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EFFECT OF OMEGA-3 FATTY ACID SUPPLEMENTATION ON SOME OF THE PHYSIOCHEMICAL CHANGES IN BOYS WITH MODERATE ADHD SYMPTOMS

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) may persist into adolescence and adulthood. It is suggested that insufficient nutritional supply of LC-PUFAs (long-chain polyunsaturated fatty acids) and minerals (including serum levels of zinc, iron, magnesium, calcium and copper) may develop ADHD symptoms. However, clear and convincing evidence is lacking. Subjects in the present report were boys with moderate ADHD symptoms who were categorized into control group (C; mean age: 8.34 years), ADHD group (mean age: 8.72 years), and ADHD-O group (or ADHD-supplemented with omega-3 fatty acids (mean age: 8.69 years). Significant reduction in serum zinc, iron, magnesium and calcium in ADHD group without omega-3 supplementation compared to healthy control subjects, and significant increase in these nutrient bioelements after omega-3 supplementation in ADHD reaching to the levels found in healthy non-ADHD control subjects were the findings in our present study. Although the definite cause/ causes of ADHD are not yet known, omega-3 and other long-chain polyunsaturated fatty acids (LCPUFA) seem promising in understanding the pathophysiology and exploring additional management of ADHD.

Keywords: ADHD, serum nutrient bioelements, moderate ADHD symptoms, omega-3 fatty acids.

INTRODUCTION

Child health is linked to a variety of factors related to physical or psychological/ mental processes in causing abnormal alterations leading to Attention-deficit hyperactivity and other medical disorders (Stevenson and Wolraich, 1989; Levy, 1991; Hussain, 1993; Richardson and Puri, 2000; Díaz-Heijtz, 2002; Antalis *et al.*, 2006; Paclt, 2009; Gillies *et al.*, 2012; Bonvicini *et al.*, 2016; Ramtekkar, 2017).

Hyperactivity disorders in children along with attention deficit are the alarming issues (Stevenson and Wolraich, 1989; Hussain, 1992; Gillies *et al.*, 2012;). In that perspective, pathobiology of Attention deficit hyperactivity disorder (ADHD) has been studied through different angles (Stevenson and Wolraich, 1989; Levy, 1991; Hussain, 1998 Gillies *et al.*, 2012; Bonvicini *et al.*, 2016; Ramtekkar, 2017).

Attention deficit hyperactivity disorder (ADHD) that may persist into adolescence and adulthood is a common psychiatric disorder in children with the main symptoms of inappropriate levels of attention, hyperactivity &

impulsivity. It is suggested that insufficient nutritional supply of LC-PUFAs (long-chain polyunsaturated fatty acids) and minerals including mainly zinc, magnesium, and iron may develop ADHD symptoms. However, clear and convincing evidence is lacking (Lange *et al.*, 2017).

It is essential to manage proper levels of zinc by dietary intake since plasma contains very little amount of zinc and our body does not store zinc (Rink and Gabriel, 2000). There is no clear evidence for the involvement of zinc in causing ADHD. However, Zinc is found involved in production as well as control of melatonin that in view of its role in modulating dopamine is considered an important factor in the pathophysiology of ADHD Lepping and Huber, 2010).

Furthermore, zinc deficiency may result to decreased levels of essential fatty acids and hence, may contribute to hyperactivity (Colquhoun and Bunday, 1981) that is quite interesting to interpret our present study wherein omega-3 fatty acids administration increased serum zinc level. This can further be proved by a previous report showing a correlation between serum free fatty acids and zinc levels, and it was suggested that the serum level of free fatty acids reduced in response to zinc deficiency in children with ADHD (Bekaroğlu *et al.*, 1996).

There is a report indicating efficacy of 80 mg ferrous sulfate for non-anemic children having ADHD and low ferritin, with some improvement in the symptoms of ADHD (Konofal *et al.*, 2008). Magnesium is also important for fatty acid synthesis and may relate with the therapeutic efficacy of omega-3 fatty acid supplementation in patients with ADHD. Children with ADHD showed lower level of RBC magnesium levels, though without any statistically significant difference of serum magnesium for control vs ADHD group (Stevens *et al.,* 1995; Mousain-Bosc *et al.*, 2006)

The 8-12 years old boys with ADHD, serum calcium showed a significant role (Arab Ameri *et al.,* 2012). Copper (Cu) - an essential trace element in human physiology, has much importance in cognitive functions (Salustri *et al.,* 2010). However, no correlation for serum Cu vs scores of ADHD symptoms on rating scales could be found.

