FOCUS

Healthy nutritional habits should be encouraged in all children independently of the existence or non-existence of neurodevelopmental disorders

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Truths, Myths and Needs of Special Diets: Attention-Deficit/Hyperactivity Disorder, Autism, Non-Celiac Gluten Sensitivity, and Vegetarianism

by Sylvia Cruchet et al.

Key insights

Maintaining healthy nutrition is a cornerstone for the management of all children, including those with attention-deficit/hyperactivity disorder (ADHD) and autism. In children with ADHD, restriction of sugar and sweeteners and elimination of food colorants/preservatives improve behavioral and attention performance. Despite the widespread use of gluten-free diets, these should only be adopted for children with a demonstrated food allergy, such as celiac disease, wheat allergy and non-celiac gluten sensitivity (NCGS). In general, elimination diets should only be used in children with specific allergies to the eliminated food item.

Current knowledge

ADHD is a growing childhood problem that affects between 1.4 and 5% of school-aged children. This multifactorial neurodevelopmental disorder has been linked to multiple genes and environmental factors. Adverse food reaction is thought to be one of the triggers. Among the food-related drivers are food allergy, non-immunologic food effects (intolerance and toxicity) and nutritional deficiencies. Although pharmacological agents are often used for controlling disruptive behavior and inattention, there is concern over the adverse reactions and long-term drug side effects. NCGS is a syndrome characterized by intestinal and extra-intestinal symptoms related to the ingestion of gluten-containing food in subjects who are not affected by either celiac disease or wheat allergy.

Practical implications

Different dietary approaches have been implemented for the treatment of ADHD. However, only three have been subjected to clinical trials: education on healthy nutritional habits, specific nutrient supplementation and elimination diets. Data from randomized controlled trials links improved attention with increased consumption of healthy foods. Beneficial effects have also been seen with iron, zinc, magnesium and omega-3 fatty acid supplements, although conclusive evidence is still lacking. Diets that eliminate synthetic food colorants may benefit a subgroup of patients. The implementation of any dietary measure should be undertaken under medical supervision in order to avoid nutritional deficiencies.

Dietary interventions for addressing specific childhood disorders

Type of dietary intervention	Target population
Healthy nutritional habits	All children
Supplementation with specific micronutrients (i.e. iron, zinc, magnesium, omega-3 fatty acids)	Children with ADHD
Gluten-free diet	Children with celiac disease, wheat allergy, NCGS
Elimination of food colorants/preservatives	Children with ADHD
Elimination of common dietary antigens (milk, eggs, soy, peanuts, wheat, seafood)	May benefit some patients with ADHD

Recommended reading

Nigg JT, Holton K: Restriction and elimination diets in ADHD treatment. Child Adolesc Psychiatr Clin N Am 2014;23:937–953.

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Truths, Myths and Needs of Special Diets: Attention-Deficit/Hyperactivity Disorder, Autism, Non-Celiac Gluten Sensitivity, and Vegetarianism

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Key Messages

- **Healthy and balanced nutrition should be encouraged in children with attention-deficit/hyperactivity disorder (ADHD) and autism. In children with ADHD, dietetic restriction of sugar, sweeteners and elimination of colorants/preservatives improve behavioral and attention performance. Other specific elimination diets should only be recommended to children with demonstrated food allergy. Supplementation with omega-3 fatty acids improves behavior.**
- **A gluten- and casein-free diet does not have strong evidence supporting its indication in the management of autism. An exclusion diet is only indicated in children with demonstrated milk and/or wheat allergy. Macro- and micronutrient deficiencies have been described in children under this diet, and health professional supervision should be encouraged.**
- **A new entity, non-celiac gluten sensitivity, with a still evolving definition and clinical spectrum, has been described. The benefits of a gluten-free diet (GFD) are clearly supported in these conditions. Until now, no long-term complication has been described in patients not adhering strictly to this diet.**
- **GFD without health professional supervision has risks of vitamin (mainly B vitamins and folic acid) and micronutrient (especially iron and zinc) deficiencies as well as lower fiber intake.**
- **Subjects on a vegetarian diet, especially vegans, are at risk of vitamin B_{12} deficiency if they are not adequately supplemented.**
- **A vegetarian diet is a feasible alternative if implemented with supervision by a specialist, especially during vulnerable periods of life.**

