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IMPACT OF OMEGA-3 FATTY ACIDS SUPPLEMENTATION ON AUTISM SPECTRUM DISORDERS: SYSTEMATIC REVIEW BASED ON RANDOMIZED CONTROLLED CLINICAL TRIALS

IMPACTO DA SUPLEMENTAÇÃO DE ÁCIDOS GRAXOS ÔMEGA-3 NOS TRANSTORNOS DO ESPECTRO AUTISTA: REVISÃO SISTEMÁTICA BASEADA EM ENSAIOS CLÍNICOS RANDOMIZADOS E CONTROLADOS

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ABSTRACT

Autism spectrum disorders (ASDs) are neurodevelopmental dysfunctions associated with a number of altered behavioral symptoms, including reduced social interactions and the performance of repetitive activities. Pharmacological treatment is currently limited, and appears to contribute to the development of cardiovascular morbidity. Associated with this profile, a restricted and selective dietary pattern promotes the development of several nutritional deficiencies, including essential fatty acids, such as omega-3 (ω-3). In this systematic review, based on randomized controlled trials, studies performed in the last 10 years were selected. The results show that the heterogeneity of the populations studied, with wide variation in the dose and type of ω-3 administered at different times during follow-up, hinder more precise assessment of the effectiveness of the intervention based on the use of ω-3. Thus, the use of ω-3 as adjuvant therapy in the treatment of ASDs should not be routinely recommended in clinical practice, even though it is essential for proper neurological development.

Keywords: Autism Spectrum Disorders; Fatty Acids, Omega-3; Cardiovascular Diseases; Nutritional Status.

RESUMO

Os transtornos do espectro autista (TEAs) são disfunções do desenvolvimento neurológico associadas à alteração de diversos sintomas comportamentais, nos quais se destacam a redução de interações sociais e a execução de atividades repetitivas. Atualmente, o tratamento farmacológico é limitado e parece contribuir para o desenvolvimento de morbidades cardiovasculares. Associado a esse perfil, o restrito e seletivo padrão alimentar, promove o desenvolvimento de diversas deficiências nutricionais, entre as quais, os ácidos graxos essenciais como o ômega-3 (ω-3). Nesta revisão sistemática, baseada em estudos randomizados e controlados, foram selecionados estudos realizados nos últimos 10 anos. Os resultados mostram que a heterogeneidade das populações estudadas com grande variação na dose e tipo de ω-3 administrados em tempos distintos de seguimento dificultam a avaliação precisa da eficácia da intervenção baseada no uso de ω-3. Desta forma, o uso de ω-3 como terapia adjuvante no tratamento de TEA não deve ser recomendado rotineiramente na prática clínica, apesar de sua essencialidade para o adequado desenvolvimento neurológico.

Descritores: *Transtorno do Espectro Autista; Ácidos Graxos Ômega-3; Doenças Cardiovasculares; Estado Nutricional.*

INTRODUCTION

Autism Spectrum Disorders (ASD) are a group of neurodevelopmental disorders that affect social interaction, communication and behavior. The term "autist" was first used in 1908 by the Swiss psychiatrist Eugen Bleuler to describe a disease characterized by social isolation of patients.[1] The first treatment for autism arose in 1952 following the publication of the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-I)[2], which established the standard nomenclature and criteria for diagnosing mental disorders.

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The third edition of the DSM was published in 1980 and autism was included as a separate diagnostic category. In 1995, several subtypes of autism spectrum disorders were added, such as Asperger's syndrome, Rett's syndrome, Heller's syndrome and pervasive developmental disorders not otherwise specified.[2] In 2013, ASD was classified by severity: level 1 - requiring support, level 2 - requiring substantial support, and level 3 - requiring very substantial support.[2]

The disorder is characterized by qualitative abnormalities in reciprocal social interactions and patterns of communication, as well as a restricted, stereotyped and repetitive repertoire of interests and activities.[2] The etiology of the disorder is not yet known, but it is considered to be multifactorial in nature and result from an interaction between environmental and genetic factors.[3,4] Although the etiological factors associated with ASD remain largely unknown, there is an increasing number of studies relating these disorders to a higher incidence of *diabetes mellitus*, obesity and dyslipidemia.[5] The study of De Vinck-Baroody et al.[6] found a 16% higher risk of obesity in individuals with ASD. Furthering the evidence for higher cardiovascular risk in individuals with ASD, a study by Tyler et al.[7] examined 108 adults with ASD and found that 34.9% were obese, 31.5% had dyslipidemia and 19.4% were hypertensive. These associations were recently confirmed in a population-based study conducted in Taiwan which found a 2.7 and 5.3 fold increased incidence of *diabetes mellitus* in adolescents and young adults with ASD, respectively, compared to the general population.[8] These authors also discussed the potential of a possible pathophysiological connection between these diseases.