The involvement and significance of omega-3 or n-3 PUFAs (omega-3 polyunsaturated fatty acids) especially the sub-optimal or insufficient levels of nutrients including PUFAs mainly omega-3 in understanding the behavioral disorders, pathogenesis and proper treatment of the children as well as adolescents with ADHD (attention deficit/ hyperactivity disorder) is still not clear owing to contradictory results. Hence, we planned to carry out the present study to evaluate the existing evidence on whether omega-3 plays a significant role as an adjunctive therapy and management.

METHODS AND MATERIALS

Sample size (total number of subjects: 73; control subjects (C): 23; ADHD patients: 26; ADHD-O (ADHD patients supplemented with omega-3): 24) (Table-1) was appropriate for the present study. Design, study setting, and sampling technique are mentioned in below.

The mean ± SD values of age (years) for control subjects, ADHD patients and ADHD patients supplemented with omega-3, respectively were 8.34 ± 2.31, 8.72 ± 3.23, and 8.69 ± 3.35 that showed statistically non-significant difference ($p > 0.05$). Values for BMI for all subjects were in the normal range since subjects included in the current study did not have weight more or less from the standard range. Furthermore, subjects having obesity or showing tendency/ family background of obesity were not included in the present study.

The subjects selected for this study were thoroughly consulted and their detailed history was recorded before starting the study. Their glycemic status, hemoglobin and lipid profile were obtained. Furthermore, they did not have cardiac, respiratory, renal, gastrointestinal, and other discomforts. Psychiatric and neuropsychiatric manifestations were properly recorded, and only those ADHD patients were included who showed moderate ADHD symptoms.

The ADHD patients were properly diagnosed. The DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th. Edition**)** criteria were employed for diagnosis. The DMS-5 diagnostic criteria (replaced version of DMS-IV) are used world over for the diagnosis of ADHD wherein inattentive or hyperactive-impulsive symptoms predominate. Symptoms of inattention, hyperactivity and impulsivity occur in various patterns. Presentation of three patterns- predominantly inattentive, predominantly hyperactive/impulsive, or combined forms may appear.

Six or more symptoms in DMS-5 criteria in children prevail for approximately 6 months to an extent that it becomes inconsistent with development and directly impacts negatively on social, and other activities of the child. Severity of ADHD is classified as a) mild, b) moderate and c) severe. Present report concerns the moderate ADHD symptoms (the functional impairment or symptoms between mild and severe). Assessment, diagnosis, and rating scales are established, and on that basis the management- optimal, non-pharmacological and pharmacological options are considered.

The subjects were categorized into two main groups-control group (C) or non-ADHD group and ADHD patients group (ADHD). The ADHD group was further divided into two groups. One ADHD group comprised patients showing the diagnosis of moderate ADHD symptoms and was studied for physiochemical changes (including serum levels of zinc, iron, magnesium, calcium and copper) in boys with moderate ADHD symptoms.

The other ADHD group (ADHD-O or ADHD-supplemented with omega 3 fatty acids) served for studying the effect of omega-3 fatty acid supplementation on some of the physiochemical changes in boys with moderate ADHD symptoms. Same doses of omega-3 fatty acid supplements were prescribed for the subjects in all three groups. However, omega-3 fatty acid blood levels could not bt estimated. Blood samples from patients were taken after the confirmation of DSM-5 diagnosis. Blood serum of patients and normal HEALTHY CONTROLS was separated and stored at appropriate temperature for bioelement estimations. Estimation of the serum bioelements was carried out using the routine laboratory facilities employing mainly the kit methods and instruments.

RESULTS

Serum physiochemical changes in all three groups (healthy non-ADHD control subjects (C Group; n:23), ADHD patients without omega-3 supplementation (ADHD group; n:26), and ADHD patients with omega-3 supplementation (ADHD-O group; n: 24) were compared (Table-1).

Table 1. Effect of omega-3 fatty acid supplementation on some of the physiochemical changes in boys with moderate ADHD symptoms.