Key Words

Attention deficit · Autism · Hyperactivity · Vegetarianism · Celiac disease · Gluten · Gluten-free diet · Food allergy · Vegan diets · Vitamin B_{12} deficiency

Abstract

Different dietary approaches have been attempted for the treatment of attention-deficit/hyperactivity disorder and autism, but only three of them have been subjected to clinical trials: education in healthy nutritional habits, supplementation and elimination diets. On the other hand, for multiple reasons, the number of people who adopt vegetarian and gluten-free diets (GFD) increases daily. More recently, a new entity, non-celiac gluten sensitivity (NCGS), with a still evolving definition and clinical spectrum, has been described. Although, the benefits of GFD are clearly supported in this condition as well as in celiac disease, in the last two decades, GFD has expanded to a wider population. In this review, we will attempt to clarify, according to the existing evidence, which are the myths and facts of these diets.

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Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD), a more and more often diagnosed childhood problem, is a multifactorial neurodevelopmental disorder, affecting 1.4–5% of school-aged children [1]. Multiple genes and environmental factors, including food adverse reactions, have been proposed as causative agents, although the definitive cause remains elusive [1]. Food allergy, non-immunologic food effects (intolerance and toxicity) and nutritional deficits are among the proposed contributors [2]. Pharmacological therapy has proven to be efficacious in controlling disruptive behavior and inattention in patients with ADHD, with a response of over 70% [1]. However, these medications have frequent adverse reactions, and some parents are also concerned about long-term side effects, preferring non-pharmacological approaches, including nutritional interventions [3–5]. Different dietary approaches have been tried for the treatment of ADHD, but only three of them have been subjected to clinical trials: education on healthy nutritional habits, specific nutrient supplementation and elimination diets. Indeed, some studies have documented deficiencies in micronutrients such as iron, zinc, and magnesium in children with ADHD compared to healthy controls [6–9]. Several vitamins, including vitamin D, may be insufficient or deficient in ADHD patients [10]. Therefore, before implementing a dietary intervention, a complete nutritional assessment to detect potential deficits and start treatment whenever necessary, should be done. Counseling by a nutritional therapist should be encouraged during nutritional intervention to avoid an unbalanced intake.

Education on Healthy Nutritional Habits

Excess of sugar and sweetener consumption has been associated, although not consistently, with hyperactive and disruptive behavior in ADHD patients [11–13]. Few interventional studies have been performed comparing healthy food against fast food/highly sweetened food. In a cross-sectional study, Park et al. [14] described an association between intake of sweetened desserts, fried food, salt and a higher inattention and hyperactivity score in ADHD school-age children compared with a balanced diet. In addition, Ghanizadeh et al. [15] reported in a randomized controlled trial (RCT) an association between improvement of inattention score and an increase consumption of 'healthier' foods. Although more evidence is necessary, the expert recommendation based on very limited research is to indicate a balanced and 'healthy' diet for children with ADHD considering its proven beneficial effects in global well-being and potential additional benefits for cognition and behavior.

Supplementation

Open-label trials and RCTs to determine the effect of iron, zinc and magnesium supplementation on inattention and hyperactivity behavior in patients with ADHD have been performed [7, 16–24]. Although some of these studies suggest a beneficial effect, especially in children with confirmed deficits, a recent systematic review concluded that current evidence is still inconclusive [16]. The expert recommendation is to treat patients with demonstrated micronutrient deficiencies and, in children who do not ingest a balanced diet and/or have stimulant-medication-related appetite suppression, to supplement with multivitamins/minerals [21]. This is based on the fact that a recommended daily dose of micronutrient intake carries little risk [10].

