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An updated systematic review on the effects of n-3 long-chain polyunsaturated fatty acids on autistic spectrum disorder

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ABSTRACT

Objectives: It has been suggested that omega-3 fatty acids deficiency could play a role in the pathogenesis of several psychiatric disorders, especially autism spectrum disorder (ASD). This systematic review of all available studies was conducted to assess the efficacy of omega-3 fatty acid supplementations on the core features of ASD.

Methods: To find the relevant articles, databases including MEDLINE, EMBASE, PsycINFO, PubMed, Scopus and Cochrane between 1966 and December 2016 were searched. The criteria of selecting studies were English language; oral administration of n-3 fatty acids supplements; clinical trials involving human patients with autism; and relationships between omega-3 fatty acids, DHA or EPA supplementation, as well as fish oil, and autism-related clinical- and social-related outcomes.

Results: We identified 337 articles in the systematic search, nine articles were finally chosen to be included in the review. Most studies have shown that omega-3 fatty acid supplementation can reduce hyperactivity and social problems in individuals diagnosed with autism. However, no significant association has been reported between omega-3 fatty acid supplementation as compared to placebo in behavioral abnormalities in most of the studies.

Conclusion: Based on the available literature, omega-3 fatty acids can act as an effective supplement in individuals with autism.

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Introduction

Autism spectrum disorder (ASD) is a neurological disorder, usually with an onset in early childhood, with symptoms such as problems in social interactions, delay in language skills and restricted behavior patterns. In addition to these core symptoms, children with autism might have serious behavioral problems such as self-injurious behaviors, aggression or tantrums. Although psychopharmacological therapies for autism have been studied for more than 50 years, only two drugs have recently been approved by the Food and Drug Administration (FDA) for the treatment of ASD symptoms (risperidone and aripiprazole for the treatment of irritability) [1]. Complementary and alternative treatments such as administering omega-3 fatty acid supplements, digestive enzymes and high doses of vitamins

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have been used widely despite lack of enough evidence for their effectiveness or safety [2]. Recently, assessing the effectiveness of omega-3 fatty acid supplementation in improving and treatment of autism symptoms has received the attention of many investigators [3]. Several studies have shown that lipids play an essential role in neuronal processes and immune modulating ─ both involved in ASD. Polyunsaturated fatty acids, especially docosahexaenoic acid (DHA), are important in growth and maturation of the brain. Some recent evidence suggests that the metabolism of essential fatty acids may change due to genetic defects and imbalances in ASD [4]. Based on the available evidence, the ratio of omega-6 to omega-3 fatty acids is higher in the blood of children with ASD, while the long-chain polyunsaturated fatty acid (LCPUFA) group concentration in their blood is lower [5].

Mothers of the autistic children usually are not willing to have their sick children treated by drugs, so they look for alternative and effective treatments due to their negligible side effects. Nutritional interventions for children with autism are safer, more holistic and "natural" [6].

Parents who give fish oil supplements to their autistic children have reported improvements in their general health, sleep patterns, cognitive and motor skills, concentration, eye contact and sociability, as well as reduced irritability, aggression and hyperactivity [7].

A review in 2011 found no evidence for the efficacy of omega-3 fatty acids in improving social interaction, communication, stereotypy, or hyperactivity in children with ASD, but a trend towards improved hyperactivity [8].

The results of studies on the benefits of n-3 LCPUFAS for the treatment of ASD are contradictory and with no decisive conclusion. This literature review was conducted to evaluate the effects of omega-3 fatty acids in the improvement and treatment of behavioral symptoms of autism.

Methods

Search strategy and data extraction

In order to find the relevant articles (with no restriction as regards language of publications), six databases including MEDLINE, EMBASE, PsycINFO, PubMed, Scopus and Cochrane between 1966 and December 2016 were searched. The following keywords were used: n-3 PUFA, fish oil, "essential fatty acid", EFA, "ω-3", "omega-3", ALA, "Eicosapentaenoic Acid", EPA, "Docosahexaenoic Acids", DHA, and "liver oil". They were combined with the following search terms for autism: "Child Development Disorders", Asperger, "Autistic Spectrum Disorder", ASDs, autism, "Social Behavior Disorders", "pervasive development disorder" and "autism spectrum disorder", so that finally a total of 337 articles were selected.

Study selection

Two researchers inspected the titles and abstracts independently. The studies with the following criteria were selected: English language; oral administration of n-3 fatty acids supplements; clinical trials involving human patients with autism, and evaluating the relationships between omega-3 fatty acids, DHA or EPA supplementation or fish oil and autism-related clinical- and social-related outcomes. We excluded any other type of documents such as letters, comments, reviews, or ecological and animal studies.

The data extracted by the researchers included full names of authors, country, year of publication, the number of patients included, intervention dose, and changes in clinical- and social-related outcome.

