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Review

Dietary strategies in Autism Spectrum Disorder (ASD)

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Summary. Many children with Autism Spectrum Disorders (ASDs) have been reported to suffer from conditions (i.e. gastrointestinal distress, abnormal sensory processing, etc.) that may interfere with their nourishment. To compensate for possible deficiencies stemming from food selectivity and idiosyncratic eating habits and to alleviate some of the symptoms of ASD, a number of dietary strategies have been implemented by caregivers. Such strategies may include supplementation of diets with probiotics, omega-3 fatty acids, antioxidants, vitamins and minerals. Exclusion of certain nutrients from the diet (such as gluten, casein, carbohydrates, etc.) has also been resorted to. There are a vast number of studies conducted on dietary interventions in children with ASD, however, the results of these studies are confusing and inconclusive. This paper aims to critically review scientific studies on dietary strategies as applied to children with ASD and deduce practical implications from existing researches.

Key words: ASD, children, dietary stategies, supplementation, reaction

Introduction

Many children with Autism Spectrum Disorders (ASD) have been reported to suffer from conditions that may directly interfere with their nourishment. Gastrointestinal distress (1–7), abnormal sensory processing (8,9), food allergy (10–15) and oromotor difficulties (16–18) are among these conditions. Children and adolescents with ASD are believed to be at risk of nutritional deficiencies, which are thought to arise from food selectivity and ritualised eating habits (19,20).

Caregiver-mediated dietary strategies in the ASD community have proliferated in parallel to the efforts of caregivers to supplement the children with what they are deficient for or isolate the children fully from what exacerbates the GI-related or behavioural symptoms of ASD. No matter how well-intentioned caregivers are in administering such diet therapies to children, without the guidance of a registered nutritionist or a dietitian these therapies may inadvertently result in increasing the risk of nutrient deficiencies, obesity or being underweight. For example, low intake of calcium has been well established in children with ASD (21–24) and it is usually ascribed to the limitation or elimination of dairy products in gluten-free casein-free (GFCF) diets, which are believed to ameliorate some of the gastrointestinal symptoms in children (25,26).

A recent paper (27) discussed the role of personalised diets in children with ASD and argued that there is an increased interest in individualised diets and nutrient supplementation. Currently, there are a number of ongoing studies that aim to further understand the real impact of dietary interventions on the health and well-being of children with ASD. Therefore a review of the most recent studies is deemed to be timely in order to stay current with evidence-based information. This review aims to critically review scientific studies on dietary strategies as applied to children with ASD and deduce practical implications from existing researches.

Method

A comprehensive electronic database search of published literature in English was conducted through ScienceDirect and PubMed using the keywords "*autism, ASD, diet, intervention, supplementation, elimination, probiotics, omega-3 fatty acids, antioxidants, gluten-free and casein-free, ketogenic*" with the corresponding Boolean operators. Other databases, Cochrane Library and EBSCOhost

were also consulted. The date of the last search was June 1, 2017. Reference lists of relevant studies were also manually searched for additional papers. Studies were excluded from review if they were conducted before 1993 and/or if they presented anecdotal evidence, survey results or included case study of only one subject. Studies concerning eating and feeding difficulties were also omitted.

Findings from the literature are summarised into the following headings: (1) dietary supplementation (probiotics, omega-3 fatty acids, antioxidants, multivitamin and mineral supplements) and (2) elimination diets (gluten-free and casein-free diet, ketogenic diet and other restrictive dietary interventions with limited research evidence).

Dietary supplementation

Probiotics

Clinical studies of individuals with ASD have shown that compositional changes in the gut microbiota, which are usually induced by a bacterial infection or chronic antibiotic exposure, frequently accompany disorders in the functioning of the brain (28–30). In a mouse model with stereotypic ASD-like behaviours, Hsiao et al. (31) were able to show that the disturbance of gut microbiota was a likely contributor to the behavioural abnormalities observed in the offspring.

Probiotics have been shown to improve immune function, produce vitamins and aid in nutrient absorption (32). Certain species of bacteria, namely *Bifidobacterium* (*bifidum, breve*) and *Lactobacillus* (*acidophilus, casei*), are commonly used as probiotics (33). A recent study conducted on mice found that selective reintroduction of a strain of probiotic bacterium (i.e. *Lactobacillus reuteri*) could restore changes in the gut microbiota and behavioural abnormalities (similar to what is observed in ASDs) that were induced by maternal high-fat diet (34).