A meta-analysis has shown that children with ADHD have a lower plasma concentration of omega-3 fatty acids than controls [25]. However, whether this observation contributes to ADHD pathophysiology or is a casual finding has not yet been demonstrated. A recent meta-analysis including 10 RCTs of omega-3 fatty acid supplementation did not find positive effects on ADHD symptoms. However, subgroup analyses of higher-quality studies found a significant reduction in emotional lability and oppositional behavior [26]. The authors concluded that current evidence supports only a small beneficial effect of omega-3 fatty acids on some behavioral symptoms [25, 26].

Elimination Diets

The hypothesis of the effect of synthetic food colorants on hyperactivity in ADHD patients was first introduced in the 1970s by Feingold [19, 27]. Either allergenic or pharmacologic mechanisms were suggested, and elimination diet was proposed as an adjuvant treatment for hyperactivity symptoms [2]. Most of the studies are open-label, non-blinded trials including few patients, with a wide heterogeneity in outcome definition, and have generated inconclusive results [2, 28]. RCTs with exclusion and challenge with colorants have demonstrated improvement of hyperactivity in 10–30% of patients [29–31]. A meta-analysis of RCTs with colorant elimination diet suggests a modest but consistent effect in non-selected ADHD patients [32–34]. This percentage may even increase when the intervention is applied to selected patients with symptoms suggestive of food allergy [2]. More restrictive diets excluding milk, eggs, soy, peanuts, wheat and seafood as well as an 'oligoantigenic diet' have also been tried in RCTs, and results have been promising with a significant decrease in hyperactive behaviors in up to 64% of children [30, 35, 36]. Taken together, these studies suggest that elimination diets can benefit a subgroup of ADHD patients, although research directed to identify the best candidates for this intervention is needed.

Non-Celiac Gluten Sensitivity

Gluten and other wheat proteins have been part of the human diet since the beginning of agriculture about 10,000 years ago. Wheat culture is simple, can adapt to different weather, has high yield, low cost compared to its nutritional value, and adds palatability to different preparations [37]. That is why it is included in most processed foods. The ingestion of gluten and other related proteins can produce well-established adverse reactions in susceptible individuals, including celiac disease and wheat allergy [38]. More recently, a new entity, non-celiac gluten sensitivity (NCGS), with a still evolving definition and clinical spectrum, has been described [37]. Although, the benefits of gluten-free diet (GFD) are clearly supported in these conditions, in the last two decades, a current promoting GFD more widely to the general population has emerged and spread through social media. There are general estimates that 10–20% of the population in the USA and Australia are consuming gluten-free foods [39–41]. GFD without health professional supervision has risks of vitamin (mainly B vitamins and folic acid) and micronutrient (especially iron and zinc) deficiencies as well as lower fiber intake [42]. On the other hand, patients on a GFD tend to consume more simple carbohydrates and fats instead of grain-containing food [42]. Therefore, a GFD has to be recommended under supervision and only for patients with a well-documented clinical condition where its benefits are evidence supported, such as in celiac disease, wheat allergy and NCGS [39].

In the last two decades, a current promoting GFD more widely to the general population has emerged and spread through social media

NCGS is a syndrome characterized by intestinal and extra-intestinal symptoms related to the ingestion of gluten-containing food in subjects that are not affected by either celiac disease or wheat allergy [43, 44]. Epidemiological studies in developed countries have reported a prevalence of 0.6–6% [39, 45, 46]. This frequency increases up to 30% in patients evaluated for irritable bowel syndrome [47, 48]. NCGS seems to be a multifactorial condition with a genetic background and environmental triggers including ingested grain proteins. An innate immune response has been implicated in its pathogenesis, although the exact mechanisms remain unclear [49]. In addition to gluten, other prolamins and amylase trypsin inhibitor have been identified as triggers of symptoms in patients with NCGS [37]. The most frequent symptoms in such patients are abdominal pain (80%), chronic diarrhea (73%), fatigue (33%) and bloating (26%), which commonly overlap with those of irritable bowel syndrome. Other presentations are eczema, migraine, blurry vision, depression, anemia, limb paresthesias and arthralgia [37, 40]. Although anti-gliadin antibodies have been reported to be elevated more frequently in NCGS patients than in healthy controls, no reliable biomarker is currently available, and diagnosis confirmation relies on clinical response to a period of exclusion diet (GFD) followed by gluten challenge [40]. Benefits of a GFD have been well documented in patients with NCGS [37]. Until now, no long-term complications have been described for this condition, therefore, adherence to a GDF does not have to be as strict as in celiac disease and wheat allergy but rather symptom adjusted [39, 49].

