

REVIEW ARTICLE

Food allergy and food-based therapies in neurodevelopmental disorders

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Abstract

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are neurodevelopmental disorders which occur in childhood and may persist into adulthood. Although the etiology of these disorders is largely unknown, genetic and environmental factors are thought to play a role in the development of ASD and ADHD. Allergic immune reactions, in prenatal and postnatal phases, are examples of these environmental factors, and adverse reactions to foods are reported in these children. In this review, we address the clinical and preclinical findings of (food) allergy in ASD and ADHD and suggest possible underlying mechanisms. Furthermore, opportunities for nutritional interventions in neurodevelopmental disorders are provided.

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Already in 400 B.C., Hippocrates described the importance of the gastrointestinal (GI) tract in health and disease, by stating 'bad digestion is the root of all evil'. Although written in a period long before the major developments of modern medicine, current understanding of the physiology of the GI tract proves him right in many ways. The intestines have a profound effect on the entire body, including the brain (1). Discovery of the enteric nervous system (ENS) around 1900 was pivotal in the field of gut-brain interactions. Consisting of a complexity comparable to the central nervous system (CNS), the ENS is often described as the 'second brain' (2). Bidirectional communications between the brain and the gut occur via various pathways, involving the vagus nerve, autonomic nervous system and neuroimmune interactions both in the GI tract and in the brain (3). Over the past few decades, strong correlations have been observed between the occurrence of GI problems and psychiatric disorders, which have augmented the interest in the gut-brain connection (4). Food allergy is suggested to be one of the GI triggers for various psychologic and psychiatric conditions. Allergic reactions to food are primarily observed in children, and an association with neurodevelopmental disorders has therefore been proposed.

Although the significance of this link is still under debate, a considerable amount of literature has been published on food allergy or food-based therapies both in the fields of autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD). However, no review has thus far combined the knowledge on food allergy, derived from both fields. In this review, we discuss the clinical and preclinical findings on (food) allergic reactions and food-based therapies in neurodevelopmental disorders of the autism and attention deficit hyperactivity spectra, and we describe possible mechanisms of action.

Food allergy

Under physiologic conditions, the body develops a tolerogenic reaction to harmless food antigens. Oral tolerance is a consequence of complex immune cell interactions, among which dendritic cells (DCs) and various subsets of T cells are involved. Oral tolerance is characterized by immunosuppressive conditions, in which regulatory T cells (Tregs) produce transforming growth factor (TGF) β and interleukin (IL) 10 to suppress the inflammatory response (5). Loss of tolerance is

most often observed toward high allergenic food proteins, derived from, for example, cow's milk, peanut, egg, soy, and wheat, resulting in an allergic response. Food allergy can be defined as an immune-mediated hypersensitivity reaction against food proteins. Although different immunologic mechanisms can underlie the pathology, food allergy is generally characterized by T helper (Th) 2 skewing of the immune system and is accompanied by reduced Treg function (5).

The majority of food-allergic reactions is mediated by immunoglobulin (Ig) E. Antigen-specific IgE is secreted by plasma cells upon antigen presentation by Th2 cells and stimulation with Th2-associated cytokines including interleukin (IL)-4, -5, and -13. IgE binds to its receptor on mast cells or basophils, and after a successive food exposure, the allergen can bind conjugated IgE, inducing mast cell degranulation and secretion of inflammatory mediators such as cytokines, histamine, leukotrienes, and prostaglandin. As the onset of symptoms evolves within several minutes to several hours after contact with the allergen, immunoglobulin-mediated allergic reactions are also referred to as 'immediate type hypersensitivities'. During non-IgE-mediated reactions, the allergic response can be mediated by Ig-free light chains (6) or by cells. Cell-mediated food allergy does not involve immunoglobulins, and onset of symptoms is observed from one hour to many days after ingestion of the food protein. Cell-mediated food allergy is therefore classified as 'delayed type hypersensitivity' and is mediated by Th1 and Th17 cells. IgE-mediated food allergy can be diagnosed by skin prick test and allergen-specific serum IgE levels. Unfortunately, no standardized test is available for detection of non-IgE-mediated food allergy, and diagnosis is based on elimination of the suspected allergenic food for several weeks. A challenge test can be used to confirm the diagnosis.