Scientific evidence suggests that prenatal and postnatal injuries, nutritional deprivation or problems, mitochondrial disorders, oxidative stress, gastrointestinal disorders or immune disorders can play a role in the etiology of ASD.[9] ASD may also be caused by maternal metabolic abnormalities that occur before and during pregnancy.[10] Moreover, some congenital conditions apparently increase the risk of ASD, as evidenced by the study of Jaworski et al.[11] who conducted a follow up of 198 children with congenital heart disease for four years. These children were at an increased risk of developing ASD compared with the general pediatric population as assessed by multiple medical and behavioral questionnaires. Subsequently, Tsao et al.[12] confirmed the association between ASD and congenital heart disease.

The incidence of ASD has greatly increased over the past two decades; globally 1 to 2% of children have ASD.[13] Studies show that there are two undiagnosed cases for every three cases diagnosed.[14] Studies have shown that 1 in 68 children are diagnosed with the disorder in the United States, while 1 in 30 are diagnosed with ASD in Korea.[4] It is more common in males and affects children of different ethnicity and socioeconomic status indiscriminately.[4] The incidence of ASD is two to three times higher in male children and gender-associated differences in genetics, epigenetics, endocrinology and environmental responses may be a key component of the pathophysiology of this neurodevelopmental disorder.[15]

This increased incidence of ASD is possibly due to changes in dietary patterns associated with increased consumption of processed products and saturated fatty acids[14] and the development of broader diagnostic criteria, such as lower thresholds for clinical diagnosis and advanced parental age.[16]

This disorder is characterized by behavioral impairments, such as selectivity, refusal and nutritional ill-discipline. Children with autism show five times greater food selectivity compared to that of other populations.[17] The high prevalence of food restriction in this population may have a negative impact on both child and family. Parents consistently report concerns about the eating habits of their children[18] and this can add stress to the family environment.[19]

In addition to language development and social interaction impairments, children with autism can have gastrointestinal disorders, e.g. decreased production of digestive enzymes, inflammation of the intestinal wall and alterations in intestinal permeability.

Although research is inconclusive, several studies have shown that children with autism can be at a high nutritional risk due to limited food variety. These children have deficiencies in magnesium, vitamin B6 and essential fatty acids.[20,23] Food selectivity and minimal food variety have been associated with aggressiveness, internalizing and externalizing repetitive behaviors, anxiety and sensory reactivity.[24,25] In addition to this profile, there is also a selectivity for certain people and limited interaction with groups, which is usually associated with reduced social interaction and participation in group games and activities during childhood and adolescence.[26] These stereotypic behaviors contribute to several nutritional deficiencies and increased occurrence of cardiovascular risk factors associated with being overweight and obesity, as shown in several studies.[27] This has a direct impact on the higher incidence of cardiovascular disease in individuals with ASD compared to the general population.[28]

The deficiency and effects of supplementation with omega-3 polyunsaturated fatty acid (PUFA) in children with ASD has been the focus of several studies.[17,24,29] Dietary intake or supplementation with omega-3 is apparently beneficial with respect to social communication disorders, stereotyped behaviors and hyperactivity, as well as aggressiveness and irritability.[30]

Despite the possible relationship between omega-3 and ASD, there are few proposed mechanisms or randomized controlled clinical studies. Animal studies indicate that antioxidant pathways[31] and greater incorporation of omega-3 into cell membranes can optimize cellular fluidity and functionality.[32] However, studies based on the use of biochemical markers and clinical parameters, which inform the efficacy of omega-3 supplementation, are scarce.

Considering that individuals with ASD are at risk of developing multiple cardiovascular risk factors, the objective of this systematic review was to provide an overview of the impact of omega-3 fatty acid supplementation on cognition, behavior and cardiovascular risk factors in individuals with ASD.

