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Review article

The effect of dietary supplements on clinical aspects of autism spectrum disorder: A systematic review of the literature

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Abstract

Background: Autism spectrum disorder is associated with significant social and financial burden and no definite treatment for this entity has been identified, yet. In recent years there has been an increasing interest in the use of dietary interventions as a complementary therapeutic option for these patients.

Objective: The aim of this systematic review is to provide high evidence level literature data about the effect of dietary supplements on clinical aspects of children with autism.

Methods: A comprehensive literature search was conducted using Pubmed as the medical database source. Randomized controlled trials conducted in pediatric populations and including measures of clinical outcomes were considered.

Results: A total of 17 eligible prospective studies were selected. Types of dietary supplements evaluated in these studies included amino acids, fatty acids and vitamins/minerals. N-acetylcysteine was shown to exert a beneficial effect on symptoms of irritability. On the other hand, literature data about the efficacy of D-cycloserine and pyridoxine-magnesium supplements was controversial. No significant effect was identified for fatty acids, N,N-dimethylglycine and inositol. Literature data about ascorbic acid and methyl B12 was few, although some encouraging results were found. No serious adverse events were reported in the vast majority of the studies, while the prevalence of adverse reactions was similar between treatment and placebo groups.

Conclusions: The use of dietary supplements in children with autism seems to be a safe practice with encouraging data about their clinical efficacy. More studies are needed to further investigate this issue.

Keywords: Autism spectrum disorder; Nutrition; Dietary supplements; Amino acids; Fatty acids; Vitamins; Minerals

1. Introduction

According to the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which was released in 2013, previously separate entities have been merged under the term of autism spectrum disorder (ASD). Diagnosis is based on 2 essential features: (i) impaired social interaction and social communication and (ii) restricted and repetitive patterns of behavior [1]. Centre for Disease Control and Prevention data published in 2014 shows a prevalence rate of ASD in USA of 1 in 68, which consists a significant increase from 2012 estimates [2]. Moreover, diagnosis of ASD

Abbreviation: ASD, autism spectrum disorder

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is associated with substantial lifetime costs to the individual, the family and the community, while annual financial burden for ASD is estimated to be on a par with estimates for diabetes and exceed the costs of stroke and hypertension [3].

The pathophysiological background of ASD is not clear, although various genetic, neurologic, metabolic and immunologic factors are suggested to be involved. On the other side, early diagnosis and initiation of therapies for these children does appear to improve outcomes such as a decreased need for special education in later years and an increase in the chance for independence as an adult. Pharmacological and behavioral interventions have been identified but their success is limited. This can be attributed to the high variability of the disorder, to adverse drug events, as well as to the difficulty in quantitatively evaluating some behavioral interventions [4].

In recent years there has been an increasing interest in the relationship between ASD and gastrointestinal symptoms. Children with ASD often exhibit nonspecific gastrointestinal symptoms (abdominal pain, constipation, very restrictive diet), while intestinal mucosal abnormalities and altered intestinal microbiome synthesis have also been reported [5]. Under the view of these findings various dietary interventions have been used as a complementary treatment option in ASD and there are studies and case reports in literature showing encouraging results from the use of specific dietary supplements in these patients [6,7].

The aim of our systematic review is to provide current high evidence level literature data about the effect of dietary supplements on clinical aspects of ASD in pediatric population.

2. Methods of literature search

2.1. Eligibility criteria

Studies with the following criteria were selected: 1. randomized clinical trials, 2. diagnosis of ASD, 3. study population consisted of pediatric or adolescent groups, 4. measures of clinical aspects (e.g. questionnaires, scales).

2.2. Search strategy and study selection

A comprehensive search was undertaken by two reviewers independently using Pubmed as the medical database source. No year-of-publication restriction was placed. The terms that were used were: "autism spectrum disorder", "autism", "nutrition", "dietary supplements", "amino acids", "fatty acids", "vitamins", "minerals", "probiotics", "prebiotics", "carnitine".

After searching the literature, data were abstracted and selected articles were scanned to eliminate studies with irrelevant topic, methodological issues or duplicate records. Groups of dietary supplements with no more than 1 eligible studies in literature evaluating their effect have not been considered in this systematic review. Fig. 1 illustrates the flow chart of how the articles were selected.

2.3. Quality of evidence

Quality of evidence provided in each study was assessed according to American Academy of Neurology guidelines. Evidence level ranges from 1 to 4 [8].

3. Description of the studies

A total of 1549 articles were initially identified, but finally only 17 met our eligibility criteria [9–25]. (Fig. 1) All of them were randomized clinical trials (15 double blind and 2 single blind) with an evidence level ranging from 1 to 2. All the studies were published in English, the publication time ranged from 1985 to 2016 and 41% of them were published in the recent 5 years.

The age of participants ranged from 2.5 to 18 years, the study sample from 9 to 67 participants, while total duration of treatment period from 4 to 35 weeks. Assessment of clinical aspects in children or adolescents with ASD was based on questionnaires and scales, while some studies were focused on specific subscales (hyperactivity, irritability). In 6 of 17 studies a combination of supplements was administered to participants (eicosapentaenoic & dososahexaenoic or pyridoxine & magnesium). In studies, which did not include a placebo group, comparisons were made between pre-treatment and post-treatment measures of clinical aspects. A significant beneficial effect on 1 or more clinical aspects of ASD was observed in 7 of 17 studies (41%). We should also highlight that during administration of dietary supplements the delivery of conventional therapeutic strategies (e.g. behavioral therapy, psychotherapy, special education, drugs) was properly continued in all children.

Tables 1–3 present basic traits and most significant findings of the studies identified in literature. We were also able to identify prospective studies about the impact of additional types of dietary supplements on ASD. However, as only 1 study for each of the above groups of supplements has been identified, they have not been considered in our review [26–31]. No eligible studies have been found about the effect of probiotics or prebiotics on clinical profile of children and adolescents with ASD.

4. Amino acids

Although the absolute pathophysiological mechanism of ASD is still debated, neurobiological models