Vegetarianism

The number of people who adopt a vegetarian diet grows permanently. In Europe, around 2–5% of the population is vegetarian and in the United States, 2% of teenagers follow this type of diet, with 0.5% of them being vegan [42].

The American Association of Nutritionists states that 'well planned vegan, lacto-vegetarian and ovo-lacto-vegetarian diets are appropriate for any stage of the life cycle, including pregnancy and lactation'. However, the association also indicates that, in special situations (as when dealing with children or teenagers), the support of a nutritionist is recommended [43].

Health Effects: Pros, Cons and Recommendations of Vegetarian Diets

Past research focused on vegetarian adults has shown that this segment of the population has a lower body mass index (BMI), total cholesterol, LDL cholesterol and glycemic levels, when compared to their omnivorous coun-

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terparts [44]. Prospective cohort studies have also shown that, in comparison to a regular diet, a vegetarian diet acts as a protective factor for entities such as ischemic cardiopathy mortality (–25% and total cancer (–8%) but not for cardiovascular and cerebrovascular diseases [45]. On the other hand, investigations focused on ovo-lacto vegetarian children have shown that their growth patterns are identical to those of omnivorous children. However, results are different for vegan children who, in general, were slimmer and wore smaller clothing sizes [42].

It is important to emphasize that correlations have been found between followers of vegetarian diets and patients with eating disorders, which is why it is highly recommended to perform a detailed history focused on the reasons behind the diet change, especially when dealing with teenagers [46].

What about Vitamin B_{12}?

Until recently it was assumed that only strict vegetarians (vegans) showed deficiency levels of vitamin B_{12}; however, a meta-analysis of subjects on different kinds of vegetarian diets showed that all vegetarians displayed deficiency in B_{12} levels, regardless of the specific type of diet, demographic characteristics, place of residence or age.

Vitamin B_{12} deficiency, in the long run, produces megaloblastic anemia, which leads to increased homocysteine levels, a substance that leads to the development of cardiovascular and cerebrovascular diseases. Studies have shown that in pregnant women, B_{12} deficiency is associated with high levels of homocysteine [47, 48]. Around 25–86% of vegetarian children also show such a deficiency, with a higher prevalence amongst vegans [49]. Another study conducted in Finland showed that supplementing this vitamin prevents its deficiency in teenagers [50].

It is fundamental to highlight that newborns that are being exclusively breastfed by their vegan mothers can show a severe deficiency of vitamin B_{12}, leading to metabolic acidosis, high levels of methylmalonic acid and ammonia, which in turn could cause damage to the central nervous system, unless the vitamin is appropriately supplemented to the baby [51–53].

Recommendations established by the Recommended Dietary Intake (RDI) are 1.8 μg a day for children between 9 and 13 years of age and 2.5 μg for teenagers between 14 and 18 years of age. The best sources for vitamin B_{12} are: bovine liver and meat, clams, fish, chicken, turkey, eggs, dairy, fortified cereals, and nutritional yeasts. Because vegetarians do not consume these kinds of foods, the only way to avoid any complications is by administering supplements such as hydroxocobalamin in doses that range from 1 to 5 mg a day (table 1).

