

Relation between Omega 3 Fatty Acid, Iron, Zinc and Treatment of ADHD

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Article information	Abstract
<p>Article history: Received: 12 Mar 2011 Accepted: 15 Mar 2011 Available online: 26 May 2013 ZJRMS 2014 Aug; 16 (8): 1-5</p> <p>Keywords: Attention-deficit/Hyperactivity Iron Zinc Omega-3 fatty acid Unsaturated Fatty Acids (UFA)</p> <p>*Corresponding author at: Department of Nutrition Sciences, Hamedan Branch, Islamic Azad University, Hamedan, Iran. E-mail: mr_shalileh@yahoo.com</p>	<p>In some studies, it is suggested that a number of dietary factors including essential fatty acid, iron and zinc deficiency, may be linked to attention-deficit/hyperactivity-disorder (ADHD). However, the exact mechanism of this relationship is yet unclear. The purpose of this study is to investigate the relationship between omega-3 fatty acids, zinc, and iron in etiopathology and management of ADHD.</p> <p>For the purpose of this study, Science Direct, PubMed, and Medline databases were explored and thirty-four relevant articles in english language were collected.</p> <p>Eighteen out of twenty-two studies confirmed the relationship between omega-3 fatty acid and ADHD. In addition, the role of insufficient store of iron in developing ADHD symptoms and the positive effect of iron supplement in improvement of ADHD behavioral symptoms have been shown. Also, plasma zinc concentration in children with ADHD was lower than the normal population, and the effect of zinc supplement on reducing on attentive-deficit symptoms was contradictory.</p> <p>Although polyunsaturated fatty acids (PUFA) and iron supplements are not suggested as main treatment for ADHD, but if future studies confirm the positive results of that, use of these supplements as complementary treatment will affect ADHD symptoms. Considering the little amount of studies on zinc, more research is necessary.</p> <p>Copyright © 2014 Zahedan University of Medical Sciences. All rights reserved.</p>

Introduction

Developmental disorders are the forms of disabilities and abnormalities with various causes. Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorders in children and the most common chronic disorder in this age group [1]. That is, 5-10% of school-age children are affected by this disorder; although, this is not the same in different countries [2] (1% in Britain and 3-5% in the United States, according to estimations) [3]. Evidence has shown various causes for this disorder, and according to some of the studies, it is suggested that nutritional factors may have relationship with this disorder [2, 4]. However, the mechanism of this relationship is yet unclear [2], but given the relatively high prevalence of this disorder and the difficulties in treatment methods, it seems that identifying effective nutritional interventions as alternative or complementary therapy to prevent and control some of its symptoms can be an useful step to reduce the problems of ADHD patients. A number of theoretical and clinical evidence have suggested that deficiencies or imbalances in polyunsaturated fatty acids (PUFAs) may affect the developmental neurological disorder, such as ADHD [4-7], and autism spectrum disorder, which are common among children [1]. It means that disorders such as ADHD and autism are usually associated with relative deficiency of omega-3 fatty acids [8]. In that regard, the most common alternative treatment for the patients with autism spectrum disorder is using omega-3 fatty acids. It has been reported that 28.7% of children with this disorder are using omega-3 fatty acids

[9]. Studies have indicated that the human brain is the organ with the highest concentration of lipids after fat tissue [10]. Fatty acids of phospholipids are the major component of nerve cell membrane which regulates its fluidity and function [10, 11]. In addition, omega-3 and omega-6 polyunsaturated fatty acids play essential role in development, normal function of the brain and the central nervous system [8]. Furthermore, several studies have proven the involvement of polyunsaturated fatty acids in regulating many biochemical reactions, such as release, absorption, and reception of neurotransmitters, receptors function in the central nervous system, and enzymatic processes [10]. Also, since dopamine is the key factor in pathophysiology of ADHD, and iron as a tyrosine hydroxylase coenzyme has a vital role in constructing and breaking down dopamine, some studies have pointed out the role of iron in pathophysiology of ADHD [12, 13]. Another nutrient that has been considered in controlling some developmental neurological disorders is the mineral 'zinc' which its deficiency is known as one of the main causes of ADHD etiopathology [14]. That is a number of studies have pointed out the relationship between plasma zinc level and data processing [15]. Thus, regarding the importance of this subject, relatively high prevalence of ADHD, and the widespread use of these therapies, in addition to the contradictory results of the existing studies, further studies are still required. Therefore this study was done with the purpose of investigating the results of other studies on the effect of omega-3 fatty

acids, zinc, and iron in etiopathology and controlling some symptoms of ADHD.