The gut microbiota composition of individuals with ASD was reported to differ significantly from that of healthy controls or non-ASD siblings (7,35–38). These studies demonstrated that the stools of the individuals with ASD were found to have elevated levels of *Clostridia, Desulfovibrio* and *Sutterella* and a lower abundance of *Prevotella* and *Bifidobacter.*

A limited number of clinical studies have investigated the effects of probiotic treatment in children with ASD. Adams et al. (7) reported that probiotics did not have a significant effect on most of the beneficial bacteria, except for a high level of lactobacillus.

In a preliminary study, Kaluzna-Czaplinska & Blaszczyk (39) investigated the effect of probiotic (*L. acidophilus*) treatment on the efficiency of reducing the amount of D-arabinitol (which is used as a marker for invasive candidiasis) in the urine of children with autism. Their results suggested that probiotic therapy could be effective in reducing the level of D-arabinitol and the ratio of D-arabinitol/L-arabinitol. A follow-up study of Finnish children, who were treated with either a probiotic strain (*Lactobacillus rhamnosis* GG) or a placebo during the first six months of life, identified that 17% of the children in the group that was treated with placebo had Asperger's syndrome or attention deficit hyperactivity disorder (ADHD) at 13 years of age in comparison to none in the group that received probiotics (40). Russo (41) found that the level of an enzyme that aids microbial killing (myeloperoxidase) was significantly lower in individuals with ASD who received probiotic therapy (content and dose information were undisclosed). Tomova et al. (42) administered probiotics (two strains of *Lactobacillus*, two strains of *Bifidumbacteria* and one strain of *Streptococcus*) to children with ASDs for four months and demonstrated that the normal balance was restored in fecal microbiota after the treatment.

Several limitations of commercial probiotics, such as variability in quality and composition and issues with efficacy, are pointed out by some researchers. They assert that commercial preparations of probiotics are limited in diversity when compared to the vast number of different types of bacteria within the human gut. Since currently available probiotics are aerobic and derived from milk cultures, they are not normally a significant part of the human gut microbiome, as the latter are primarily composed of anaerobic microorganisms (43,44).

Omega-3 fatty acids

There is a high prevalence of the use of omega-3 fatty acids among children with ASD as a complementary and alternative medicine (CAM) (45). Omega-3 long-chain poly unsaturated fatty acids (PUFAs), namely docosahexaenoic acid (DHA, C22:6) and eicosapentaenoic acid (EPA, C20:5), are conditionally essential nutrients with important physiological roles and potential health

benefits (such as being part of cell membranes, having anti-inflammatory and cardio-protective properties and taking part in neurotransmission) (46–48). DHA, in particular, is fundamental for brain function and development and normal visual development in infants (49,50) and EPA has been reported to be more influential on behaviour and mood (49).

The rationale for supplementing diet with long-chain omega-3 PUFAs came from studies that investigated children with ASD, who were reported to have low levels of omega-3 fatty acids in their blood tissue and/or a higher total omega-6 PUFA to omega-3 PUFA ratio when compared to typically developing children (51–59). In individuals with ASD, the metabolism of PUFAs is thought to be deficient or abnormal, leading to increased production of pro-inflammatory cytokines, increased oxidative stress and an imbalance in the formation and action of neurotransmitters (50).

A number of randomised controlled trials (RCTs) investigating the effect of dietary supplementation with omega-3 fatty acids (60–64) and open label studies (65–68) have yielded mixed results. Two systematic reviews assessing these studies (45,69) could not assert supplementation as an effective treatment for individuals with ASD. A recent review suggested that omega-3 PUFA supplementation could potentially improve some ASD symptoms, but pointed out that there is a need for further research with larger sample sizes and longer follow-up periods (70).

Antioxidants

When the balance is disturbed between generation of reactive oxygen species (ROS) and elimination due to body's antioxidant defence system, "oxidative stress" ensues. Growing evidence suggests that oxidative-stress-induced mechanisms are believed to be associated with the pathophysiology of ASD (71–73). Impairments in antioxidant defence systems may lead to alterations in neuronal structure and brain function, inflammation and disruption of immune function (71,74,75).