MATERIAL AND METHODS

This is a systematic literature review that includes randomized controlled clinical trials conducted from 2007 to 2017. The review of the literature was performed using the PubMed, SciELO and LILACS databases and the following descriptors: Autism Spectrum Disorder, omega-3, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), eicosapentaenoic acid, docosahexaenoic acid, linolenic acid, autism, children and

adolescents. Studies published in English, Portuguese and Spanish were accepted. The assumptions for identification and selection of articles were based on the criteria established by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[33] and the qualitative and critical assessment was based on the PICO criteria (Participant, Intervention, Comparison and Outcome)[34] described in Chart 1.

RESULTS

Figure 1 describes the selection of articles and indicates the number of excluded articles and the reasons for each exclusion (n=67).

A total of 11 articles published from 2007 to 2017 were selected and all met the PICO criteria, although the studies offered fluctuating levels of detail. Based on the 11 selected articles, the sample size ranged from 10 to 57 individuals, the age ranged from 2 to 28 years, the follow-up time ranged from one to six months and the interventions included exclusive DHA supplementation (200 mg/day), combination of EPA and DHA (EPA: from 13 mg/day to 693 mg/day and DHA: from 60 mg/day to 840 mg/day), as well as a combination of PUFAs, as described in Table 1.

DISCUSSION

Despite scientific advances in the treatment of neurodevelopmental disorders, longitudinal clinical studies are still scarce. The treatment of ASD is currently based on intensive educational and behavioral strategies introduced in early childhood.[35] Psychopharmacological therapies have been studied for more than 50 years and, to date, only the antipsychotics Risperidone and Aripiprazole have been approved to control the irritability seen in individuals with ASD.[36]

The use of atypical antipsychotics to treat ASD symptoms is controversial as they can be associated with adverse cardiovascular events.[37] Straus et al.[38] conducted a retrospective cohort study with follow-up at seven years on 481,744 participants aged 18 years and over to assess the risk of sudden death associated with antipsychotics. The data was obtained from the Integrated Primary Care Information (IPCI) based on about 150 hospital units in the Netherlands. The study was conducted prior to the introduction of Risperidone and, therefore, did not include newer atypical agents. However, the results indicated that the use of antipsychotics in the general population is associated with an increased risk of sudden cardiac death, even at low doses and in people who use antipsychotics for indications other than schizophrenia.

Chart 1. PICO criteria for qualitative assessment of controlled clinical trials.

P should provide relevant information about the study participants. Who are the study participants? The question is about who? What is the context? Are they sick individuals? What is the disease? Ultimately, what is the problem?
I informs about the type of treatment/action/intervention that is being studied, analyzed.
C defines the comparison intervention, which can be a drug treatment, exercise or nutritional supplement.
O leads to the results we hope to find with the study. **O** is the clinical indicator of the change in the patient's condition after the intervention.

De Winter et al.[39] included 980 participants with borderline to profound intellectual disability in a cross-sectional study and found no association between metabolic syndrome and the use of atypical antipsychotics. However, the authors acknowledged that these results were probably due to a lack of statistical power and lack of information about treatment duration.

A very elegant meta-analysis of randomized and blinded clinical trials aimed at comparing 15 antipsychotic drugs and placebos in the acute treatment of schizophrenia (including Risperidone and Aripiprazole) analyzed several outcomes, including weight gain, extrapyramidal side effects, increased prolactin levels and QT interval prolongation (duration of systole). The results showed that Paliperidone and Risperidone were associated with increased prolactin levels compared to other drugs and Aripiprazole was not associated with QT interval prolongation. However, all drugs were associated with a greater weight gain compared to the placebo.[40] This agrees with the study of Cashin et al.[41] which showed that individuals with ASD have a high prevalence of comorbidities and increased risk of chronic diseases.

Bishop-Fitzpatrick et al.[42] conducted the first study to characterize health problems in individuals with ASD using a machine learning algorithm based on population-representative mortality data. The study collected information about 91 descendent individuals with ASD and 6,186 community controls who had died since 1979 and were mostly middle aged or older at the time of their death. All ICD-9 codes, V-codes and E-codes available at the electronic health record of the Marshfield Clinic in the United States were analyzed. The decedent individuals with ASD had an increased risk of coagulopathy, congestive heart failure, iron-deficiency anemia, hydroelectrolytic disorders, hypothyroidism, paralysis, heart valve disease and neurological disorders compared to all community controls combined. This study was of importance as it was the first to show high rates of cardiovascular disease in individuals with ASD.