Materials and Methods

In order to get access to the studies on the relationship between omega-3 fatty acids, iron, and zinc, and conducting a review study, searching Science Direct, Pubmed, and Medline databases was done using (ADHD, PUFA, omega-3 fatty acid), (Iron, ADHD), (Zinc, ADHD) keywords, and 34 relevant articles in English were collected, from 1997 to 2009. Of them, seven articles were in form of review study of human model, one article was in form of review study of animal model, 26 papers were in form of descriptive studies, clinical trials, and pilot studies, and one article was in form of case-study.

Instruments: Some of these studies had used a number of following variable evaluation and measurement instruments for the purpose of diagnosis ADHD and its severity: psychiatrists report and other tests such as Amen Questionnaire, Conners Parent and Teacher Rating Scale (CPRS, CTRS), Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Abbreviated Symptom Questionnaire (ASQ) for parents, Teacher's Disruptive Behavior Disorders (DBD), Clinical Global Impression (CGI) Scale, ADHD Rating Scale, Sleep Disturbance Scale for Children (SDSC), were used for diagnosis and severity of ADHD symptoms. Also, plasma phospholipid fatty acid concentration and red blood cell membrane were taken as the basis to estimate the amount of fatty acids. In order to measure iron levels, ferritin and hemoglobin indices, Mean Corpuscular Volume (MCV), Red cell Distribution Width (RDW) were used. Moreover, zinc concentration in plasma was measured to determine zinc status samples in the studied samples.

Sampling: Due to the significance of the subject, and for evaluating and identifying key point in order to design future surveys, and regarding the small number of published studies, regardless of the differences in research methods including the number of samples, method and criterion used in evaluating variables, all thirty-four collected studies were investigated.

Results

Omega-3 fatty acids and ADHD: From the total of 22 collected studies that investigated the relationship between omega-3 fatty acids and ADHD, two controlled double-blind randomized studies on 104 children, 7 to 12 years old, were conducted for 15 weeks. Significant positive effects were seen in PUFA supplementation group (PUFA: Poly Unsaturated Fatty Acids) in comparison with placebo group. After 15 weeks of crossover study the very same effect was observed [16, 17]. In another study on 57 children and adults, from 8 to 18, conducted for three months and continued for another three months in crossover fashion, 26% of participants responded to the treatment. Of them, 25% showed decrease the ADHD symptoms [18]. In another study, 41

children were randomly assigned to two groups of unsaturated fatty acid supplement and placebo for 12 weeks. The results indicated a significant difference in the supplement group compared with the placebo group based on Conners Parent Rating Scale (CPRS) [19]. In a randomized double-blind parallel study on 50 children in 4 months with PUFA supplement and olive oil placebo, increased PUFA in red blood cell and plasma phospholipids was reported. Also, in this study a significant correlation between increase in eicosapentaenoic acid (EPA) of red blood cell and ADHD symptoms reduction was observed ($p < 0.05$) [20]. The results of uncontrolled daily supplementation with high dosages of EPA and docosahexaenoic acid (DHA) (EPA/DHA 16.2 g) in 90 children with ADHD, conducted by Sorgi in 8 weeks, showed a significant increase in DHA and EPA, and plasma phospholipids. In addition, a significant improvement in behavior was observed, based on CPRS [21]. In a case-control study on 11 children with ADHD and 12 children in the control group, the intake of essential fatty acids were investigated and it was observed that receiving less amount of omega-3 fatty acids was correlated with higher score on Conners Behavioral Scale [22]. In case-control study conducted by Antalis et al. on 35 children with ADHD and 112 normal people it was observed that omega-3 fatty acids in plasma phospholipids of ADHD group and erythrocytes was significantly [23].

