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Original article

The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: A double-blind placebo-controlled trial, followed by an open-label extension☆

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ABSTRACT

Objective: To study the efficacy and safety of phosphatidylserine (PS) containing Omega3 long-chain polyunsaturated fatty acids attached to its backbone (PS-Omega3) in reducing attention-deficit/hyperactivity disorder (ADHD) symptoms in children.
Method: A 15-week, double-blind, placebo-controlled phase followed by an open-label extension of additional 15 weeks. Two hundred ADHD children were randomized to receive either PS-Omega3 or placebo, out of them, 150 children continued into the extension. Efficacy was assessed using Conners' parent and teacher rating scales (CRS-P,T), Strengths and Difficulties Questionnaire (SDQ), and Child Health Questionnaire (CHQ). Safety evaluation included adverse events monitoring.
Results: The key finding of the double-blind phase was the significant reduction in the Global:Restless/impulsive subscale of CRS-P and the significant improvement in Parent impact-emotional (PE) subscale of the CHQ, both in the PS-Omega3 group. Exploratory subgroup analysis of children with a more pronounced hyperactive/impulsive behavior, as well as mood and behavior-dysregulation, revealed a significant reduction in the ADHD-Index and hyperactive components. Data from the open-label extension indicated sustained efficacy for children who continued to receive PS-Omega3. Children that switched to PS-Omega3 treatment from placebo showed a significant reduction in subscales scores of both CRS-P and the CRS-T, as compare to baseline scores. The treatment was well tolerated.
Conclusions: The results of this 30-week study suggest that PS-Omega3 may reduce ADHD symptoms in children. Preliminary analysis suggests that this treatment may be especially effective in a subgroup of hyperactive-impulsive, emotionally and behaviorally-dysregulated ADHD children.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioural disorder affecting 3 to 7% of school-aged children. ADHD can be categorized into three main subtypes according to predominant behavioral features: primarily inattentive, primarily hyperactive-impulsive, and mixed presentation. Although characterized as a childhood disorder, ADHD frequently persists into adolescence in 40 to 70% of cases and into adulthood in 50% of cases [23]. ADHD is a chronic neurological disorder with a complex etiology. Behavioral genetic investigations and twin studies have suggested that it is a highly heritable disorder, and several genes have been linked to its occurrence [14,37]. In addition, various environmental factors such as maternal smoking, excessive alcohol consumption, or preterm birth have been associated with ADHD [1,46].

Phosphatidylserine (PS), an acidic phospholipid (PL) molecule, comprises of a glycerol backbone esterified to the hydroxyl group of the amino acid serine via a phosphate group and to two fatty acids moiety. PS is found mainly in animal innards and in plants, the origin, however, determines the fatty acids composition at position *sn*-1 and 2. Plant-derived PS differs from animal-derived PS mainly in the absence of Omega3 long chain polyunsaturated fatty acids (LC-PUFA). PS has a structural role in maintaining the integrity of cell membranes [30] and was shown to affect multiple neurochemical systems, including the dopaminergic and cholinergic systems [2,8,9,28,44,48]. PS is the most effective acidic PL in

☆ Clinical trial registry information: A single-center, randomized, double-blind, placebo-controlled study of the efficacy and safety of phosphatidylserine-Omega3 in children with attention-deficit/ hyperactivity disorder; URL: http://www.clinicaltrials.gov; identifier: NCT00418184.

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activating protein kinase C [24] and stimulates sodium-potassium dependent ATPases [39]. In addition, PS supplementation increases brain glucose concentration independent of an increase in blood glucose levels [8]. The precise mechanism of action of PS, however, remains unclear. At the clinical level, PS attenuates both physical [22] and mental stress [3,18], which is suggested to be mediated mainly through a reduction in cortisol secretion. Additionally, administration of PS to elderly with age-associated memory impairment, as well as to patients with mild cognitive impairment, results in a consistent improvement in memory test performance [10,12]. Most of the abovementioned PS scientific evidence is based on PS purified from bovine cortex (BC-PS); however, this source which is relatively highly enriched in Omega3 LC-PUFA is no longer available due to safety concerns of the risk for prion contamination.

Similar to PS, Omega3 LC-PUFA have been linked to brain and central nervous system functioning [25,33–35] and a deficiency in Omega3 fatty acids in rats and monkeys is associated with behavioral, sensory, and neurological dysfunction [13,32,47].

