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Omega-3 Fatty Acid Supplementation - a Potential Treatment for Autism?

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## **Introduction**

Autism is a neurodevelopmental disorder characterized by three distinctive behaviors: inappropriate or inadequate social interactions, impaired language and communication, and repetitive patterns of restricted activities and interests<sup>1</sup>. These behaviors may appear during infancy or after a period of normal development, a finding that is consistent with the fact that autism is a complex disorder with both genetic and environmental components. Several genetic and non-genetic causes of autism have been identified. They include intrauterine infection by rubella or cytomegalovirus, recurrent single-stranded deoxyribose nucleic acid (DNA) microdeletions or microduplications, and alteration in chromosomal number<sup>1</sup>. However, since these causes only account for less than one fifth of the cases, autism continues to remain a puzzle especially in respect to causes and cures.

## **The Process of Neurodevelopment**

Neurodevelopment is a complex and dynamic process. It begins with the formation of a primitive neural tube, followed by the proliferation and differentiation of precursor cells into neurons and glia. At the same time, there are organization of major brain regions, migration of cells from their sites of generation to their final destinations, formation of axonal pathways, and outgrowth of synaptic connections. Myelination is a late-occurring event that allows for the structural maturation of the brain. It progresses most rapidly in the third trimester of pregnancy and early postnatal period, and continues into the third decade of life and possibly beyond<sup>2</sup>. The process of myelination occurs in a well-defined and predictable fashion, and correlates with childhood developmental milestones, such that a disruption of normal myelination may lead to significant developmental delays.

In the late prenatal period, there is a striking increase in the formation of axonal and synaptic connections, resulting in a several fold increase in the volume of the brain. This is followed by a series of regressive events involving apoptosis and pruning of previously-made connections<sup>2</sup>. The process of formation and then reduction is strongly influenced by environmental input, and continues into the adult life. Even though it may appear to be energetically wasteful and inefficient, these processes are absolutely necessary for brain plasticity. It also demonstrates the importance of environmental influences on gene expression in shaping the neural circuits, cognitive abilities, and behaviors.

## **Omega-3 Fatty Acid and Autism**

Approximately 20% of the dry weight of the adult human brain is composed of long-chain polyunsaturated fatty acids, of which docosahexaenoic acid (DHA) is the most abundant one<sup>2,3</sup>. DHA is an omega-3 fatty acid derived from the essential fatty acid precursor  $\alpha$ -linolenic acid. Humans must obtain DHA from their diets, either as DHA itself, its precursor  $\alpha$ -linolenic acid, or the intermediates in the biosynthesis of DHA such as eicosapentaenoic acid (EPA). The

level of DHA in the brain fluctuates with the amount of dietary intake and the stage of life<sup>3</sup>. DHA accumulates rapidly in the grey matter of the cortex in the late prenatal and early postnatal period when the growth in volume is the greatest, and declines progressively during the aging process when there is a reduction in cortical volume. Animal studies showed that DHA enhances synaptic plasticity, and learning and memory by increasing the levels of brain-derived neurotrophic factor (BDNF), a protein that facilitates synaptic transmission in the central and peripheral nervous systems<sup>4,5</sup>.

There is some evidence suggesting an association of DHA deficiency with cognitive and behavioral deficits<sup>3</sup>. A high prevalence of autism is found in infants who are born prematurely or who have low birth weight<sup>6</sup>. Given that the rate of DHA accumulation is the greatest during the third trimester of pregnancy, this may indicate a link between DHA deficiency and autism. The theory concurs with the high 4:1 male-to-female ratio of autism, which could be partly attributed to females being better at synthesizing DHA than males and hence having more DHA available for neurodevelopment than males<sup>7</sup>. It may also explain why advanced maternal age (which is associated with decreased maternal synthesis of DHA), and multiple birth pregnancy (which means the fetuses have to compete for a limited supply of DHA) are risk factors for autism<sup>7</sup>. Vancassel et al. found that autistic children, as compared to mentally retarded ones, have a significant increase in the omega-6 to omega-3 ratio that is attributed to a reduction in the level of omega-3, or more specifically the level of DHA, without any changes in the level of omega-6<sup>8</sup>. Even though Vancassel et al. only studied children between the age of 3 and 17 it may be plausible to extend this finding to include even younger children and hypothesize a relationship between DHA deficiencies and the development of autism.