Saphis et al. in an investigation on dietary patterns and composition of plasma fatty acid in 58 children with ADHD and 52 children as control group, reported a number of differences in fatty acid composition of erythrocyte membranes of the two groups [24]. In comparing 37 children with ADHD and 35 normal people, lower amount of PUFA in the ADHD group was reported [24]. A review study on rat suggested that ADHD patients have less omega-3 fatty acids [11]. In another study, three-day food record of the ADHD children showed half of the omega-3 fatty acids intake reported in previous similar study ($p < 0.05$). However, there was no significant correlation between fatty acids and ADHD symptoms [25]. Additionally, another investigation showed a significant increase in red blood cell fatty acid in study group over control group after supplementation with fatty acids and significant improvement of ADHD symptoms [5]. In a case control study on 37 ADHD adults, with a control group of thirty-five subjects, it was observed that PUFA concentration in serum phospholipids and erythrocyte membranes was significantly lower in ADHD group. However, in this study, this condition was not correlated with the severity of ADHD symptoms [26]. Although, in a similar study lower concentration of essential fatty acids was reported in a group of fifty-three people with ADHD, compared with a control group with 43 subjects. In addition, it was revealed that essential fatty acids deficiency symptoms were significant in the ADHD group, compared to the control group [27]. Sinn examined the results of two studies. The first study was conducted on 347 normal people and the second one on 104 children with ADHD.

Correlation between fatty acid deficiency and ADHD symptoms was first observed in the first study, but not in the second one. After 15 weeks of supplementation with PUFA, fatty acids deficiency symptoms in the supplement group were not eliminated [28]. In a review study, the relationship between essential fatty acids and ADHD was investigated and it was reported that this relationship was still unclear. Additionally, therapeutic studies had conflicting results. However, the use of omega-3 and omega-6 fatty acids could significantly reduce ADHD symptoms [29]. In a systematic review study on using essential fatty acids in ADHD, it was claimed that children with ADHD have lower levels of essential fatty acids in their blood, and supplementation with these fatty acids will lead to increased fatty acids in blood and reduce ADHD symptoms. However, randomized controlled studies failed to confirm this relationship [30]. In another review study, Richardson argues that the results of controlled clinical studies are contradictory. He adds, despite supplementation with fish oil has reduced ADHD symptoms, at least in some children, but omega-3 is not suggested as a treatment, and further studies are enquired [6]. Sinn states that, based on the evidence, diet and nutrition affect behavior and learning of ADHD children, and the strongest effect, in this case, is related to omega-3 fatty acids [31].

Iron and ADHD: Two out of the total seven relevant studies reported a correlation between low serum ferritin levels and higher score for hyperactivity based on Conners Parent Rating Scale in 52 children. Additionally, a significant negative correlation between serum ferritin and the scores from Conners Parent Rating and Conners Teacher Rating Scales in 151 ADHD people was reported [12, 32]. In a case control study, with forty-three children in ADHD group and twenty-seven in control group, a correlation between lower average of serum ferritin and the severity of ADHD symptoms, based on Conners Parent Rating Scale, in ADHD group was observed ($p=0.001$) [33]. In a case study on a three years old child with low levels of serum ferritin (13 ng/ml), a significant improvement was seen after 8 months of treatment with 80 mg/day ferrous sulfate, based on Conners Parent Rating and Conners Teacher Rating Scale. In addition, serum ferritin level increased to 102 ng/ml [13]. Konofal conducted a double-blind investigation on 23, 5-8 year old, non-anemic ADHD children. In this study, the participants went through a twelve-week iron supplementation (80 mg/day). According to ADHD rating scale, a progressive and significant reduction was seen in iron group ($p<0.008$). However, the improvement of children was not significant based on CPRS and CTRS [34]. Cortese et al. investigated the relationship between sleep disorders and serum ferritin levels in 68 children with ADHD. They observed that those with serum ferritin levels lower than 45 $\mu\text{g/L}$ displayed significantly higher score on the Sleep Disturbance Scale for Children, in comparison with children with more than 45 $\mu\text{g/L}$ (SDSC) ($p=0.042$) [35]. In a thirty days study on fourteen boys, using 5 mg/kg/day iron supplement, a significant increase in serum ferritin level and decrease in CPRS

were observed. However, other blood parameters and CTRS showed no change [36].

