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Polyunsaturated fatty acids in the treatment of attention deficit hyperactivity disorder

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ABSTRACT

Background: Attention deficit/hyperactivity disorder (ADHD) is one of the most common behavioral disorders in children. Insufficient dietary intake of long-chain polyunsaturated fatty acids (LC-PUFAs) has been suggested to have an impact on the development of symptoms of ADHD in children. Individuals with ADHD have been demonstrated to have significantly reduced blood concentrations of PUFAs and, in particular, reduced levels of omega-3 (n-3) PUFAs. These findings suggest that PUFA supplementation may reduce the attention and behavior problems associated with ADHD.

Objective: To provide an overview of the efficacy of dietary LC-PUFA supplementation in the treatment of ADHD.

Methods: Literature published up until December 2013 on the effects of n-3 PUFA supplementation on ADHD symptoms was obtained using a PubMed search and critically reviewed.

Results: Dietary PUFA supplementation appears to have beneficial effects on ADHD symptoms although these effects are small. The clinical relevance of these observations remains to be determined.

Conclusion: There is only limited support for the efficacy of PUFA supplementation for the core symptoms of ADHD. Given the small effect sizes regarding PUFA supplementation, it may not be a sufficient therapy for a majority of patients with ADHD.

Keywords: diet, nutrition, polyunsaturated fatty acid, PUFA, attention deficit/hyperactivity disorder, ADHD

Background

Attention deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood and adolescence and is characterized by age-inappropriate levels of inattention, impulsivity and hyperactivity, and is associated with long-term academic, social, and mental health problems. Approximately 3-5 % of school children and adolescents are affected by ADHD; the prevalence is higher in boys than girls [1-4]. Environmental, social, genetic and neurobiological factors appear to be relevant in the etiology of ADHD [1, 5, 6].

Neurobiological studies suggest that ADHD is a neurodevelopmental disorder involving dysfunctional neurotransmission of, among others, central dopaminergic systems [7-14]. For example, it has been proposed that a decrease in activity of frontal cortical dopaminergic neurotransmission plays a role in regard to cognitive deficits, while dopaminergic over-activity in sub-cortical regions may lead to behavioral hyperactivity [2, 15]. Stimulant medications such as methylphenidate are the most frequently used treatments for ADHD, but these are not always effective and can be associated with side effects.

The role of diet and dietary supplementation in the etiology and therapy of ADHD is controversial. ADHD has recently been linked with a Western-style diet which is high in fat, refined sugars and sodium and low in fiber, folate and omega-3 polyunsaturated fatty acids (n-3 PUFAs) [16]. Dietary treatments proposed in ADHD include sugar-restricted, additive- and salicylate-free, oligoantigenic, ketogenic, megavitamin, and PUFA supplement diets [17]. PUFA supplementation is the latest ADHD therapy to receive positive evaluations.

Links between ADHD and PUFAs

The brain relies on both macro- and micro-nutrients for optimal brain development and function [18]. PUFAs are known to play an important role in neuronal development and functioning of the central nervous system [19, 20]. The brain of mammals is particularly rich in long-chain (LC) PUFAs from n-3 and omega-6 (n-6) families, particularly docosahexaenoic acid (DHA, C22:6ω-3) and arachidonic acid (AA, C20:4ω-6) [21, 22]. These PUFAs are synthesized by sequential desaturation and elongation of their respective precursors which cannot be synthesized by mammals and need therefore to be provided by the diet (essential fatty acids, EFAs).

LC-PUFAs such as eicosapentaenoic acid (EPA C20:5ω-3), DHA and AA have an influence on numerous neuronal processes, such as expression of proteins involved in signal transduction and neural plasticity and learning [19, 20, 23]. Increasing evidence points to the importance of nutrition, particularly n-3 PUFAs, for mental health. LC n-3 PUFAs may exert their effects on cognitive function through modulation of neuronal membrane which can influence membrane receptors, neurotransmission and signal transduction [22]. Studies in humans indicate that a deficiency in n-3 fatty acids leads to an imbalance of the n-3/n-6 PUFA ratio, affects neurocognitive abilities and is associated with developmental disorders such as ADHD [19, 20, 23, 24]. Effects of n-3 PUFAs have been explored on psychiatric problems such as childhood developmental disorders, depression, schizophrenia and dementia [25]. Mental disorders can lead to poor diet [26, 27] which could contribute to the PUFA status in patients with psychiatric problems. In this context, a possibly impaired metabolism of PUFAs has been discussed as a potential risk factor for the development of ADHD [19, 23].