The bioavailability of LC-PUFA has been suggested to vary based on its carrier. Wijendran et al. reported that dietary LC-PUFAs attached to PL rather than to triacylglycerol (TG) backbone are more effective substrates for brain tissues accretion in term baboons [45]. Similar results were shown also in mice [20,21]. Similarly, supplementing middle-aged rats with Omega3, mainly Eicosapentaenoic (EPA, C20:5 Omega3) and Docosahexaenoic acid (DHA, C22:6 Omega3) attached to either TG or PL resulted in increased accretion of DHA in brain tissues in the PL-treated group (17 and 42% as compared with control oil-fed rats, respectively) [42]. Improved bioavailability of LC-PUFA conjugated to PL has also been demonstrated for other tissues including liver, lung, plasma, and erythrocytes [7,29,40,45].

Recently, the effect of administration of PL containing Omega3 (PL-Omega3) LC-PUFA, as compared to fish oil, on the executive functions of school children with ADHD was reported [41]. In this study, children received placebo, fish oil or PL-Omega3 (providing 300 mg PS and 250 mg EPA/DHA daily) for 3 months. Efficacy was evaluated using the Test of Variables of Attention (TOVA). Study findings showed a marked improvement in visual sustained attention performance in the PL-Omega3 group, in comparison to both placebo and fish oil supplementation. Additionally, the group of children receiving PL-Omega3 had the highest proportion of children whose symptoms improved, with 11/18 of the PL-Omega3 children becoming asymptomatic versus 3/21 and 7/21 of the control and fish-oil treated children, respectively.

In the present exploratory study, we evaluated the effect of PS-Omega3 in reducing ADHD symptoms in children in a two-phase study: double-blind, placebo-controlled followed by an open-label extension, each consisting of 15 treatment weeks. Children were monitored for their ADHD symptoms through 30 weeks.

2. Subjects and methods

The efficacy and tolerability of PS-Omega3 were initially examined in a 15-week, double-blind, placebo controlled phase (week 0 through week 15) that was subsequently followed by a 15-week open-label extension period (week 15 through week 30).

2.1. Participants

Two hundred participants entered the double-blind phase (133 boys and 67 girls), out of them, 150 continued into the open-label extension. Children aged between 6 and 13 with normal weight and height measurements according to the Israeli standard and who regularly attended school were included if they met the following criteria:

a) confirmed DSM-IV-ADHD diagnosis following assessment by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL) Version 1 [36];
b) a score of at least 1.5 standard deviations above the normal for the patient's age and gender in the Teacher-rated ADHD Rating Scale-IV (RS-IV) School Version;
c) a score of 4 or higher (moderately ill or worse) in the Clinical Global Impression of Severity of Illness (CGI-S) test;
d) willingness of the parent and a teacher who is familiar with the child to participate.

Children were excluded from the study if any of the following conditions existed:

a) girls who reached menarche and presented with three previous regular menstrual cycles;
b) history or current diagnosis of any serious systemic (e.g., diabetes, hyper/hypothyroidism) or neurological condition (e.g., epilepsy, brain tumor);
c) failure to respond to two or more adequate courses of stimulant therapy (among those previously treated children);
d) pervasive developmental disorder (diagnosed according to DSM-IV criteria) or nonverbal learning disability [19,26];
e) diagnosed with psychotic disorders (e.g., schizophrenia) according to the DSM-IV axis;
f) any evidence of suicidal risk or any current psychiatric comorbidity that required psychiatric pharmacotherapy;
g) concomitant use of prescription or nonprescription agents with potent psychotropic properties, including ADHD treatments and dietary supplements, 4-week prior to the study entry;
h) history of alcohol or substance abuse as defined by DSM-IV criteria;
i) consumption of $>$ 250 mg/day of caffeine;
j) history of allergic reactions or sensitivity to marine products, soy, or corn as well as any illness that could jeopardize the participant's health or limit their successful completion of the trial.

Children suffering from ADHD symptoms were recruited using advertisements in newspapers, on the Internet, and in medical centers. The study was conducted according to the principles of the Declaration of Helsinki and good clinical practice and was approved by the Israeli Health Ministry and the institutional review board committee of the Geha Mental Health Center (Petach Tikva, Israel). All parents or legal guardians and children gave their written informed consent prior to participation. Inclusion assessment tools were conducted by a qualified and experienced psychiatrist (K-SADS-PL and CGI-S) or by a psychiatric social worker (K-SADS-PL).

2.2. Study design

The design was a single-center, randomized, double-blind, placebo-controlled phase followed by an open-label extension. Participants were randomly assigned to the study groups according to a computerized randomization process based on random block size using a 2:1 ratio (PS-Omega3: placebo) and stratified by gender. A web-based random allocation procedure was used to enhance the concealment and ease of use.

During the double-blind phase participants received four capsules (two capsules twice a day) of PS-Omega3 or an identical-looking capsule filled with cellulose as placebo. The