Dietary antioxidants include vitamin E (alpha-tocopherol), vitamin C (ascorbic acid), carotenoids (a form of vitamin A), selenium, manganese, copper and zinc (76,77). Supplementing diets with vitamin C (78), vitamin B6 (combined with magnesium) (79) and flavonoids (luteolin and quercetin) (80) or administering foods with potential therapeutic properties (such as camel milk) (81) were reported to ameliorate symptoms of ASD. However, currently no general recommendations could be advanced regarding the use of these interventions, partly due to the small sample sizes and lack of rigorous experimental designs employed in these studies.

Multi–vitamin and mineral supplements

Supplementation is used to support the diets of children with ASD (82–86), especially when these children are on gluten-free and casein-free (GFCF) diets (87–90). Calcium supplementation via consumption of enriched cows' milk together with weight-bearing exercise was found to have a synergistic and positive effect on bone mineral density accrual (91). One recent double-blinded randomised controlled trial of oral vitamin D supplementation in children with ASD revealed significant effects on the core manifestations of ASD and 300 IU vitamin D3/kg/day was reported to be generally well tolerated (92).

A review included a list of randomised controlled trials where the diets of children with ASD had been supplemented with various vitamins (methyl B12, folate, vitamin B6, etc.) (93). After assessing numerous clinical studies with varying experimental designs (ranging from open label to randomised controlled trials), this review highlighted the need for stronger evidence to reach a conclusion. Among the relevant studies listed as "ongoing" in the review, one involving folinic acid supplementation (trial identifier NCT01602016) was terminated; one involving oral administration of folic acid was completed (NCT00672360), but unpublished at the time of writing; one was completed and published (NCT01039792) (94) and no information could be found about a study registered in Japan that aimed to study the effect of vitamin B6 on children with ASD (JPRN-UMIN 000002650). Although it is not a "dietary" supplementation study, it may be noteworthy to include the study of Hendren et al. (94) here. In this study, researchers treated children with ASD with injectable methyl B12 and found that there was a statistically significant improvement in overall clinician-rated symptoms compared with the control group, and this improvement was reflected in biochemical parameters.

In a small-scale study, Kaluzna-Czaplinska et al. (95) found that folic acid and vitamins B6 and B12 were more effective in reducing the level of homocysteine (whose level was shown to be elevated in children with ASD)

in the urine of children than a combination of vitamins B6 and B12. A study measuring micronutrient intake from both food and supplements from a large sample of children with ASD (n=288) found that the children were able to meet daily requirements for many nutrients from meals alone and children who were taking supplements still had inadequate intakes of calcium, vitamin D, potassium, pantothenic acid and choline (88). The authors pointed out that many supplement users exceeded the tolerable upper intake level (UL) of vitamin A, folic acid and zinc. The excess intake of some nutrients in the study was thought to be related to the consumption of highly fortified foods such as cereals and grains as a part of the restrictive and repetitive eating habits of the children.

With a different approach on supplementation, Ranjan & Nasser (96) suggested that providing children with fortified foods rather than additional vitamins or food supplements may help to meet their nutritional needs.

Elimination diets

Gluten-free and casein-free (GFCF) diet

A gluten-free and casein-free (GFCF) diet appears to be the dietary intervention that is most commonly used as an alternative treatment for individuals with ASD (97–99). Among various theories explaining the pathological action of gluten and casein in ASD, the hypothesis that the peptides derived from these proteins leak into the bloodstream and trigger an immune response resulting in gastrointestinal inflammation is the most persuasive (99).

Reviews evaluating the effectiveness of GFCF diets on ASD symptoms yielded a number of studies and posited that most of these studies lacked methodological rigour and controlled evidence (25,100,101). Two small randomised controlled trials (102,103) reported benefits of the GFCF diet on some outcome measures, which were based on the reports of the parents. Concomitant treatments during the course of these two studies were not monitored, as noted by another study (89). Two other randomised studies with small sample sizes (n=15 and 22, respectively) did not report any improvement in ASD symptoms (21,22). A double-blind challenge trial (n=14) did not detect any impact of dietary challenges on ASD-related behaviours (89). In contrast, a randomised controlled trial conducted with 80 children suggested that the diet could be effective in controlling gastrointestinal symptoms and ASD behaviours (104). All in all, due to the sheer paucity of studies with robust experimental designs, the evidence in support of GFCF was deemed to be limited and inconclusive (25,97,100,101,105). The urgent need for well-conducted and adequately powered randomised controlled trials (98) still awaits to be fulfilled.