A possible link between ADHD and EFAs was first proposed on the basis of clinical observations. Hyperactive children had signs of fatty acid deficiency including polydipsia, polyuria as well as dry hair and skin [28]. These signs have been shown to be at least 30 % more frequent in children or young adults with ADHD than in controls [29-32]. Further clinical and biochemical evidence suggests that deficiencies of PUFAs could be related to ADHD. For example, several studies demonstrated that blood plasma levels of fatty acids such as DHA, EPA, AA and dihomogammalinolenic acid (DGLA, C20:3ω-6) were significantly reduced in children with ADHD when compared with controls [29, 30, 33, 34]. The potential mechanisms leading to abnormal levels of EFAs in individuals with ADHD may include reduced PUFA intake, decreased conversion of EFAs to LC-PUFAs and an increase in LC-PUFA metabolism [33]. However, none of these hypotheses are supported by convincing evidence. For example, no difference in the consumption of n-3 PUFAs could be demonstrated in patients with ADHD, although differences in n-3 PUFA levels in both plasma phospholipids and erythrocytes were found [31]. The above mentioned findings suggest that PUFA supplementation may reduce the attention and behavior problems associated with ADHD. In theory n-3 PUFA supplementation may offer a therapeutical approach addressing not only symptoms but also an underlying etiological factor. As a consequence, an increasing number of clinical studies have assessed the effects of PUFA supplementation on ADHD symptoms.

Methods

Literature published up until December 2013 on the effects of n-3 PUFA supplementation on ADHD symptoms was obtained using a PubMed search and critically reviewed.

Dietary PUFA supplementation in ADHD

Evidence for effects of dietary treatments of ADHD varies widely, from anecdotal evidence to placebo-controlled and double-blind trials. Various methodological problems make it difficult to evaluate clinical trials aimed at assessing the effects of dietary PUFA supplementation in ADHD. There exists a great heterogeneity of several parameters including the kind of fatty acids used (EFA precursors, n-3 PUFAs, n-6 PUFAs or combinations thereof), the form in which the supplement is administered, the dose and duration of supplementation as well as the tests/assessments used to evaluate ADHD symptom prior to and following treatment. Not all studies investigated n-3 PUFA status before and after the intervention. In addition, the diagnosis of ADHD was not always made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, [35]) and various comorbid disorders existed in numerous subjects. Since some studies included subjects with ADHD under pharmacological therapy, it is difficult to draw conclusions as to the effects of an interaction between PUFA supplementation and stimulant medication.

Using meta-analysis Bloch and Qawasmi [36] examined the efficacy of n-3 PUFA supplementation in children with ADHD. Ten trials involving 699 children were included. N-3 PUFA supplementation demonstrated a small but significant effect in improving ADHD symptoms. N-3 PUFA supplementation, particularly with higher doses of EPA was modestly effective in the treatment of ADHD. The relative efficacy of n-3 PUFA supplementation was modest compared to currently available pharmacotherapies of ADHD such as psychostimulants or atomoxetine [36].

Another meta-analysis by Gillies et al. [37] compared the efficacy of PUFAs to other forms of treatment or placebo in treating the symptoms of ADHD in children and adolescents. Thirteen trials with 1,011 participants were included in the analysis. Overall, there was little evidence that PUFA supplementation provides any benefit for the symptoms of ADHD in children and adolescents. The majority of data showed no benefit of PUFA supplementation, although there were some limited data that did show an improvement with combined n-3 and n-6 supplementation [37].

