

Research Article

Role of Plasma Fatty Acids in Egyptian Children with Attention Deficit Hyperactivity Disorder

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ABSTRACT

The present study aimed to assess the effectiveness of n-3 PUFA supplementation on ADHD clinical symptoms and its tolerability in a randomized controlled study on Egyptian children. Vigil continuous performance test and Conners' questionnaires were used to assess changes in ADHD symptoms in 40 children; another 40 matched children were included in the study as controls. Supplements rich in EPA, DHA were randomly allocated for 4 months for only 20 cases. Plasma omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids) were assessed using Tandem Mass Spectrometry. The results revealed low levels of plasma omega-3 fatty acids were noted in children with ADHD compared to controls. Supplementation with n-3 PUFA resulted in significant increase in plasma EPA, DHA in children with ADHD. No adverse effects were detected after n-3 PUFA supplement. According to parent version of the Conners' questionnaire improvement in symptoms was observed but it was not statistically significant except for the subscale measuring inattention. We concluded that Egyptian children with ADHD exhibited low levels of omega-3 fatty acids in polar lipids isolated from their plasma and are inversely correlated with degree of inattention. Our results support n-3 PUFA safety and tolerability and appear to be effective in alleviating symptoms of inattention.

Keywords: Egyptian, Fatty acids, ADHD

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is one of the most widespread behavior disorder that affect children. Epidemiological studies indicate that ADHD affecting 5.3% of children worldwide¹. In USA current prevalence estimates for childhood ADHD range from 5% to 8%, while in Europe it is significantly lower than this range². This range is higher in Arabian countries reaching 9.4% in Egypt³, 9.4% in Qatar⁴ and up to 44% in Saudi Arabia among primary school children⁵. Pharmacological intervention for ADHD children was effective after two to five years of treatment⁶, but it has many side effects. It was estimated that 7% to 64% of ADHD children are treated assortment of alternative approaches⁷.

The n-3 PUFA as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are implicated in important aspects of brain function including cell growth, neural signaling, and gene expression⁸. Previous studies have reported decreased plasma levels of PUFAs in neuropsychiatric disorders such as schizophrenia⁹, depression¹⁰, autism¹¹ and attention deficit hyperactive disorder (ADHD)¹², which have been found in DHA (docosahexaenoic acid) and total omega-3 and in the omega-6 arachidonic acid, which may persist until adulthood¹³. Our study aimed to evaluate plasma PUFA in a

randomized group of ADHD Egyptian children and to determine the effectiveness of n-3 PUFA supplementation on the clinical symptoms by monitoring the changes in plasma PUFA levels after supplementation.

METHODS

Study design

Case-controlled study followed by open label interventional phase.

Participants

40 children (29 males and 11 females) diagnosed of ADHD, participated in the study, with age ranges between 6 and 12 years and IQ levels above 90 with no chronic medical, neurological or fish allergy were included in the study. All cases were recruited from the outpatient clinic of child psychiatry - The institute of psychiatry - Ain-Shams university hospital and the outpatient clinic of the children with special needs in the National Research Centre, Cairo, Egypt. Forty age and sex matched children were recruited as a control group.

Ethics approval and consent

A written informed consent was obtained from the parents of the participants, according to the guidelines of the ethical committee of the National Research Centre

Table 1: Scores of Conner's Scale in children with ADHD before treatment.

Conner's parents rating scale subscales	Mean± SD	Significance
Opposition	61.09± 10.8	mildly atypical
Inattention	71.27± 7.29	markedly atypical
Hyperactivity	71.73± 11.04	markedly atypical
Anxiety-Shyness	47.27± 2.68	typical score
Perfectionism	47.36± 2.58	typical score
Social problems	56.55± 10.4	slightly score
Psychosomatic	47.27± 4.02	typical score
Conners' ADHD index	71± 8.07	markedly atypical
Conners' index: Restless-Impulsive	72.73±12.15	markedly atypical
Conners' index: Emotional lability	67.09± 11.42	moderately atypical
Conners' index: total	72±11.05	markedly atypical
DSM-IV: Inattentive	68.82 ± 8.14	moderately atypical
DSM-IV: Hyperactivity-Impulsive	69.45±11	moderately atypical
DSM-IV: Total	67.45± 7.85	moderately atypical

Table 2: Scores of Vigil continuous performance test in children with ADHD before treatment.

Vigil continuous performance test	Mean ± SD	Significance
Total omission	21.55±6.13	markedly impaired
Total commission	18.73±5.4	markedly impaired
Total error	40.28±8.5	markedly impaired
Total average delay (in milliseconds)	573.91±33.4	markedly impaired

Table 3: Plasma levels of omega-3 fatty acids in children with ADHD and controls.

Omega-3 fatty acids	Cases n.=40 Mean±SD	Controls n.=40 Mean± SD	P value
EPA level	1.343± 0.539	3.036± 0.425	0.000
DHA level	1.347± 0.465	2.579±0.706	0.000

EPA: eicosapentaenoic acid
DHA:docosahexaenoic acid

and the ethical committee of Scientific Research- Faculty of Medicine-Ain Shams University, Cairo, Egypt.