Serum physio-chemical changes	Healthy non-ADHD control subjects (C Group; n:23)	ADHD patients without omega-3 supplementation (ADHD group; n:26)	ADHD patients with omega-3 supplementation (ADHD-O group; n: 24)	Significance (Unpaired t test results for two-tailed p value)
Zinc (µg/dL)	111.17 ± 14.33	67.82 ± 10.01	72.57 ± 9.75	ADHD vs C: <0.0001 ADHD-O vs C: <0.0001 ADHD vs ADHD-O: =0.0961
Iron (µg/dL)	98.23 ± 13.67	84.55 ± 12.43	89.06 ± 12.89	ADHD vs C: =0.0006 ADHD-O vs C: =0.0223 ADHD vs ADHD-O: =0.2140
Magnesium (mmol/L)	0.97 ± 0.07	0.80 ± 0.10	0.89 ± 0.07	ADHD vs C: <0.0001 ADHD-O vs C: =0.0003 ADHD vs ADHD-O: =0.0006
Calcium (mmol/L)	2.45 ± 0.13	2.28 ± 0.15	2.41 ± 0.11	ADHD vs C:= 0.0001 ADHD-O vs C: = 0.2601 ADHD vs ADHD-O: =0.0011
Copper (µg/dL)	120.99 ± 15.25	126.81 ± 23.78	111.19 ± 32.88	ADHD vs C: = 0.3203 ADHD-O vs C: =0.1998 ADHD vs ADHD-O:=0.0588

All values are Mean ± SD

Highly significant alterations for serum zinc were found for ADHD vs C ($p < 0.001$), ADHD-O vs C ($p < 0.001$) whereas non-significant change in serum zinc was obtained for ADHD-O vs ADHD-O ($p < 0.0961$) (Table-1).

Serum iron (Table-1) showed highly significant variations for ADHD vs C and ADHD-O vs C but non-significant change for ADHD vs ADHD-O.

Highly significant changes in serum magnesium for ADHD vs C, ADHD-O vs C, and ADHD vs ADHD-O were obtained (Table-1). Effect of omega-3 fatty acid supplementation on serum magnesium in ADHD-O indicated p value for ADHD vs ADHD-O as 0.0006).

Serum calcium was estimated that showed highly significant variations for ADHD vs C, and ADHD vs ADHD-O whereas no significant change for ADHD-O vs C (Table-1).

Serum copper in all groups did not differ significantly (Table-1). Effect of omega-3 supplementation on serum copper in ADHD patients was also found statistically non-significant.

DISCUSSION

Although clear and convincing evidence is lacking (Lange *et al.,* 2017) and there is no enough evidence to prove the clear involvement of nutrient bioelements including zinc and magnesium as the cause of ADHD, though there are reports showing reduced serum/ plasma concentration of zinc, magnesium, calcium and other bioelements in children with ADHD. This basic information, however, may help the clinicians for better management of children with ADHD.

Our report is similar to several of previous reports in children with ADHD showing reduction in serum zinc levels (Colquhoun and Bunday, 1981) and correlation between free fatty acids and serum zinc levels (Colquhoun and Bunday, 1981; Bekaroğlu *et al.,* 1996); efficacy of iron (Konofal *et al.,* 2008); and beneficial role of calcium supplementation (Arab Ameri *et al.,* 2012). However, our results vary from some of the other reports indicating no statistically significant difference of serum magnesium for control vs ADHD group (Stevens *et al.*, 1995; Mousain-Bosc *et al.*, 2006); and no clear role of serum copper levels in ADHD (Salustri *et al.*, 2010).

Significant reduction in serum zinc, iron, magnesium and calcium in ADHD patients without omega-3 supplementation compared to healthy non-ADHD control subjects, and significant increase in these nutrient bioelements after omega-3 supplementation in ADHD reaching to the levels found in healthy non-ADHD control subjects in our present study need further comprehensive studies to be conducted for verification.

Although the definite cause/ causes of ADHD are not yet known, omega-3 and other long-chain polyunsaturated fatty acids (LCPUFA) seem promising in understanding the pathophysiology and exploring additional management of ADHD (Pusceddu *et al.,* 2016).

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