In recently published meta-analyses, Sonuga-Barke et al. [38] assessed non-pharmacological interventions for ADHD. The authors used a rigorous methodology by including only randomized controlled trials. In regard to PUFA supplementation, eleven trials met inclusion criteria. Five of these studies used n-3 supplements [24, 39-42], two involved n-6 supplements [43, 44] and four used supplements with both n-3 and n-6 PUFAs [45-48]. Supplementation effects were significant and the probably blinded assessment effects remained significant when the analysis was limited to the nine trials with no/low medication [38]. It is, however, possible that the outcomes in the studies analyzed by Sonuga-Barke et al. [38] included individuals with attention problems who were incorrectly diagnosed as having ADHD or by the presence of co-occurring conditions. In addition, the authors noted that while their findings demonstrate the efficacy of PUFA supplementation, the effect size is less than that of medications, i.e. PUFA supplementation has a small but significant effect on symptoms.

The standardized mean differences (effect sizes) for PUFA supplementation in the meta-analysis by Sonuga-Barke et al. [38] were smaller than those reported by Bloch and Qawasmi [36] who included trials with non-ADHD populations. The studies by Sonuga-Barke et al. [38] and Gillies et al. [37] differed in regard to inclusion criteria, the number of studies included and the statistical model employed. The differences between the findings of meta-analytical reviews highlight the sensitivity of results to small variations in protocol.

Given the high prevalence of co-occurring conditions with ADHD, many individuals included in the clinical trials of PUFA supplementation may have had comorbidities. Observations of other studies showed that treatment response varied based on the patients' comorbid conditions [49]. It is possible that PUFA supplementation in some studies was insufficient to influence the PUFA content in the brain due to too low doses of PUFAs or too short durations of administration. In addition, it needs to be investigated whether there is a critical age at which PUFAs are supplemented. In a rat model of chronic n-3 PUFA deficiency, it was demonstrated that the introduction of an equilibrated diet through the mother during the pre-/postnatal period was able to restore monoaminergic functions affected by the deficiency only if it occurred before the 21st day of life [50, 51]. These results suggest that an optimal time frame for PUFA supplementation might also exist during brain development in humans.

Conclusions

A link appears to exist between reduced PUFA levels and the occurrence of ADHD. PUFA supplementation appears to produce small but significant reductions in ADHD symptoms. The differences between the results of recent meta-analytical studies emphasize the need for caution when discussing the clinical relevance of small effects reported for the efficacy of PUFA supplementation [36-38].

Various factors may have influenced the results of studies on PUFA supplementation in ADHD, e.g. heterogeneity of design type, type of PUFA employed (n-3 or n-6 or combination), dose of LC-PUFAs, method of administration, duration of treatment or assessment of response. Future research needs to address various weaknesses of treatment studies of PUFA supplementation, which include relatively small sample sizes, variability of selection criteria, differences in the type and dosage of supplementation and short follow-up periods. Little is known about optimal ratio between supplemented PUFAs and the necessity of weight-adjusted doses. Moreover, ecologically valid outcome measures are needed [52].

Baseline n-3 PUFA status may influence the outcome of PUFA supplementation in ADHD. Whether or not individuals with low n-3 PUFA status are more responsive to dietary n-3 PUFA supplementation is as yet not resolved. It is therefore important to identify subgroups of individuals who may most likely benefit from n-3 PUFA supplementation, including those with lower baseline PUFA status. In addition, there may be a threshold n-3 PUFA status above which dietary supplementation has little effect on outcome measures. In addition, the ratio between DHA, EPA and AA requires consideration in future studies.

If an optimal time frame in early childhood exists for successful dietary supplementation of n-3 PUFAs as suggested by animal studies [50, 51], the administration of these compounds at the time of school-age diagnosis ADHD may come too late. Future studies may investigate if maternal prenatal LC-PUFA supplementation or dietary PUFA administration at young age are able to prevent the occurrence of ADHD or reduce the severity of symptoms.

In summary, there is at present only limited support for the efficacy of PUFA supplementation for the core symptoms of ADHD. Given the small effect size of PUFA supplementation, it may not be a sufficient therapy for a majority of patients with ADHD.

Abbreviations: arachidonic acid (AA), attention deficit/hyperactivity disorder (ADHD), dihomogammalinolenic acid (DGLA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), essential fatty acids (EFAs), long-chain polyunsaturated fatty acid (LC-PUFA), omega-3 polyunsaturated fatty acid (n-3 PUFA), omega-6 polyunsaturated fatty acid (n-6 PUFA)

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Authors' Contributions: All authors contributed to this study.

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