Table 1. Nutritional support to mothers and vegetarian children (0–12 months)

Breastfeeding
Lacto-vegetarian mother: vitamin B_{12} and measuring methylmalonic acid levels in newborn
Vegan mother: mother and child should be supplemented with vitamin B_{12} during pregnancy and subsequently
Infant formula: infant formula or soy milk (enriched with methionine)
Solids (from month 6):
Preserve breast milk or infant formula (protein and calcium)
Puree vegetables with tofu cereals or seeds
Evaluate iron supplement
Caloric density: oil essential fatty acids, DHA
Educate parents in the preparation of food
Derive a nutritional assessment
Vegetarian nutritional support in preschoolers
Ensure adequate intake of calcium (dairy or fortified foods or supplements)
Evaluating caloric density of foods is enough
Limit foods with unprocessed raw materials: whole foods (lower digestibility, are difficult to swallow because of lower chewing)
Vegetarian diet: intake record and lead nutritionist for evaluation

DHA = Docosahexaenoic acid.

How Does Consuming Low-Biological-Value Protein Affect the Individual?

Protein quality is associated with the type of amino acid that it contains. The highest-quality protein available comes from animal sources: eggs, dairy and meat in general. Protein that comes from legumes is deficient in methionine; however, its quality is improved when blended with other kinds of food, making it comparable to protein of animal origin. Thus, adding cereal (as rice, pasta or seeds) to these meals can be highly beneficial. This is why consumption of mixed foods such as beans and noodles, chickpeas and boiled corn or lentils and rice are an excellent source of good-value proteins in vegetarian diets.

The amount of protein consumption that vegetarians require is somewhat higher than that recommended for the omnivorous population. This is because when a diet is very rich in fiber, the bioavailability of protein is estimated to be only 75%. This means that vegetarians need a protein intake that is at least 1.3 times higher than that recommended for omnivorous subjects [54]. In the case of vegan mothers whose babies are not being breastfed, it is recommended to use infant soy-based formulas that are closer to breastmilk than regular soy milk, as these formulas have added methionine, which helps to improve the quality of the vegetal protein. Soy milk or any milk substitute, cereal-based products, nuts, legumes (rice, oatmeal, etc.) do not cover the nutritional basics for children, as they are deficient in amino acids, vitamins and minerals [55].

In children and teenagers, the consumption of tofu, tempeh, dehydrated soy, etc. combined with cereals is an excellent source of high-value protein but does not provide sufficient quantities of iron or vitamin B_{12}, which need to be supplemented.

What Is the Status of Bone Mineral Density, Calcium Consumption and Vitamin D?

Calcium and Vitamin D deficiencies have been reported in strict vegetarians; however, no differences have been noted in bone mineral density (BMD) between omnivorous subjects and ovo-lacto vegetarians [56]. Despite this information, not all studies agree that these deficiencies are associated with bone density loss, nor with a higher fracture incidence. Nonetheless, a correlation has been proven to exist between age and lean mass with lower levels of BMD [57]. A longitudinal study in adults showed that there were no abnormalities present in the bone health of vegetarian women [58].

Past research stated that children who are exclusively fed non-supplemented soy milk show no signs of rickets. In addition, it was determined that BMD and fracture risk are similar in ovo-lacto-vegetarian and omnivorous children. However, in vegan children and teenagers, a lower BMD and a higher risk of bone fracture was observed, associated with low levels of calcium consumption.

It is important to state that there are a large number of vegetables, nuts and legumes that are rich in calcium (broccoli, spinach, almonds, beans, etc.), but the presence of oxalates makes the absorption of this mineral deficient [59].

Vitamin D is mainly obtained by exposure to sunlight, and there are very few foods that contain it. Some of them are marine oils, fatty fishes (herring, for instance, contains 1,600 UI or 40 g), liver or aquatic animal fat, such as from seals and polar bears, and eggs from hens that have been fed this vitamin. For this reason, a large portion of vitamin D that is ingested by teenagers comes from fortified foods such as dairy or cereal.

Iron and Zinc Deficiencies

Despite the large consumption of non-heme iron found in green leafy vegetables, which has a lower bioavailability than the heme iron found in red meat, iron deficiency is not commonly found in vegetarians, as their consumption of cereals, legumes, nuts, seeds, fortified foods and food rich in vitamin C favors non-heme iron absorption and also counteracts the inhibitor effects that phytates have on absorbing this mineral [60, 61].