Clinical symptoms of food-allergic reactions are not restricted to the GI tract, but also involve the skin and airways. In addition to these non-GI symptoms, it has also been suggested that behavioral and psychologic symptoms can be evoked by allergic reactions (7). Food allergy has been implicated in anxiety, depression (8), migraine (9), schizophrenia (10), ASD (11), and ADHD (12). Not only food allergy, but also allergic asthma has been associated with behavioral dysfunction (13). A meta-analysis revealed that internalizing behaviors were more frequently reported in children with asthma and asthma severity correlated with behavioral scores (14). Furthermore, the prevalence of developmental and behavioral dysfunction, including ADHD, was shown to be twice as high in children with, compared to children without asthma and was associated with disease severity (15). It is unknown whether this association has a direct cause-effect relationship or an underlying common etiology. A meta-analysis not only demonstrated a positive association between overall allergic disorders and psychosocial abnormalities, but also claimed that psychosocial factors and neurodevelopment can contribute to the development of allergic disorders (16). Recently, Meldrum and colleagues observed that children suffering from allergic diseases in the first year of life scored lower in behavioral outcomes compared with controls, indicating that allergic diseases during infancy predict later

neurodevelopmental scores. More specifically, children with eczema in the first year of life had relatively poorer gross motor skills, whereas food allergy was predominantly associated with lower social emotional scores and internalizing behaviors (17). We hypothesize that both prenatal and postnatal allergic immune activation regulates complex, but critical, neuroimmune interactions and therefore affects neurodevelopment and brain function. Together with a genetic pre-disposition and multiple environmental factors, these effects of allergic immune activation might contribute to the development of ASD and ADHD (Fig. 1).

Food allergy in autism spectrum disorder

Autism spectrum disorder is a heterogeneous cluster of neurodevelopmental disorders characterized by impairments in communication and social interaction and by repetitive behavior (18). The gut-brain axis is an emerging field of research on ASD. Accumulating evidence strongly suggests that GI dysfunctions and abdominal pain are often present in children with ASD (19). The reported prevalence of GI symptoms ranges from 9% to 91%, an immense range probably due to varying interpretations of GI problems, inability of ASD children to express their discomfort and the heterogeneity of the disorder. The cause of these GI symptoms has been attributed to increased intestinal permeability (20), intestinal inflammation (21), changes in microbial composition (22), and allergic reactions (11). Parents of autistic children reported more often that their child suffered from food allergies than parents of healthy children or children with special education needs (23, 24). Indeed, serum levels of immunoglobulins IgA, IgG, and IgM specific for cow's milk-derived allergens and total IgE were increased in children with ASD compared with healthy controls (25). In addition, peripheral blood mononuclear cells (PBMCs) of ASD children produced more tumor necrosis factor (TNF)- α and IL-12 in response to cow's milk-derived allergens than those from control subjects (26). Furthermore, milk intake by autistic patients was a significant predictor of constipation (27) and led to the worsening of some of the behavioral symptoms specific for ASD (25). Gluten intake has also been suggested to exacerbate autistic behavior (28, 29) although no association between gluten sensitivity or celiac disease and ASD has been reported (30).

Supporting the assumed role of allergy in ASD, an imbalance in T-cell subsets has been suggested in these patients. Low numbers of Th1- type interferon (INF)- γ and IL-2 positive cells were observed in blood of ASD children compared with healthy controls (31). Moreover, significant differences were observed between Th2 cytokine production by PBMC from autistic children when compared to age-matched controls regarding IL-4, IL-5, and IL-13 (32). Concerning regulatory T-cell responses, reduced levels of IL-10 and TGF- β were observed in children with ASD (33, 34), indicating reduced tolerance to antigens. Furthermore, these low TGF- β levels correlated with worse behavioral scores (33), suggesting that reduced regulatory T-cell responses could be involved in the regulation of autistic behavior.