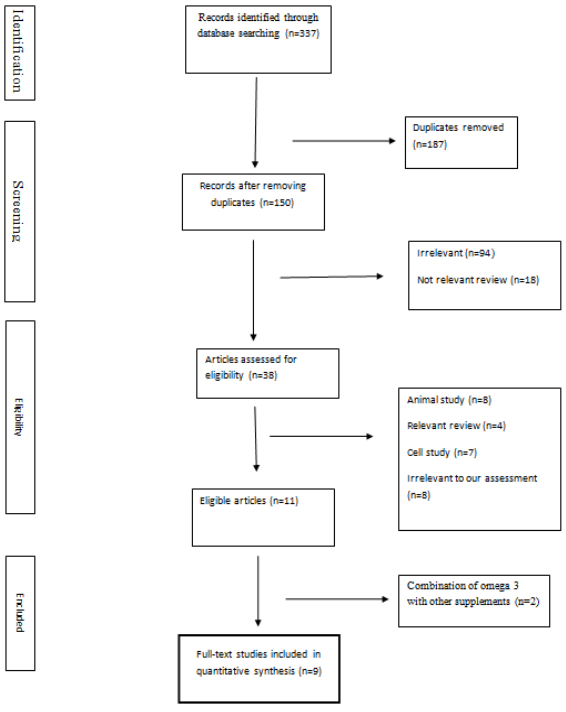

Table 1: Characteristics of the studies included in the review

Authors	Country	Design	Jaded score	No. of patients	Intervention (N)	Received placebo	Omega-3 dosage	Follow-up time (weeks)
Bent et al.	USA	RCT	5	25	13	12	1.3	12
Mankad et al.	Canada	RCT	4	37	19	18	1.5	24
Amminger et al.	Australia	RCT	4	12	7	5	1.5	6
Meiri et al.	Israel	open-label	0	8	8	-	1	12
Bent et al.	USA	RCT	5	57	29	28	1.3	6
Ooi et al.	Singapore	open-label	0	41	41	-	2	12
Politi et al.	Italy	open label	0	19	19	-	1.86	6
Voigt et al.	USA	RCT	5	48	24	24	0.2 (DHA)	24
Yui, et al.	Japan	RCT	5	13	7	6	0.24 (DHA)	16

RCT: Randomized clinical trial

Publication bias

Publication bias was minimized by using multiple online databases in combination with manual reference searches.

Quality Assessment

Two authors independently assessed the quality of each study by the Jadad scale. The Jadad score is calculated based on the following three criteria: methods of blinding, randomization, and reporting of dropouts and withdrawals

Results

Description of included studies

In the electronic literature search, finally 337 articles were identified, from which some were excluded for reasons such as duplication and lack of relevance, as shown in Figure 1; two studies were excluded due to combining omega-3 fatty acids with other supplements. Finally, nine articles met all the inclusion criteria. The characteristics of the included studies are shown in Table 1.

The studies had been carried out in the United States [9-11], Singapore [12], Canada [13], Japan[14] , Israel [3], Italy [15] and Austria [7]. One study included adults [15] and others children. The number of children with autism enrolled in the trials varied widely from eight [3] to fifty-seven [9], and the ages in the studies ranged between 2 and 40 years. And, finally, the omega-3 fatty acids and DHA doses ranged between 0.93 to 2gram/day.

Social Function

One of the most common problems in patients with autism is a pervasive social function [16]. Ooi et al. in an open-label pilot study [12] assessed the effects of omega-3 supplementations on 41 children and adolescents with ASD for 12 weeks. The results showed significant improvements in the ASD-related symptoms such as social awareness, cognition, communication, motivation and attention problems. Concomitant with the results of this study, in another study significant improvements were observed in the withdrawal scores ($P < 0.01$) and the social responsiveness scale (SRS) communication subscale scores ($P < 0.05$) in the omega-3 fatty acid supplementation compared to the placebo group [14]. Also, in another open-label pilot study [17] 1 gram daily, for 12 weeks, of omega-3 fatty acids in ten children 4 to 7 years old with ASD led to improvements in social skills. However, in two studies no significant difference was observed between omega-3 fatty acid-supplementation and placebo groups as regards social functions [10, 13].

Hyperactivity

Bent et al. [9] conducted an internet-based randomized controlled trial to determine the effects of omega-3 fatty acid supplementation on hyperactivity in patients with autism and showed that 1.3 gram/day omega-3 fatty acids for six weeks did not result in any significant improvement in hyperactivity compared to placebo (omega-3 group improvement = 1.9 points higher than placebo, 95% CI, – 2.2 to 5.2, $p = 0.38$). Similar conclusions were drawn in three other studies [10, 11, 17]. However, in a pilot study in 2006, researchers showed that 6 weeks of supplementation with 1.5g/day of omega-3 fatty acids in 13 children 5-17 years old resulted in significant reductions in hyperactivity and stereotypy [7].