It is know that phytates affect zinc's bioavailability, which in turn could produce deficiencies in vegetarians [62]. A meta-analysis conducted on pregnant women found significant differences in this mineral ingestion when compared to non-vegetarian women. However, no differences were found in their plasma or serum levels. Further studies are suggested to determine whether physiological adaptations in the absorption of this mineral exist [63].

Autism and Special Diets

The broad range of conditions that are grouped under the autism spectrum is characterized by the presence of alterations in development, with important deficiencies in the areas of communication, behavior and social interaction. A child's capacity to adapt to their environment is highly dependent on the level of intellectual development and improved by early psychosocial rehabilitation. It is estimated that these disorders affect around 30–60 children in 10,000, while their life expectancy is the same as that of the regular population [64].

A number of pharmacological treatments and dietary adaptations have been created in order to make improvements in the sensory and behavioral aspects of these conditions. One of the dietary treatments used is gluten- (wheat and cereals) and casein- (milk and derivatives) free diet, which has been associated with improvements in learning processes. Many studies have evaluated its effects, but none of them have been controlled or double-blind [65–67]. A single-blinded study that focused only on 10 cases was carried out and showed that gluten and casein elimination resulted in improvements in communication and language, although these effects could not be directly associated with a dietary change, due to the very small sample size and the short evaluation period of only one year [68].

Another study, in which parents of autistic children with special diets were surveyed, showed that 20–29% of parents mentioned significant improvements in relation to their children's condition [69]. However, studies on the impact of these diets on other aspects associated with autism, such as gastrointestinal disorders, attention and concentration deficits, are non-conclusive.

It is important to state that the implementation of a diet without nutritional and medical control can cause very specific deficiencies. A study conducted in Spain showed that a gluten- and casein-free diet resulted in weight loss and a lower BMI, as well as a lower intake of essential nutrients (like phosphorus and calcium among others), but an appropriate intake of legume fiber and vegetables [70]. However, vitamin D supplementation is recommended, as well as an evaluation of the long-term nutritional and behavioral effects. One case of vitamin deficiency-induced xerophthalmia was observed in an autistic patient following a GFD [71].

A gluten- and casein-free diet should only be implemented if an allergy or intolerance to gluten or milk is diagnosed

The exposure to a gluten- and casein-free diet for a week did neither affect the maladaptive behavior nor the intensity of the gastrointestinal symptoms or the urinary excretion of the fatty acid-binding protein (I-FABP) in autistic children [72]. More long-term studies to evaluate the physiopathological mechanisms of the enterocyte in autistic children are needed.

Most of the research that evaluates the effectiveness of a gluten- and casein-free diet in autistic children presents serious methodological problems. The evidence that is shown to support the therapeutic value of this diet is limited and weak. A gluten- and casein-free diet should only be implemented if an allergy or intolerance to gluten or milk is diagnosed [69].

Conclusions

Healthy nutritional habits should be encouraged in all children independently of the existence or non-existence of neurodevelopmental disorders. Restriction of sugar and sweeteners, elimination diet of colorants/preservatives and supplementation of omega-3 fatty acids may be recommended to ADHD patients to improve behavioral and attention performance. Vegetarian diets are widely recommended to have a beneficial effect on human health. However, it is recommended to be controlled by specialists, especially in childhood and adolescence, to prevent iatrogenic deficiencies.

The scientific evidence of the use of a diet free of gluten and casein in the treatment of autism is weak and poor. It is proposed that a diet free of gluten and casein should only be administered if a food allergy or gluten intolerance is diagnosed. GFD is indicated for the treatment of celiac disease, wheat allergy and NCGS. This diet has to be implemented under professional supervision to avoid imbalanced ingestion.

Vegetarianism does not pose any nutritional threat as it includes egg and milk. With adequate supplementation of calcium, vitamin B_{12} and other micronutrients as well as under professional supervision, children will receive all necessary nutrients. On the other hand, vegan diets are not recommended at any age, vegetarian diet is a feasible alternative if implemented with supervision by a specialist, especially during vulnerable periods of life.

Disclosure Statement

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