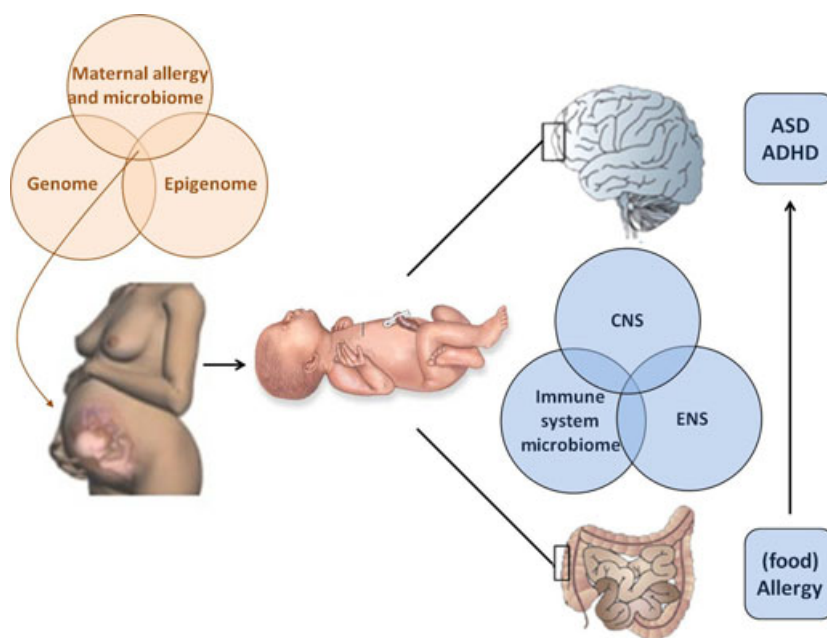


Figure 1 Multifactorial etiology of neurodevelopmental disorders. In addition to the genetic pre-disposition via genetic mutations (genome), epigenetic changes in gene expression by means of DNA methylation and histone modification (epigenome) can cause deficits in neurodevelopment leading to autism spectrum disorder and attention deficit hyperactivity disorder. Maternal allergic immune reactions might enhance such epigenetic changes. Furthermore, also during postnatal development, (food) allergic immune activation is thought to affect brain function via neuroimmune interactions that affect the enteric nervous system and central nervous system. As food allergy changes microbial composition (microbiome) in the gastrointestinal (GI) tract of the mother and new born, it is compelling to consider the microbiome-gut-brain axis as a mediator in these neuroimmune interactions in the GI tract.

Food allergy in attention-deficit hyperactivity disorder

Attention deficit hyperactivity disorder is a neurodevelopmental disorder that is characterized by inappropriate symptoms of inattention, impulsiveness, and hyperactivity (18). Although little research in the field of ADHD is focused on the involvement of the gut-brain axis, the importance of allergic diseases and the influence of dietary factors have received considerable attention. The relationship between allergic diseases and ADHD has been a matter of debate ever since Geschwind and Behan hypothesized on an association between left-handedness, immune disease, and developmental learning disorders (35). Subsequent studies provided conflicting results, where some groups found no significant association between prevalence of ADHD and allergic diseases (36–39), but others did (40). From a systemic review in 2010, it was concluded that ADHD was positively associated with eczema and asthma, but not with allergic rhinitis and total serum IgE levels (40). On the contrary, a successive study showed that only the prevalence of allergic rhinitis, but not other allergic diseases, was associated with ADHD. In this study, the frequency of any positive skin prick test, however, was higher in ADHD patients compared with controls (41). More recent data revealed that pediatric patients with allergic disorders had a substantially increased risk of developing ADHD (42, 43), and conversely, patients with ADHD had an elevated risk of developing allergic diseases (44, 45).

Research on atopic diseases in ADHD patients is predominantly focused on asthma, eczema, and rhinitis, but findings regarding food allergy are limited. One case study showed that a 7-year-old boy with ADHD and severe IgG-mediated food allergy received a dietary supplement intervention that lowered IgG antibodies and was accompanied by improvement in behavior (46). However, in a small study of 40 patients with ADHD, no significant increase in a positive skin prick test to food allergens was observed compared with controls (41). A different approach to test the importance of food allergens in ADHD children is a food challenge. Hyperactive children reacted badly to allergenic foods like cow's milk, wheat, and eggs (47–49). This reaction was not associated with a positive skin prick test although total serum IgE levels were higher in responders compared with non-responders (48). Because of the mixed results on the involvement of a food-allergic reaction, Pelsser and colleagues postulated a new intriguing hypothesis. They suggested that ADHD is not caused by the allergic response, but that ADHD is a (non-) allergic hypersensitivity disorder itself. Food-derived allergens trigger a hypersensitivity reaction that causes ADHD symptoms, possibly via an IgE or non-IgE allergic response or a non-allergic mechanism (12). According to the hypothesis, ADHD can be subdivided in hypersensitive and non-hypersensitive ADHD, derived from different pathophysiologies. This would provide opportunities for nutritional interventions or elimination diets for a subset of children with ADHD.