Therefore, this review reinforces the importance of studies on adjuvant therapies to control ASD that can affect the development of cardiovascular risk factors. The search for alternatives for the treatment of ASD raised the hypothesis that fatty acid metabolism disorders could be associated with mental disorders. Omega-3 fatty acids are the most studied as they are considered essential components of nerve cell membranes and fundamental to brain development.[52]

Cysneiros et al.[37] suggested that omega-3 fatty acid supplementation in ASD patients treated with atypical antipsychotics can be an important co-adjuvant in the treatment of ASD due to the beneficial cardioprotective effects of omega-3.

There is an increasing number of studies in the literature aimed at establishing a relationship between omega-3 fatty acids and neurodevelopmental disorders, such as ASD.[36,46]

In a double-blind randomized controlled trial, Amminger et al.[43] evaluated the effects of 1.5 g/day omega-3 supplementation (120 mg EPA/day + 100 mg DHA/day + 1 mg vitamin E) for six weeks in 13 children with ASD aged 5 to 17 years. The placebo group received gelatin capsules containing 1 g of coconut oil, 1 mg of vitamin E and 1 mg of fish oil to mimic the taste of the other interventions. Coconut oil was selected

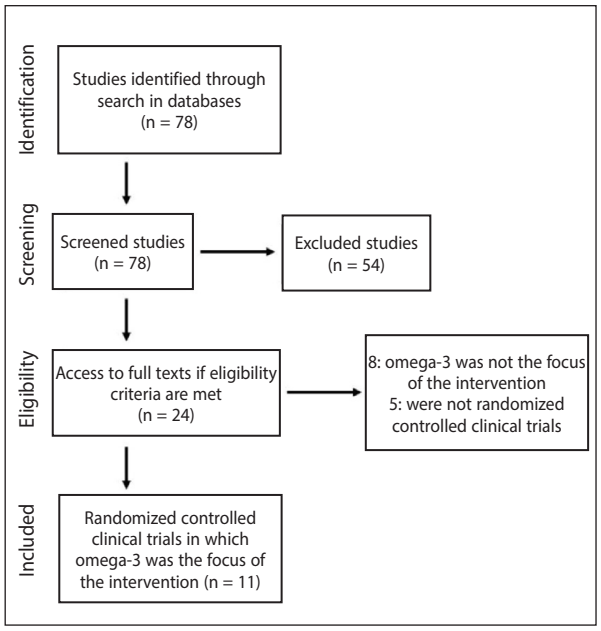

Figure 1. Flowchart of the selection of randomized controlled studies on autism spectrum disorders and omega-3 fatty acids according to the PRISMA criteria.

as it does not contain PUFAs and has no effect on omega-3 fatty acid metabolism. Outcome was assessed using the Aberrant Behavior Checklist (ABC), which of 57 behaviors which are typical of ASD and are organized into five areas: sensory, relating, body image, language, social interaction and self-care. In this study, the supplemented group showed improved social interaction and argumentation. Therefore, the results of this study provide preliminary evidence that omega-3 fatty acids may be effective in the treatment of children with autism.

Meguid et al.[44] evaluated the effects of DHA (60 mg/day), EPA (13 mg/day), AA (5 mg/day) and gamma-linolenic acid - GLA (12 mg/day) supplementation for three months in 30 children with ASD (18 boys and 12 girls) aged 3 to 11 years. The control group consisted of 30 age and gender-matched healthy children. The Childhood Autism Rating Scale (CARS) was used to assess the efficacy of the intervention, which consists of a 15-item scale that evaluates interaction with people, imitation, emotional response, body use, object use, adaptation to change, response to visual and auditory stimuli, response to and use of taste, smell and touch; fear or nervousness, verbal communication, nonverbal communication, activity level, level and coherence of the intellectual response and general impressions. This tool helps diagnose and identify

Table 1. Studies selected to analyze the impact of omega-3 fatty acid supplementation on individuals with ASD.