Behavioral problems

In most of the studies reviewed no significant changes were observed in behavioral problems due to omega 3 fatty acid supplementation in children with ASD compared to placebo [9, 10, 13, 18], while one study suggested that such supplementation in patients with autism led to a greater remission of irritability [7].

Discussion

Based on the evidence summarized above, omega-3 fatty acid supplementation may bring about some protection effects on autism-related problems such as hyperactivity or communication problems, but no effect on behavioral problems.

According to population-based studies, among subjects with a lower intake of food sources of omega-3 fatty acids such as walnuts, flaxseeds, fish, seafood and fish oils, the rates of psychiatric disorders specially depression and bipolar disorder were higher [19, 20]. N-3 fatty acids, especially DHA, are involved in brain cortical maturation and synaptic signal transduction [21]. Also, in animal studies, it has been shown that perinatal deficits in brain DHA can influence behavioral and neurocognitive processes due to disruption in hippocampus-dependent spatial learning and, finally, lead to some behavioral abnormalities such as anxiety, aggression, and depression [22, 23]. Based on neuroanatomical analyses, autism disorder can be mediated by damage to medial-temporal lobe (hippocampus and amygdala) and the cerebellum. These areas of the brain are prone to damage due to deficiencies of nutrients, specially n-3 polyunsaturated fatty acids [24, 25]. No significant association has been reported between omega-3 intake and behavioral problems in the papers reviewed, except in one open-label study [7], which indicated that omega-3 supplementation can decrease severity of irritability in children with autism. In this systematic review we tried to assess the efficacy of omega-3 fatty acid supplementation in patients with autism based on clinical trial studies. The studies reviewed provide interesting, hypothesis-generating information about omega-3 fatty acid efficacy in autism-related disorders. The strength of this systematic review was the use of rigorous search and methodology. However, some of the studies reviewed had several limitations, which might have influenced their overall conclusions. In three of the studies [12, 15, 17] with an open-label design no effective randomization procedures were used , and the number of samples in some studies [14, 17] was low. Also, in different studies different types of questionnaires were used for assessment of autism-related problems.

Some of the conclusions drawn in our review are in line with those of the Cochrane review [8], although the number of studies included in our review was higher. Furthermore, our study shows that omega-3 fatty acid supplementation in children with autism can decrease the severity of some problems such as hyperactivity and social abnormalities. Finally, we found no adverse events associated with n-3 fatty acids supplementation.

It seems that studies with higher sample sizes are essential to be able to draw more definite conclusions about effective doses of omega-3 fatty acids for individuals with ASD.

Conclusion

Based on this review, there is evidence to support the theory that omega-3 fatty acids supplementation can act as a protective or treatment agent against some problems in individuals with ASD.

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DH and SAH conceived the research idea and designed the research; MR and ER performed data collection and wrote the manuscript draft. MR performed the statistical analysis. DH and SAH interpreted the results, and all authors read and approved the final manuscript.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

1. Lee YJ, Oh SH, Park C, Hong M, Lee AR, Yoo HJ, et al. Advanced pharmacotherapy evidenced by pathogenesis of autism spectrum disorder. Clin Psychopharmacol Neurosci 2014, 12(1), 19-30, DOI: 10.9758/cpn.
2. Green VA, Pituch KA, Itchon J, Choi A, O'Reilly M, Sigafoos J. Internet survey of treatments used by parents of children with autism. Res Dev Disabil 2006, 27(1), 70-84. DOI :10.1016/j.ridd.2004.12.002.
3. Meiri G, Bichovsky Y, Belmaker R. Omega 3 fatty acid treatment in autism. Child Adolesc Psychiatry