Mechanisms

Maternal factors

Maternal allergy has been shown to be a stronger determinant of allergy in offspring than paternal allergy, indicating that the maternal allergic response affects the immune system of the developing fetus *in utero* (50, 51). In addition to prenatal development of the immune system, development of the brain is also highly sensitive to maternal immunologic and psychologic challenges. Chronic maternal stress not only affects behavioral and cognitive functions later in life (52), it also affects immune system development. High blood levels of cortisol have been shown to shift the cytokine balance to a Th2-type profile (53). As high maternal cortisol levels reflect those of the fetus, it is likely that this Th2-type profile is also provoked in the developing fetus. Indeed, adult women who were exposed to chronic stress during prenatal development established a Th2-type dominated immunity (54), which increases the risk of allergic sensitization.

Accumulating evidence indicates that maternal infection during pregnancy is a significant risk factor for the development of schizophrenia in offspring (55). Also in patients with ASD, prenatal immune activation is suggested as an environmental risk factor. Maternal viral infection in the first trimester and bacterial infection in the second trimester were found to increase the risk of ASD in the offspring (56). In addition, animals prenatally exposed to infections display features relevant to autism in humans, suggesting a causal link between maternal immune activation and autistic behavior (57). Maternal allergies are also implicated to put the offspring at risk of developing ASD. In a large study population, a greater than twofold elevated risk of ASD was observed for maternal asthma and allergy diagnosed during the second trimester, but not for maternal autoimmune diseases (58). Furthermore, a preliminary report indicated that mothers with mastocytosis during pregnancy, characterized by increased number of mast cells in many organs, had a higher risk of delivering a child with ASD (59). Although little research is conducted on the importance of prenatal immune activation in patients with ADHD, one study suggested that viral rashes during pregnancy increased the risk of developing ADHD in the offspring (60).

Elevated levels of proinflammatory cytokine IL-6 have been claimed as a mechanism underlying the effect of maternal immune activation on neurodevelopment. Indeed, prenatal exposure to IL-6 alone is sufficient to initiate abnormal behavior and neurodegeneration in the hippocampus of rodents (61). IL-6, which is able to cross the placenta and the blood-brain barrier (62), has been shown to affect developing serotonergic and dopaminergic neurons *in vitro* (63). In patients with autism, increased levels of serotonin in platelets have been repeatedly described and it is hypothesized that this phenomenon is due to an enhanced serotonin transporter (SERT) activity (64). Treatment with selective serotonin reuptake inhibitors (SRRI) has favorable effects in some children (65). Furthermore, associations with important genes in the dopaminergic pathway have also been reported in both ASD and ADHD (66), including the dopamine transporter gene DAT1. Cytokines in the CNS can activate monoamine transporters

(67), resulting in reduced neurotransmission, which may lead to symptoms observed in ADHD and ASD (68). Interestingly, maternal immune activation in animal models caused defects in dopaminergic development in the offspring (69–71), and neutralization of IL-6 in pregnant dams prevented the dopaminergic and behavioral alterations induced by maternal immune activation (72). These findings suggest that prenatal immune activation disturbs neurodevelopment via IL-6, leading to behavioral abnormalities as found in ADHD and ASD.

Mast cells

One of the most crucial cells in allergy is the mast cell. Not only immunoglobulins, but also several neuropeptides can trigger mast cell activation, including substance P, nerve growth factor (NGF), vasoactive intestinal peptide (VIP), and neurotensin (73). In food allergy, mast cells express various substances that can trigger enteric neurons, such as tryptase, histamine, 5-HT, NGF, and TNF- α (74). Mast cell–neuron interactions occur in the GI tract, for instance in inflammatory bowel disease and irritable bowel syndrome (74). In theory, an allergic reaction in the gut might therefore influence behavior via intestinal mast cells, which are able to trigger enteric neurons to convey information through afferent sensory pathways to the CNS. Although there is very little direct evidence suggesting that mast cells are involved in neurodevelopmental disorders, a preliminary report indicated ASD to be more prevalent among children with mastocytosis (59).