### **Effects of Omega-3 Fatty Acids Supplementation in Children with Autism**

Amminger et al. conducted a double-blind, randomized, placebo-controlled 6-week study to investigate the effects of omega-3 fatty acids supplementation in Austrian children with autism<sup>9</sup>. Thirteen male children aged 5 to 17 participated in the study; seven of whom received 1.5 g of omega-3 fatty acids (0.7 g of DHA and 0.8 g of EPA) plus 7 mg of vitamin E per day, and six of whom received a placebo consisted of 7 g of coconut oil plus 7 mg of vitamin E per day. The outcomes were assessed using the Aberrant Behavior Checklist (ABC) which has 58 items that are resolved into five subscales: irritability, social withdrawal, stereotypic behavior, hyperactivity and inappropriate speech. At the end of the 6-week period, it was found that omega-3 fatty acids supplementation was superior over placebo for reducing symptoms of hyperactivity and stereotypic behaviors<sup>9</sup>. Given the relatively mild side effects of the supplementation which consist primarily of gastrointestinal upsets, these findings suggest that omega-3 fatty acids may be an effective treatment for children with autism.

Exploring this issue from a different angle, Meguid et al. examined the possible correlation between behaviors and plasma free polyunsaturated fatty acids in Egyptian children with autism before and after fatty acids supplementation in an open label, placebo-control group study<sup>10</sup>. Thirty autistic children (12 females and 18 males) between the age of 3 and 11, and thirty healthy children participated in the study. On average the autistic children had

significantly reduced levels of omega-3 and omega-6 fatty acids, and an elevated omega-6 to omega-3 ratio compared to the healthy children. After three months of Efalex® supplements at a daily dosage of 292 mg of omega-3 fatty acids and 68 mg of omega-6 fatty acids, there was a significant improvement in the plasma levels of the investigated polyunsaturated fatty acids and the omega-6 to omega-3 ratio<sup>10</sup>. In addition, two-third of the autistic children exhibited a statistically significant improvement with regard to the autistic behaviors as measured by the Childhood Autism Rating Scale (CARS), a 15-item assessment that diagnoses and estimates the severity of autistic symptoms based on direct observation and parent reports<sup>10</sup>. Consequently, the study concluded that supplementation of polyunsaturated fatty acids such as omega-3 and omega-6 may ameliorate and improve symptoms of autism.

However, the beneficial effects of omega-3 fatty acid supplementation in autism may diminish with age. Politi et al. investigated the effect of a daily 0.93 g of EPA and DHA plus 5 mg of vitamin E in an open-label study consisting of nineteen severely autistic adults (4 females, 15 males) aged 18 to 40 years<sup>11</sup>. The study uses the Rossago Behavioral Checklist (RBC), a 22-item ad-hoc caregiver questionnaire focusing on behavioral problems, to assess behavioral changes over a period of 18 weeks. No significant improvements in terms of the frequency or severity of problematic behaviors were noticed during the 6-week pre-treatment observational period, 6-week treatment period, or 6-week post-treatment observational period<sup>11</sup>. These results suggested that omega-3 supplementation may not have any beneficial effects in alleviating problematic behaviors in adults with severe autism.

## **Discussion**

Omega-3 polyunsaturated fatty acids supplementation has been shown to be beneficial in a number of psychiatric illnesses including attention deficit hyperactivity disorder and anxiety disorder<sup>12</sup>. Since autistic children exhibit many of the hyperactive symptoms such as distractibility, impulsivity, and disobedience, it is certainly possible that omega-3 supplementations may also play a beneficial role in mitigating these behavioral problems. Animal studies conducted by Salvati et al. showed that EPA and DHA injections stimulated the process of myelination<sup>13</sup> which is crucial to the proper functioning of both the central and peripheral nervous systems. Even though this effect has not been successfully studied in humans, there is still potentially a role for EPA and DHA to enhance human brain function. Moreover, recent research has found that dynamic structural remodeling of the brain does not only take place during the critical period but also in later life<sup>14</sup>, supporting the notion that events occurring after the critical period can influence the structure and hence the functioning of the brain in a positive or negative direction. Consequently, supplementation of omega-3 fatty acids to restore the absolute DHA level as well as the omega-6 to omega-3 ratio may play a beneficial effect in structural remodeling of the brain, improving brain functions, and ameliorating the behavioral symptoms exhibited by children with autism.

To date, there have only been a few studies investigating the role of omega-3 fatty acid supplementation in autism. Their descriptions and findings are summarized in Table 1. The results of studies conducted by Amminger et al. and Meguid et al. are supportive of omega-3

supplementation in autistic children, while the results of study conducted by Politi et al. are unresponsive of omega-3 supplementation in autistic adult. The interpretation of these results is limited by the studies' small sample sizes (13 - 60 subjects), short intervention duration (6 - 12 weeks), differences in entry-criteria (age range, ethnicities, ABC versus CARS), differences in methods for assessing improvements (ABC versus CARS versus RBC), and the fluctuating nature of the outcomes measured.