Author	Sample size	Age range	Intervention strategy	Follow-up	Monitored Outcomes	Result
Amminger et al (2007)[43]	13	5 – 17 years	120 mg EPA + 100 mg DHA + 1 mg vitamin E	6 weeks	ABC	Positive
Meguid et al (2008)[44]	30	3 – 11 years	13 mg EPA + 60 mg DHA + 5 mg AA + 12 mg GlA	12 weeks	CARS	Positive
Meiri et al (2009)[45]	10	4 – 7 years	380 mg EPA + 180 mg DHA	12 weeks	ATEC	Positive
Bent et al (2011)[46]	27	3 – 8 years	350 mg EPA + 230 mg DHA	12 weeks	ABC	Neutral
Yui et al (2011)[47]	13	6 – 28 years	240 mg DHA + 240 mg ARA + 0.96 mg astaxanthin	16 weeks	ABC, ADI-R, PUFAS plasmáticos	Positive
Yui et al (2012)[48]	13	6 – 28 years	240 mg DHA + 240 mg ARA + 0.96 mg astaxanthin	16 weeks	ABC, SRS, transferrina plasmática e superóxido dismutase	Positive
Bent et al (2014)[49]	57	5 – 8 years	350 mg EPA + 230 mg DHA	6 weeks	ABC	Neutral
Voigt et al (2014)[50]	48	3 – 10 years	200mg DHA	6 months	CGI-I	Neutral
Mankad et al (2015)[36]	38	2 – 5 years	EPA + DHA – 1500mg	6 months	PDDBI, BASC-2, CGI-I, VABS-II, PLS-4	Negativo
Ooi et al (2015)[51]	41	7 – 18 years	192 mg EPA + 840 mg DHA + 66 mg AA + 144 g GLA + 60 mg vitamin E + 3 mg thyme oil	12 weeks	SRS, CBCL, amostras de sangue	Positive
Parellada et al (2017)[32]	68	5 – 17 years	693 mg EPA + 462 mg DHA + 2.01 mg vitamin E	8 weeks	Composição de ácidos graxos na membrana eritrocitária, antioxidantes plasmáticos, SRS, CGI-I	Positive

ABC: Aberrant Behavior Checklist; CARS: Childhood Autism Rating Scale; ATEC: Autism Treatment Evaluation Checklist; ADI-R: Autism Diagnostic Interview-Revised; SRS: Social Responsiveness Scale; CGI-I: Clinical Global Impression; PDDBI: Pervasive Developmental Disorders Behavioral Inventory; BASC-2: Behavior Assessment System for Children; VABS-II: Adaptive Behavior Scale; PLS-4: Preschool Language Scale; CBCL: Social and Attention Problems Syndrome Scales of the Child Behavior Checklist.

children with autism and is sensitive in distinguishing autism from other neurodevelopmental disorders. This questionnaire can be used to differentiate the level of autism as mild, moderate or severe. Twenty children in the supplemented group showed a clinically relevant improvement in classic ASD behaviors.

In the study of Meiri et al.[45], 10 children (aged four to seven years old) with ASD were supplemented for 12 weeks with two 500 mg/day omega-3 fatty acid capsules containing 190 mg EPA and 90 mg DHA. The assessment was done using the Autism Treatment Evaluation Checklist (ATEC), which consists of 77 items divided into four parts which address the areas of language, sociability, sensory/cognitive perception and health/behavior. Of the nine children who completed the study, eight showed improvement in 33% of the symptoms assessed in the applied questionnaire.

Bent et al.[46] conducted a randomized controlled pilot study to determine the viability, initial safety and efficacy of omega-3 fatty acid supplementation through the consumption of orange flavored puddings containing 350 mg EPA and 230 mg DHA, in a total of 1.3 g of omega-3/day was administered. The study included 27 children aged 3 to 8 years with ASD as well as symptoms of hyperactivity. After 12 weeks of supplementation, the Aberrant Behavior Checklist (ABC scale) was used. This consists of 58 items divided into five subscales: I - irritability, agitation and crying (15 items); II - lethargy and social avoidance (16 items); III - stereotyped behavior (7 items); IV - hyperactivity (16 items); V - inappropriate speech (4 items). An improvement in the hyperactivity of the supplemented group was seen and this was correlated with the expected increase in the percentage of omega-3 fatty acids in the serum of supplemented children. However, there was no significant difference compared to the control group.