Activated Th2 and mast cells produce IL-6, which promotes B cell differentiation and production of immunoglobulins (75) and inhibits Tregs (76), leading to an enhanced allergic reaction. The production of IL-6 by activated mast cells is mediated by the mammalian target of rapamycin (mTOR) pathway (77). Deficiency of PTEN, a negative regulatory molecule of mTOR, caused mastocytosis in mice and increased mast cell degranulation and IL-6 production, leading to a higher allergic response (78). Interestingly, besides the effect on the allergic response, PTEN-deficient mice also developed autistic features in behavior (79). Indeed, increased mTOR signaling has been suggested to be involved in neurodevelopmental disorders. For example, tuberous sclerosis, a genetic disorder of mutations in tuberous sclerosis complex (Tsc) 1 or Tsc2 genes that negatively regulate mTOR, is associated with ASD (80) and ADHD (81). In conclusion, increased activity of the mTOR-signaling pathway causes higher IL-6 production by mast cells and mastocytosis in mice, leading to a higher allergic response. Furthermore, it is associated with neurodevelopmental disorders and causes behavioral deficits in mice. Possibly, the effects of mTOR activity on behavior are partially mediated by IL-6, as enhanced mTOR activation results in IL-6 production, and IL-6 has been shown to induce behavioral deficits and is enhanced in post-mortem brains of patients with ASD (82, 83).

Microbiome

The microbiome has been a major point of attention in research on the gut-brain axis. Recently, it has been shown that gut

bacteria influence CNS development and therefore behavioral and cognitive responses. For example, germ-free mice expressed decreased anxiety-like behavior, while colonization of these mice early in life, but not as adults, normalized these behavioral deficits (84). This indicates that the microbiome contributes to neurodevelopment, and it is compelling to consider its influence on ASD and ADHD. Several groups have studied the intestinal microbiota of the autistic human population and found differences in composition of *Ruminococcus*, *Bacteroides*, and *Desulfovibrio* genera from the Clostridia, Bacteroidetes, and Proteobacteria classes, respectively (85–88). A recent study demonstrated lower levels of *Bifidobacterium* and higher levels of *Lactobacillus* in ASD, both considered to be beneficial bacteria (89). Interestingly, antibiotic treatment for ASD children not only led to GI improvements, but also improvements in cognitive skills (90). However, more research on the microbiome of children with ASD is required to understand the role of a microbial factor in ASD. To our knowledge, no studies have been published on the microbial status of children with ADHD. Investigating the microbial composition of children with ADHD could lead to new insights on the effects of food or food allergy on behavior in these patients.

Interestingly and very recent, the first proof in human showing that the microbiome–gut–brain axis exists has been reported (91). In this study in healthy women, chronic ingestion of several strains of gut bacteria, including *Bifidobacterium* and *Lactobacillus*, reduced activity of brain regions involved in processing of emotion and sensation. Several possible mechanisms have been proposed in which the microbiome can modulate brain activity. Preclinical models indicate that the microbiome can signal to the brain via vagal afferent nerves and the nucleus tractus solitarius (NTS) (1). This signaling could be mediated by direct communication of microbiota with the intestinal epithelium and serotonin-producing enterochromaffin cells, affecting the ENS and immune system. The microbiome can also target epithelium and enteric nerves via the production of short-chain fatty acids and neuroactive signaling molecules (1, 92). Nevertheless, more (pre)clinical research is needed to identify the signaling pathways by which the microbiome communicates with the brain in health and in neurodevelopmental disorders.

Food-based therapies

If children with a genetic pre-disposition are more susceptible to develop ASD or ADHD when exposed to an allergic immune challenge, allergen-free diets and immunomodulatory dietary interventions could be beneficial for the treatment of behavior. Indeed, approximately 30% of ASD patients (93) and 12% of ADHD patients (94) are using complementary and alternative medicine (CAM). Examples of such treatments include the exclusion of hyperallergenic foods and use of polyunsaturated fatty acids (PUFAs), vitamins, and mineral supplements.