Measures

Both cases and controls were assessed using Mini International Neuropsychiatric Interview for Children¹⁴ for diagnosis of ADHD and exclusion of other psychiatric comorbidities in cases and exclusion of psychiatric disorders in the controls. Also IQ was assessed using Wechsler Intelligence Scale for Children¹⁵. Estimating omega-3 fatty acids - EPA and DHA - was done for both patients and controls using High performance liquid chromatography / Mass spectroscopy. Twenty children of the patient group were further assessed using the Conners' parent rating scale-revised long version¹⁶ and Vigil continuous performance test¹⁷ for assessment of the severity of their symptoms. These 20 children were prescribed omega-3 fatty acid supplement in the form of gelatinous capsules with daily dose of 900 mg EPA and 600 mg DHA for 3 months. At the end of the 3 months those children were assessed again using the Conners' parent rating scale-revised long version and Vigil continuous performance test and omega-3 fatty acids - EPA and DHA- were re-estimated.

Statistical Analysis

Data are expressed as mean ± SE. Statistical significance was determined using student t- test and anova test. A probability value of P less than 0.05 was considered statistically significant.

RESULTS

The study included 40 ADHD children (both sexes) with mean age of 8.15 years and 40 normal healthy children matched for age and sex served as controls. There was no statistically significant difference between both groups regarding gender, age, paternal consanguinity, residency and IQ. The initial assessment of the patient group with Conners' parent rating scale showed that they had significant problems on the Inattention, Hyperactivity, Conners' ADHD index, Conners' global index: Restless-Impulsive, Conners' global index: Emotional lability, Conners' global index: total, DSM-IV: Inattentive, DSM-IV: Hyperactivity-Impulsive and DSM-IV: Total score subscales (Table 1). The initial assessment of the patient group with Vigil continuous performance test revealed significant problems in total omission, total commission, total error and total reaction time (Table 2). Regarding levels of omega-3 fatty acids the results revealed that children with ADHD exhibit statistically significant low levels of EPA and DHA compared to controls as shown in Table 3. Our results showed negative correlation between DHA level and Conners' ADHD index, DSM-IV: Inattentive and DSM-IV: Total subscales of Conner's Parent Rating Scale and of total omission and total error of the Vigil continuous performance test before starting the treatment. No significant correlations had been found between these measures and level of EPA. Regarding Vigil continuous performance test there negative correlation between DHA level and scores of total error

Table 4: Plasma levels of EPA and DHA before and after supplementation.

Omega-3 fatty acids	Before supplementation n.=40 Mean ± SD	After supplementation n.=20 Mean ± SD	P value
EPA level	1.343±0.539	3.645±0.522	0.000
DHA level	1.347±0.465	3.764±0.576	0.000

EPA: eicosapentaenoic acid
DHA: docosahexaenoic acid

Table 5: Scores of Conner's Parent Rating Scale before and after supplementation.

Conner's parents rating scale subscales	Before supplementation n.=20 Mean± SD	After supplementation n.=20 Mean± SD	P value
Opposition	61.09±10.8	62.73±12.37	0.543
Inattention	71.27±7.29	65±11.68	0.052
Hyperactivity	71.73±11.04	69.18±12.38	0.136
Anxiety-Shyness	47.27±2.68	46.45±1.63	0.251
Perfectionism	47.36±2.58	46.18±1.6	0.052
Social problems	56.55±10.40	51.82±9.93	0.076
Psychosomatic	47.27±4.02	46.55±3.01	0.455
Conners' ADHD index	71±8.07	64.09±11.66	0.048
Conners' index: Restless-Impulsive	72.73±12.15	68±12.19	0.066
Conners' index: Emotional lability	67.09±11.42	64.27±12.69	0.274
Conners' index: total	72±11.05	68.82±12.27	0.09
DSM-IV: Inattentive	68.82±8.14	62.91±11.39	0.067
DSM-IV: Hyperactivity-Impulsive	69.45±11	66.09±11.37	0.059
DSM-IV: Total	67.45±7.85	63.45±8.29	0.089

and total omission only. After omega-3 fatty acids supplementation the results showed significance increase in levels of plasma EPA and DHA in children with ADHD (Table 4). Regarding severity of ADHD symptoms after omega-3 fatty acids supplementations as assessed by Conner's Parent Rating Scale, there was statistically significant improvement on the Conners' ADHD index subscale only (Table 5). Assessment of symptoms using Vigil continuous performance test revealed non-significant improvement of total omission and total error.