In 2011, Yui et al.[47] analyzed the efficacy of PUFA (AA and DHA) supplementation with respect to repetitive and stereotyped behavior in individuals with ASD in a 16-week randomized double-blind placebo-controlled study that included 13 individuals with ASD aged 6 to 28 years. The supplemented group (n=7) received six daily SUNTGAS20 capsules containing 40 mg DHA/capsule, 40 mg AA/capsule and 0.16 mg astaxanthin/capsule, while the control group (n=6) received six identical daily capsules containing only olive oil. The results were evaluated using the Aberrant Behavior Checklist (ABC scale) and the repetitive behaviors were evaluated by the Autism Diagnostic Interview-Revised (ADI-R), which is a semi-structured diagnostic interview consisting of five sections: introductory questions; questions about communication; social development and play; research on repetitive and restricted behaviors; and a limited number of questions about general behavioral problems. To study the mechanisms underlying the effects of supplementation, plasma levels of major PUFAs (EPA, DHA and AA) were analyzed. There was a significant improvement in social isolation as measured by the ABC and the ADI-R C3 subdomain (stereotyped and repetitive motor mannerisms). The ADI-R C3 subdomain scores were significantly correlated to inadequate speech measured by the ABC. At the end of the study, AA plasma levels were significantly increased in the supplemented group. Therefore, it was suggested that the observed improvements in social interaction and repetitive stereotyped behavior, were possibly mediated through AA-mediated signal transduction.

Yui et al.[48] conducted another study which evaluated the effects of supplementation, with high doses of AA in combination with DHA, on social impairment in individuals with ASD. The 16-week randomized double-blind placebo-controlled trial evaluated the effects of daily supplementation with six capsules containing 40 mg of DHA and AA/capsule and 0.16 mg of astaxanthin/capsule in 13 individuals aged 6 to 28 years compared to placebo capsules containing olive oil. The follow-up was conducted using the Aberrant Behavior Checklist (ABC scale) and the Social Responsiveness Scale (SRS), which assesses awareness, cognition, communication, motivation and stereotyped behaviors. To determine the mechanisms underlying the effects of supplementation, plasma transferrin and superoxide dismutase levels, which are useful signal transduction markers, were analyzed. The results suggested that the intervention improved social isolation as measured by the ABC scale and communication as measured by the SRS in the supplemented group. There were significant differences in plasma transferrin levels and a trend towards a significant difference in plasma superoxide dismutase levels between the two groups. This study suggests that supplementation with high doses of AA in combination with DHA improves social interaction in individuals with ASD by positively regulating signal transduction.

Bent et al.[49] reported a randomized controlled trial to analyze the efficacy of daily supplementation of 1.3 g of omega-3 (350 mg EPA + 230 mg DHA) for six weeks on hyperactivity symptoms of 57 children with autism. Children who were supplemented showed reduced hyperactivity (-5.3 points) compared to the placebo group (-2.6 points), although this difference was not statistically significant.

In the same year, Voigt et al.[50] studied 48 children aged 3 to 10 years who were supplemented daily with 200 mg of DHA for six months. The children's behavioral changes were listed by parents, teachers and researchers. Treatment adherence was confirmed by a 431% increase in plasma DHA levels. This study showed no changes in the reported symptoms of children who received supplementation, as assessed by the Clinical Global Impression (CGI-I). The researchers referenced the sample size as a possible limitation of the study. In addition, it included children who did not have a deficiency in serum DHA levels, which could be a possible explanation for the negative result.

In 2015, Mankad et al.[36] conducted a randomized controlled trial with 38 children (28 boys and 10 girls) aged two to five years with ASD and daily supplementation of EPA and DHA (3:1 ratio), with a dose increasing gradually to 1.5 g/day of omega-3 for six months. Patients were randomly assigned to case and placebo groups at a 1:1 ratio and matched according to the severity of autism symptoms, adaptive functions or language gains. This study showed an improvement in externalizing symptoms in the placebo group compared to the supplemented group. According to the authors, the young age (up to five years), high level of verbal limitations and stress may have contributed to the unexpected results. Therefore, the study does not support the hypothesis that

omega-3 fatty acid supplementation in children with ASD is beneficial for the improvement of symptoms or adaptive functions. Moreover, it suggests that high doses of omega-3 fatty acids could impair externalizing behavior and further studies in this area are required.