There are limitations specific to each study, including a use of repeated-measures analysis which may cause misinterpretation of the data in the study conducted by Amminger et al., a lack of blinding in the study conducted by Meguid et al, and a lack of a control group in the study conducted by Politi et al. Despite these shortcomings, it is recognized that omega-3 supplementation may have beneficial effects in children with autism, although this effect may phase out with age such that it has no beneficial effects in adults with autism. Therefore, better designed, larger-scale, longer-study period, randomized, and placebo-controlled studies are necessary before any definitive recommendations regarding the role of omega-3 supplementation in treating children with autism may be made.

Taking this a step further, there is a possibility that omega-3 supplementation during pregnancy may play a role in the prevention of autism. In a randomized and double-blind study, Helland et al. found that maternal supplementation with omega-3 fatty acids (from cod liver oil) during pregnancy and lactation improves the intelligence of children at 4 years of age as assessed by the Kaufman Assessment Battery for Children<sup>15</sup>. Even though the relationship between a maternal omega-3 fatty acid deficiency and the development of autism has not been well studied, given the importance of omega-3 fatty acids in the neurodevelopment process and the possible beneficial effects of omega-3 supplementation in treating autism, it is not too farfetched to hypothesize that adequate levels of omega-3 during pregnancy may decrease the risk of autism.

Unfortunately, the majority of pregnant women who follow the typical Western diet do not consume an adequate amount of omega-3 fatty acids, especially because their seafood intake, a major source of omega-3 fatty acids, is limited to 2 servings per week as recommended by the Food and Drug Administration<sup>16</sup>. Therefore, it is likely beneficial for pregnant women to take omega-3 fatty acid supplements. Freeman et al. showed that 1.84 g/day of DHA and EPA was well tolerated by pregnant women, with few side effects such as unpleasant breath, bad taste, and heartburn<sup>17</sup>. However, more research is necessary to determine the role of omega-3 supplementation in autism prevention.

## **Conclusion**

There is still much to learn about the role of omega-3 fatty acids in neurodevelopment. In recent years, increasing evidence has emerged indicating that omega-3 fatty acid deficiencies or imbalances may be associated with childhood neurodevelopmental disorders including attention-deficit hyperactivity disorder and autism spectrum disorders<sup>18</sup>. As a result, it is reasonable to hypothesize that a restoration of this level may have some beneficial effects in treating children with autism. Several clinical trials attempted to study this, but their findings

were not yet strong enough to support a definitive recommendation. This suggests a need for better designed, larger-scale, randomized, placebo-controlled trials to tease out the subtleties involved in this kind of studies. Furthermore, besides focusing on studies with clinical end points, research efforts should also be directed at understanding the role of omega-3 fatty acids in the development of autism. This will not only help in identifying future treatment but also future prevention for autism.

Author, date and country	Patient group	Study type & outcome measure	Key results & conclusion	Study weaknesses
Amminger et al. 2007. Austria	<p><u>Group 1</u>: 7 male autistic children aged 5 to 17 received 1.5 g of omega-3 fatty acids plus 7 mg of vitamin E per day for 6 weeks</p> <p><u>Group 2</u>: 6 male autistic children aged 5 to 17 received 7 g of coconut oil plus 7 mg of vitamin E per day for 6 weeks</p>	<p><u>Study type</u>: double-blind, randomized, placebo-controlled</p> <p><u>Outcome measure</u>: symptoms were assessed at baseline and at 6-week follow-up after the intervention using the Aberrant Behavior Checklist</p>	<p><u>Key result</u>: remission of hyperactive and stereotypic symptoms in group 1 (treatment group) as compared with group 2 (placebo group)</p> <p><u>Conclusion</u>: omega-3 supplementation was superior over placebo for reducing symptoms of hyperactivity and stereotypic behaviors in autistic children</p>	Small number of subjects, short intervention period, possible misinterpretation of the data by the use of repeated-measures analysis
Meguid et al. 2008. Egypt	<p><u>Group 1</u>: 30 autistic children (12 females and 18 males) aged 3 to 11 received 292 mg of omega-3 fatty acids and 68 mg of omega-6 fatty acids per day for 3 months</p> <p><u>Group 2</u>: 30 healthy children received 292 mg of omega-3 fatty acids and 68 mg of omega-6 fatty acids per day for 3 months</p>	<p><u>Study type</u>: open label with a placebo-control group</p> <p><u>Outcome measure</u>: blood fatty acid status was determined at baseline and at 3-month follow-up using tandem mass spectrometry; autistic behavior was assessed at baseline and at 3-month follow-up after the intervention using Childhood Autism Rating Scale</p>	<p><u>Key results</u>: correction of blood fatty acid status (increase in serum linolenic, DHA, linoleic, and arachidonic acids), and improvement in autistic behavior</p> <p><u>Conclusion</u>: omega-3 supplementation may ameliorate and improve symptoms of autism in children</p>	Small number of subjects, risk of bias due to a lack of blinding of persons involved in this study
Politi et al. 2008. Italy	19 severely autistic adults aged 18 to 40 received 0.93 g of EPA and DHA plus 5 mg of vitamin E per day for 6 weeks	<p><u>Study type</u>: open-label without a placebo-control group</p> <p><u>Outcome measure</u>: problematic behaviors were assessed daily using the Rossago Behavioral Checklist during the 6-week pre-treatment period, 6-week treatment period, and 6-week post-treatment period</p>	<p><u>Key result</u>: no change in frequency and severity of problematic behaviors was detected</p> <p><u>Conclusion</u>: omega-3 supplementation may not have any beneficial effects in alleviating problematic behaviors in adults with severe autism</p>	Small number of subjects, no control group for comparison

