms and Global Impression scores.	No significant adverse effect
Raz et al.[15]	2009	73	Not effective.	No significant adverse effect
Gustafsson et al.[16]	2010	92	Effective in symptomatic treatment but no improvement in Conner's total score.	No significant adverse effect
Hariri et al.[17]	2012	103	Effective in terms of ASQ-P score (measure of hyperactivity).	Decrease in CRP and increase in SOD and glutathione reductase levels.
Johnson et al.[18]	2012	75	Effective	No significant adverse effect
Milte et al.[19]	2012	90	Effective (more pronounced in case of learning difficulty).	No significant adverse effect
Perera et al.[20]	2012	94	Effective	No significant adverse effect
Manor et al.[21]	2013	162	Not evaluated	Safe and well-tolerated, no significant adverse effect
Behdani et al.[22]	2013	69	Not effective	No significant adverse effect
Widenhorn et al.[23]	2014	95	Effective in terms of working memory.	No significant adverse effect
Bos et al.[24]	2015	40	Effective	No significant adverse effect
Matsudaira et al.[25]	2015	76	Not effective	No significant adverse effect
Milte et al.[26]	2015	90	Effective	No significant adverse effect
Wu et al.[27]	2015	179	Effective in terms of visual acuity	No significant adverse effect
Barragan et al.[28]	2017	90	Effective	Less compared to MPH treatment alone

when combined to regular medications, mostly methylphenidate, compared to regular medication alone. Furthermore, no significant adverse effects have been associated with this new therapeutic approach. In addition, few studies indicate possible beneficial outcomes in case of co-morbid conditions such as epilepsy.[29] Even though current evidence regarding omega-3 fatty acid supplementation in ADHD patients is supportive, it is important to note that they are not conclusive and more comprehensive studies are required.

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