DISCUSSION

Studying the relation between omega-3 fatty acids and ADHD may provide a new line of management of ADHD or at least help augment the effect of the psycho-stimulants or lower the cases of non-responsiveness. The present study showed that ADHD children had significant low EPA and DHA levels compared to controls, these results agreed with previous finding reported by Colter 2008¹⁸. The lower levels of both omega-3 fatty acids (EPA and DHA) in ADHD children could be attributed to altered their absorption and metabolism¹⁹. Regarding the correlation between levels of omega-3 fatty acids and severity of ADHD symptoms, DHA levels had medium negative correlation with scale rating for Conners' ADHD index, DSM-IV: Inattentive and DSM-IV: Total. On the other hand no significant correlations could be detected between EPA levels and severity of ADHD symptoms. DHA is more related to the pathogenesis of ADHD, preterm delivery is associated with elevated rates of ADHD²⁰, as it results in low third trimester cortical DHA accrual. So dietary supplementation of the preterm infants with DHA postnatal exhibited marked improvements in visual attention processes²¹. DHA was also correlated to the

inattentive component of ADHD rather the hyperactivity and impulsivity components. These findings are confirmed objectively by the results of Vigil continuous performance test. Also we found significant correlation between DHA level in children with ADHD and scores of Vigil continuous performance test before treatment. These results agreed with those reported by Colter 2008¹⁸, who found significant correlation between DHA level in cases with ADHD and their scores on Conner's Parent Rating Scales. DHA level was negatively correlated with scale rating for opposition inattentive, hyperactivity Conners' index: Restless-Impulsive, DSM-IV: Inattentive and DSM-IV: Total. The cases of the ADHD in the current study were prescribed high doses of omega-3 fatty acids supplementations for 3 months after which they were reassessed, the results showed significant high EPA and DHA levels after treatment this results were similarly reported by Germano et al., 2007²². This improvement in levels of omega-3 fatty acids following omega-3 supplementations excludes impairment of PUFA absorption as a causative factor for low levels of omega-3 fatty acids in children with ADHD. Therefore the most accepted explanations for low levels of omega-3 in ADHD children are the inefficient conversion to long chain polyunsaturated fatty acids from their precursors²³ or the enhanced metabolism of long chain polyunsaturated fatty acids as indicated by the increased level of exhaled ethane - a non-invasive measure of oxidative damage to omega-3 fatty acids - in children with ADHD²⁴. Regarding severity of ADHD symptoms the results showed improvement in most of subscales of Conner's Parent Rating post treatment. Also using Vigil continuous performance test following treatment showed an improvement of the total omission which is an indicator for inattention, but this

improvement had no statistical significance. Several studies proved our results of improvement of ADHD symptoms – notably functions of attention – following PUFA supplementation^{25,26}, the authors reported a statistically significant improvement of the Conners' ADHD index subscale, more over they found significant improvements of the inattention and hyperactivity subscales of Conners' Parent's Rating Scale. They also reported significant improvement of the oppositional behavior of the children following treatment. The discrepancy between their results and ours can be explained by the difference of the doses of omega-3 supplementation, as the dose used in their study was more than 10 folds of our dose with different duration of treatment. A meta-analysis of studies about omega-3 fatty acid supplementation for the treatment of children with ADHD was conducted by Bloch and Qawasmi²⁷. Ten trials involving 699 children were included in this meta-analysis. The authors reported significant improving in ADHD symptoms after supplementation with omega-3 fatty acid. On the contrary Raz et al., 2009²⁸ found no improvement following PUFA supplementations in children with ADHD. Contradictory results may be due to ethnic factors as well as dietary factors that may play an important role in the results. The findings of the current study raise many questions about relation between omega-3 fatty acids and ADHD; whether increasing blood levels of fatty acids is corresponding to similar increase of brain levels of fatty acids and whether we need more time or higher doses of fatty acids to be expressed as improvement in symptoms' severity. Another question imposes itself; could we explain increasing fatty acids levels without equivalent symptoms improvement by the fact that ADHD is a multifactorial disorder, involving both biological and environmental influence and that EFA deficiency is just one of its causes. One of the query findings of the current study is that improvement of ADHD symptoms following omega-3 supplementation is evident in the subjective assessment using Conner's Parent Scale, while the objective assessment using Vigil continuous performance test could not detect similar improvement. This could be explained by the emotional bias of the family or even the researcher who is expecting improvement following treatment and this bias could affect the results of subjective tool such as Conner's Parent Scale, while an objective tool such as Vigil continuous performance test could not be affected with this bias. Another remarkable finding of the current study is that improvement of ADHD symptoms following omega-3 fatty acids supplementation was mainly improvement of symptoms related to inattention and cognitive problems, while symptoms related to hyperactivity and impulsivity showed modest improvement. The fact here that some aspects of this complex disorder are more amenable to omega-3 supplements than others, and the question was addressed as to whether ADHD is a single disorder or two related disorders; disorder of inattention and disorder of hyperactivity with two distinct pathologies. Another question that imposes itself; whether omega-3 supplements affect mainly areas of prefrontal cortex

involved in the attention process with their related circuits which could explain the preferential action of omega-3 on ADHD symptoms and whether omega-3 supplements is indicated only in ADHD- inattentive type and whether more doses could be prescribed in ADHD- hyperactive/impulsive and combined types.

CONCLUSION

Children with ADHD exhibit low levels of omega-3 fatty acids plasma, DHA level is inversely correlated with degree of inattention in these children and finally administration of high doses of omega-3 fatty acids supplements for 3 months is successful in normalizing the levels of omega-3 fatty acids and alleviating symptoms of ADHD, especially the cognitive problems and inattention.

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