**Table 1:** This table describes and summarizes the findings of studies conducted by Amminger et al., Meguid et al., and Politi et al.

## References

1. Rapin I, Tuchman RF. Autism: Definition, Neurobiology, Screening, Diagnosis. *Pediatric Clinics of North America*. 2008 Oct; 55(5):1129-46, viii.
2. Wainwright PE. Dietary Essential Fatty Acids and Brain Function: A Developmental Perspective on Mechanisms. *The Proceedings of the Nutrition Society*. 2002 Feb; 61(1):61-9.
3. Innis SM. Dietary (n-3) Fatty Acids and Brain Development. *The Journal of Nutrition*. 2007 Apr; 137(4):855-9.
4. Gomez-Pinilla F. Brain foods: the effects of nutrients on brain function. *Nature Reviews. Neuroscience*. 2008 Jul; 9(7):568-78.
5. Wu A, Ying Z, Gomez-Pinilla F. Docosahexaenoic acid dietary supplementation enhances the effects of exercise on synaptic plasticity and cognition. *Neuroscience*. 2008 Aug 26; 155(3):751-9.
6. Limperopoulos C, Bassan H, Sullivan NR, et al. Positive Screening for Autism in Ex-preterm Infants: Prevalence and Risk Factors. *Pediatrics*. 2008 Apr; 121(4):758-65.
7. Field SS. Omega-3 Fatty Acids, Prematurity, and Autism. *Pediatrics*. 2008 Dec; 122(6):1416-7.
8. Vancassel S, Durand G, Barthelemy C, et al. Plasma Fatty Acid Levels in Autistic Children. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. 2001 Jul; 65(1):1-7.
9. Amminger GP, Berger GE, Schafer MR, et al. Omega-3 Fatty Acids Supplementation in Children with Autism: A Double-blind Randomized, Placebo-controlled Pilot Study. *Biological Psychiatry*. 2007 Feb 15; 61(4): 551-3.
10. Meguid NA, Atta HM, Gouda AS, Khalil RO. Role of Polyunsaturated Fatty Acids in the Management of Egyptian Children with Autism. *Clinical Biochemistry*. 2008 Sep; 41(13):1044-8.
11. Politi P, Cena H, Comelli M, et al. Behavioral Effects of Omega-3 Fatty Acid Supplementation in Young Adults with Severe Autism: An Open Label Study. *Archives of Medical Research*. 2008 Oct; 39(7):682-5.
12. Ross BM, Sequin J, Sieswerda LE. Omega-3 Fatty Acids as Treatments for Mental Illness: Which Disorder and Which Fatty Acid? *Lipids in Health and Disease*. 2007 Sep 18; 6:21.
13. Salvati S, Natali F, Attorri L, et al. Eicosapentaenoic Acid Stimulates the Expression of Myelin Proteins in Rat Brain. *Journal of Neuroscience Research*. 2008 Mar; 86(4):776-84.
14. Lee WC, Chen JL, Huang H, et al. A Dynamic Zone Defines Interneuron Remodeling in the Adult Neocortex. *Proceedings of the National Academy of Sciences of the United States of America*. 2008 Dec 16; 105(50):19968-73.
15. Helland IB, Smith L, Saarem K, et al. Maternal Supplementation with Very-Long-Chain n-3 Fatty Acids During Pregnancy and Lactation Augments Children's IQ at 4 Years of Age. *Pediatrics*. 2003 Jan; 111(1):e39-44.
16. Greenberg JA, Bell SJ, Ausdal WV. Omega-3 Fatty Acid Supplementation During Pregnancy. *Reviews in Obstetrics and Gynecology*. 2008 Fall; 1(4):162-9.
17. Freeman MP, Sinha P. Tolerability of Omega-3 Fatty Acid Supplements in Perinatal women. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. 2007 Oct-Nov; 77(3-4):203-8.



18. Richardson AJ. Long-Chain Polyunsaturated Fatty Acids in Childhood Developmental and Psychiatric Disorders. *Lipids*. 2004 Dec; 39(12):1215-22.