A recent study conducted by Ooi et al.[51] evaluated the effects of 1 g/day omega-3 supplementation (840 mg DHA, 192 mg EPA, 66 mg AA, 144 g GLA, 60 mg vitamin E, 3 mg thyme oil) in 41 children with autism aged 7 to 18 years (36 boys and 5 girls) over a 12-week period. The study found significant improvements in social and attention problems using the Social Responsiveness Scale (SRS; communication and behavior) and the Social and Attention Problems Syndrome Scales of the Child Behavior Checklist (CBCL; screening for problem behaviors) questionnaires. The SRS showed improvements in all aspects analyzed (awareness, cognition, communication, motivation and stereotyped behaviors). In addition, the CBCL showed that social and attention problems also improved. In the study, blood samples were collected from all children before and after supplementation and changes in the omega-6/omega-3 and AA/EPA ratios and a possible general increase in omega-3 fatty acid levels were observed after treatment. DHA was the omega-3 fatty acid which showed the greatest increase in children's plasma. The results were corroborated with the significant correlation between plasma fatty acid concentration and changes in the main symptoms of ASD. Basal fatty acid concentration was predictive of treatment response, that is, the best responses were observed in children with initially lower omega-3 levels. The results of this study support the hypothesis that children with ASD can benefit from omega-3 supplementation.

In 2017, Parellada et al.[32] conducted a randomized double-blind placebo-controlled crossover study with 68 children and adolescents aged 5 to 17 years over an 8-week period to determine whether omega-3 supplementation improves the omega-3/omega-6 ratio in erythrocyte membranes, plasma antioxidant status and typical autistic behaviors. Children aged 5 to 11 years received one capsule/day (577.5 mg EPA, 385 mg DHA and 1.6 mg vitamin E), while children aged 12 to 17 years also received one capsule/day but with higher doses of omega-3 (693 mg EPA, 462 mg DHA and 2.01 mg vitamin E). The placebo group received an identical capsule containing liquid paraffin and vitamin E at the same doses as the supplemented group. The primary outcomes were analyzed by measuring erythrocyte membrane fatty acid composition and plasma antioxidant status. The secondary parameters were assessed by the Social Responsiveness Scale (SRS) and Clinical Global Impression (CGI-I) questionnaires. Omega-3 supplementation improved the omega-3/omega-6 ratio in erythrocyte membranes without changing the plasma antioxidant status. The supplemented group also showed significant improvements in SRS social motivation and communication subscale scores, but no treatment effect (treatment-placebo order). Carry over effects could possibly explain some of these results. Therefore, the authors suggested that omega-3 supplementation should be studied as a complement to behavioral therapies for ASD and the optimal treatment time requires further investigation.

The wide heterogeneity of ASD phenotypes and etiologies shows that it is unlikely that a given treatment will have the same effects in all patients. In addition, studies with longer follow-up periods and larger sample sizes are required as well as using standardized omega-3 supplementation doses.

There are still open questions regarding omega-3 supplementation in children with autism: I - Which omega-3 dose should be administered to modify plasma concentrations? II - How much omega-3 crosses the blood-brain barrier? III - Which specific brain areas benefit the most from supplementation with this fatty acid? IV - Does high-dose omega-3 supplementation have toxic effects, and can it be administered to children?

In addition to the answers to these questions, studies aimed at identifying the external and metabolic causes of omega-3 deficiency in children with ASD are required.[17,24,29]

CONCLUSION

ASD, especially in children, is an extremely complex clinical condition that requires multidisciplinary approaches that focus not only on educational issues and symptoms but also on the identification of etiologies and the prevention and management of morbidities that may increase cardiovascular risk in these individuals during adulthood.

The current review discusses the need to include a severity marker based on levels of disability in social communication and restricted and repetitive behaviors. Therefore, the development of quantitative methods and practical recommendations to differentiate the classification levels are discussed. The lack of classification of level of autism severity represents one of the major limitations of intervention studies as the impact of interventions based on drugs or nutrients may have their response inhibited or enhanced by disorder severity. Autism is a complex condition in which nutrition and environmental factors play crucial roles in improving the quality of life of the individual and reducing the associated morbidities. Lastly, it is urgently required to establish more rigorous study methodologies and conduct placebo-controlled trials to provide evidence-based guidance to families as well as the scientific and clinical community on alternative and complementary treatments. In the absence of these studies, the efficacy of omega-3 as adjuvant therapy in the treatment of ASD in children remains undefined.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

AUTHORS' CONTRIBUTIONS: MCHB, MMGG, NRTD: acquisition, analysis, interpretation of data, writing of the manuscript and critical review of its intellectual content; IMS: writing of the manuscript and critical review of its intellectual content.

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