2009, 19(4), 449-451. DOI: 10.1089/cap.2008.0123
4. Madore C, Leyrolle Q, Lacabanne C, Benmamar-Badel A, Joffre C, Nadjar A, et al. Neuroinflammation in Autism: Plausible Role of Maternal Inflammation, Dietary Omega 3, and Microbiota. Neural Plast 2016, 2016, 3597209. DOI: 10.1155/2016/3597209
5. Mazahery H, Conlon C, Beck KL, Kruger MC, Stonehouse W, Camargo CA, Jr., et al. Vitamin D and omega-3 fatty acid supplements in children with autism spectrum disorder: a study protocol for a factorial randomised, double-blind, placebo-controlled trial. Trials 2016, 17(1), 295. DOI: 10.1186/s13063-016-1428-8
6. Wong HH, Smith RG. Patterns of complementary and alternative medical therapy use in children diagnosed with autism spectrum disorders. J Autism Dev Disord, 2006,36(7), 901-9. DOI: 10.1007/s10803-006-0131-0
7. Amminger GP, Berger GE, Schafer MR, Klier C, Friedrich MH, Feucht M. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. Biological psychiatry 2007, 15;61(4), 551-3. DOI: DOI: 10.1016/j.biopsych.2006.05.007
8. James S, Montgomery P, Williams K. Omega-3 fatty acids supplementation for autism spectrum disorders (ASD). Cochrane Database Syst Rev 2011, 09(11). DOI: 10.1002/14651858.
9. Bent S, Hendren RL, Zandi T, Law K, Choi JE, Widjaja F, et al. Internet-based, randomized, controlled trial of omega-3 fatty acids for hyperactivity in autism. J Am Acad Child Adolesc Psychiatry 2014, 53(6), 658-66. DOI: 10.1016/j.jaac.2014.01.018.
10. Voigt RG, Mellon MW, Katusic SK, Weaver AL, Matern D, Mellon B, et al. Dietary docosahexaenoic acid supplementation in children with autism. J Pediatr Gastroenterol Nutr 201458(6), 715-22. DOI: 10.1097/MPG.0000000000000260.
11. Bent S, Bertoglio K, Ashwood P, Bostrom A, Hendren RL. A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. J Autism Dev Disord 2011, 41(5), 545-54. DOI: 10.1007/s10803-010-1078-8
12. Ooi YP, Weng SJ, Jang LY, Low L, Seah J, Teo S, et al. Omega-3 fatty acids in the management of autism spectrum disorders: findings from an open-label pilot study in Singapore. EJCN 2015 , 69(8), 969-71. DOI: 10.1038/ejcn.2015.28
13. Mankad D, Dupuis A, Smile S, Roberts W, Brian J, Lui T, et al. A randomized, placebo controlled trial of omega-3 fatty acids in the treatment of young children with autism. Molecular autism. 2015, 6:18. DOI: 10.1186/s13229-015-0010-7.
14. Yui K, Koshiba M, Nakamura S, Kobayashi Y. Effects of large doses of arachidonic acid added to docosahexaenoic acid on social impairment in individuals with autism spectrum disorders: a double-blind, placebo-controlled, randomized trial. J Clin Psychopharmacol. 2012, 32(2):200-6. DOI: 10.1097/JCP.0b013e3182485791
15. Politi P, Cena H, Comelli M, Marrone G, Allegri C, Emanuele E, et al. Behavioral effects of omega-3 fatty acid supplementation in young adults with severe autism: an open label study. Arch Med Res 2008, 39(7):682-5. DOI: 10.1016/j.arcmed.2008.06.005
16. Gilotty L, Kenworthy L, Sirian L, Black DO, Wagner AE. Adaptive skills and executive function in autism spectrum disorders. Child Neuropsychol 2002, 8(4):241-8. DOI: 10.1076/chin.8.4.241.13504
17. Meiri G, Bichovsky Y, Belmaker RH. Omega 3 fatty acid treatment in autism. J Child Adolesc Psychopharmacol. 2009, 19(4):449-51. DOI: 10.1089/cap.2008.0123
18. Politi P, Rocchetti M, Emanuele E, Rondanelli M, Barale F. Randomized placebo-controlled trials of omega-3 polyunsaturated fatty acids in psychiatric disorders: a review of the current literature. Curr Drug Discov Technol 2013, 10(3):245-53. PMID: 21838664
19. Hibbeln JR. Fish consumption and major depression. Lancet 1998, 351(9110),1213. DOI: 10.1016/S0140-6736(05)79168-6.
20. Noaghiul S, Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. Am J Psychiatry. 2003, 160(12):2222-7. DOI: 10.1176/appi.ajp.160.12.2222
21. McNamara RK, Carlson SE. Role of omega-3 fatty acids in brain development and function: potential implications for the pathogenesis and prevention of psychopathology. Prostaglandins Leukot Essent Fatty Acids 2006,75(4), 329-49. DOI: 10.1016/j.plefa.2006.07.010
22. Moriguchi T, Greiner RS, Salem N. Behavioral deficits associated with dietary induction of decreased brain docosahexaenoic acid concentration. J. Neurochem 2000, 75(6), 2563-73. PMID: 11080210
23. Moriguchi T, Salem N. Recovery of brain docosahexaenoate leads to recovery of spatial task performance. J. Neurochem. 2003;87(2):297-309.
24. auman ML. Brief report: neuroanatomic observations of the brain in pervasive developmental disorders. J Autism Dev Disord 1996, 26(2):199-203.
25. Aylward EH, Minshew NJ, Field K, Sparks B, Singh N. Effects of age on brain volume and head circumference in autism. Neurology 2002, 59(2), 175-83.