Zinc and ADHD: Of five studies investigated zinc's role in etiopathology and ADHD treatment, one case control study drew a comparison between the plasma zinc levels of 28 ADHD boys and that of twenty-four boys in control group. It was observed that plasma zinc levels in the ADHD group was significantly lower than the control group ($p<0.017$) [15]. A double-blind study was carried out on 400 ADHD children who were randomly assigned to supplementation or placebo groups. The subjects in the supplementation group received 150 mg/day zinc for 12 weeks. The results, indicated that zinc sulfate was more effective in reducing some ADHD symptoms (including hyperactivity and socialization deficit), determined by Attention Deficit Hyperactivity Disorder Scale (ADHDS) and Conners Teacher Questionnaire. However, this result was not observed with respect to attention deficit symptoms [14]. A randomized double-blind study on forty-four ADHD children was reported. In this investigation, the participants that received 55 mg/day zinc supplementation for 6 weeks, showed improvement based on CPRS and CTRS [37]. Study conducted on forty-eight ADHD children also indicated a correlation between serum zinc levels and ADHD symptoms, based on CPRS and CTRS [38]. Regarding the results of study by Arnold, further investigations on the subject were recommended [39].

Discussion

Fatty acid and ADHD: The results of the existing studies about diet and nutrition roles in hyperactivity, attention, and concentration difficulties, associated with ADHD in children, further support omega-3 fatty acids role. That is, most of the studies which described essential fatty acids levels in erythrocyte membrane phospholipids, reported lower amount of essential fatty acids in these children. In addition, most of the review and clinical studies showed significant improvement of ADHD-related symptoms after receiving different dosages of omega-3 supplementation during different periods of time. Therefore, based on the obtained results, although employing PUFA supplements is not recommended as the primary treatment of this disorder [6], but given other positive effects of these fatty acids on health, using them as complementary therapy will have an effective role in reducing ADHD symptoms. This could be so only if the results are confirmed by a large number of further studies. The issue is important in several respects: this method, as a complementary treatment, is relatively less expensive, in comparison. Therefore, if concrete results are achieved, the effectiveness of omega-3 fatty acids can probably be expected. For that reason, conducting controlled and double-blind studies again with a larger sample size and different dosages of omega-3 fatty acids, using the same ADHD-related behavior assessment methods, on same age and sex groups, are required to control and treat this disorder.

Iron and ADHD: Existing studies indicate the positive effect of iron supplement on improvement of hyperactivity symptoms, especially in children with low serum ferritin levels. However, given the limited number of studies, conducting further controlled investigations with different doses and in longer periods of time is required to achieve concrete result.

Zinc and ADHD: The results of a few published studies indicate that plasma zinc level in ADHD children is lower in comparison with normal population. However, these results do not acknowledge zinc deficiency as the causative factor in affection to and treatment of this disorder. Studies have pointed out the relationship between plasma zinc levels and information processing [15], and its positive treatment effect in reducing hyperactivity symptoms and socialization process of these children [14]. However the results gained on reduction of attention deficit symptoms are contradictory and it is reported that the positive effect of zinc on ADHD is related to zinc deficient endemic parts of the world [39]. For the following reasons and regarding a few number of studies to date, it seems that conducting more investigations, controlled with different dosages and time periods of zinc supplement, is of the effective measures to achieve a controlling strategy, especially in countries like Iran: 1. The role of zinc in growth, health, and disease prevention; 2. The role zinc, as one of the ten major causes of disease in developing countries, according to World Health Organization; and 3. The results of the investigation conducted by Health Ministry in 2001 in Iran that indicates 31% of six-year old children, 28% of

young adults, and 19% of 15 to 23 months infants are suffering from zinc deficiency [40].

It also seems that in designing future studies careful evaluation of mineral zinc status in body before intervention can be helpful in estimating its impact. In conclusion, due to differences in sampling methods, samples number, age, and sex, inclusion and exclusion criteria, statistical tests, duration, type of the employed supplement, and ADHD-related behavior assessment tests, the obtained results are not enough for making definite conclusion regarding the usefulness of the supplements.

However, given the dietary problems in these children and high prevalence of iron and zinc deficiency and also the inadequate dietary intake of omega-3 fatty acids by most children, it seems that even if using foods containing these nutrients or their supplements has no effect on behavioral difficulties in attention-deficient/hyperactive children, they still can be effective in maintaining other aspects of health.

Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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