It is assumed that for children with ASD who consume a wide variety of foods, the GFCF diet may not have medical consequences (106). However, the safety of GFCF diets in children with ASD still needs to be addressed due to the high prevalence of food selectivity in this population (97,107). As discussed previously, GFCF diets can give rise to low intake levels of calcium, which may be associated with reduced bone density in children with ASD (26,108,109). Children following these types of diets may also have a higher prevalence of essential amino acid deficiencies (106).

Ketogenic diets

Ketogenic diets (KDs) have been implemented since the 1920s, particularly for the treatment of epilepsy, which is one of the common comorbidities of ASD (110–112). KDs consist of a high amount of fat (65–90% of the total energy), sufficient protein to promote growth and a low amount of carbohydrate (111). KDs trigger the starvation metabolism and force the body to use oxidation products of fatty acids (ketone bodies) instead of glucose, which is the primary energy source for the brain and CNS. As a consequence of this, ketosis ensues (113,114).

There is accumulating evidence on the effect of KDs demonstrating behavioural improvement in human subjects (115–118) and attenuating some autistic-like features (e.g. self-directed repetitive behaviour and reduced sociability) in animal models of ASD (119–122). An animal study also found that the KD altered microbiota composition in caecal and faecal samples and reduced the abundance of total host bacteria, reiterating the possible impact of the gut–microbiota axis on ASD (123).

Although regarded as a good target for being investigated as a potential therapy for the symptomatology of ASD, KDs are still far from providing researchers with definitive answers (124). This was partly due to limitations in both human and animal studies (122,124).

In individuals with ASD, the implementation of KDs requires careful consideration of various issues, such as food selectivity and rigid and repetitive feeding be-

haviour, GI-related disturbances (diarrhoea, constipation and vomiting), poor tolerance of the diet due to palatability issues, low intake levels and subsequent deficits in nutrients (112,124,125). It is also important to assess actual total energy intake in order to be able to establish that ketosis occurs due to the KD and not low-calorie consumption (124).

Other restrictive dietary interventions with limited research evidence

Fermentable oligo-di-mono-saccharides and polyols (FODMAPs) form a heterogeneous group of poorly absorbed short-chain carbohydrates that are subsequently fermented in the small or large intestine. FODMAPs include fructose (e.g. fruits and high-fructose corn-syrup), lactose (e.g. milk and dairy products), fructans (e.g. grains, vegetables and fruits), galactans (e.g. legumes and vegetables) and sugar alcohols (polyols, e.g. sorbitol, fruits and vegetables) (126). FODMAP-restricted diets have been used for a long time to ameliorate the symptoms of irritable bowel syndrome (IBS), such as abdominal pain, bloating, constipation, diarrhoea, abdominal distention and flatulence (126,127). A FODMAP-restricted diet was listed as a common dietary intervention applied by parents/caregivers in children with ASD (3).

Specific carbohydrate diet (SCD) stems from studies demonstrating that some of the gastrointestinal problems in ASD can be attributed to abnormalities in carbohydrate digestion and absorption (25). It is hypothesised that when digestion and absoption is impaired, undigested carbohydrates will accumulate in the intestinal lumen, giving rise to overpopulation of harmful microorganisms with production of excess short-chain fatty acids (SCFAs) and possibly bacterial toxins (128). SCD mainly recommends monosaccharides (found in fruits, some vegetables and honey) and restricts the consumption of complex carbohydrates (3,86).

Conclusions

Current research evidence remains unable to substantiate potential effects of aforementioned dietary interventions on the symptoms of ASD. Studies incorporating dietary intake, biochemical tests and other measurements with control groups should be initiated and supported to produce more reliable findings. Clinical trials with larger sample sizes, more robust experimental designs and the use of clearly defined outcomes to observe the changes in physiological, social and psychological measures following dietary interventions are needed. Data from scientific studies should be disseminated to the public and families in a clear and concise manner.

Multifaceted aspects of nutrition-related ASD symptoms should be managed through a team of experts including psychologists, nutritionists, dieticians and paediatricians. Families should not be the sole decision-makers of the diets of children with ASD. Combined efforts of experts and families will surely be an important step forward to improve the quality of life of children with ASD.

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