Both in ASD and ADHD, elimination diets have received most attention. Although the efficacy of an elimination diet in children with both disorders is still under debate, exclusion of hyperallergenic foods was claimed to be beneficial in multiple

studies. Considering ASD, studies indicate that gluten and milk-free diets improved behavior in children with ASD (95, 96). In addition to these behavioral improvements, gluten and milk-free diets were also shown to reduce the enhanced intestinal permeability observed in ASD patients (20). However, large double-blind and well-controlled trials are required to strengthen these observations. Considering ADHD, foods that are often eliminated are cow's milk, wheat, egg, chocolate, cheese, nuts, and citrus fruits. Two early studies reported that behavioral symptoms improved in children with ADHD (47, 48). More recently, Pelsser and colleagues observed improvements in behavior in 62% of ADHD patients using an elimination diet (97). The effectiveness of this diet was further investigated in a randomized controlled 'INCA' trial (98). In this successive study, 64% of children with ADHD on the elimination diet responded by showing improvement in behavior after 5 wk. However, serum levels of food-specific IgE and total IgE did not differ between responders and non-responders. These findings suggest that ingested foods can affect behavior in a subset of children with ADHD through a mechanism that involves a non-IgE-mediated, cell-mediated, or non-allergic response.

In addition to the use of an elimination diet in ASD or ADHD patients, dietary ingredients such as omega-3 PUFAs, non-digestible oligosaccharides, and beneficial bacterial strains might also be beneficial to the dietary management of behavior, because of their effects on CNS, immune system, and microbiota profile. Nutritional supplementation with omega-3 was observed to be beneficial in both ASD (99) and ADHD (100). Decreased levels of incorporated omega-3 PUFAs have been observed in peripheral blood cells of ASD and ADHD (100) patients repeatedly. After treatment with (omega-3 rich) fish oil, PUFA levels and ratio of omega-6/omega-3 were restored and a significant improvement of behavior was observed in patients with ASD (99) and ADHD (100). PUFAs are present in neuronal membranous phospholipids, where they modulate membrane fluidity and thereby affect receptor function, resulting in changes in neurotransmitter release and uptake (101). In addition to effects on the brain, omega-3 PUFAs have also been claimed to modulate the immune response. Omega-3 PUFAs can be incorporated in the membrane of immune cells, where they modulate intracellular pathways, such as nuclear factor κ B (NF κ B) and peroxisome proliferator-activated receptor (PPAR)- γ , leading to an anti-inflammatory response through the production of resolvins and inhibition of leukotrienes, prostaglandins, proinflammatory cytokines, and adhesion molecules (102). Therefore, supplementation of omega-3 PUFAs could be beneficial for patients with ASD and ADHD, either by acting directly on neuronal responses or indirectly via the immune system and GI tract. (103).

The effects of non-digestible oligosaccharides and beneficial bacterial strains in the treatment for neurodevelopmental disorders have not been studied. Regarding allergic diseases, non-digestible oligosaccharides were shown to be beneficial for disease progression and immune status (104, 105). Non-digestible oligosaccharides consist of naturally occurring sugar base units that are not hydrolyzed in the upper small intestine

and reach the large intestine intact to serve as substrates for bacterial metabolism. Non-digestible oligosaccharides are suggested to selectively stimulate growth and/or activity of Bifidobacteria and lactic acid bacteria in the colon, which are important markers of a healthy gut microbiota (106, 107). Considering the increased recognition of a microbial role in the regulation of behavioral responses and neurodevelopment, children with ASD and ADHD may benefit from dietary supplementation with non-digestible oligosaccharides or beneficial bacterial strains. Beneficial bacterial strains were thought to reduce intestinal permeability and restore a 'healthy' gut (108), which could be of specific importance in the treatment for GI disturbances and behavioral deficits of ASD patients. However, preclinical studies in disease models of ASD and ADHD are required to study the benefits and safety of supplementation with non-digestible oligosaccharides and beneficial bacterial strains in the treatment of behavior.

As prenatal (immune) factors are thought to have detrimental effects on behavior of the offspring later in life, it may be even more interesting to provide genetically or environmentally predisposed mothers with beneficial diets during pregnancy. Preclinical murine studies showed that a maternal diet rich in omega-6 during gestation and lactation induced autism-like behavior in offspring (109). Omega-3-rich fish consumption during pregnancy was shown to be protective of ADHD-related behavior in children (110). Furthermore, a traditional Dutch diet during pregnancy was positively associated with externalizing behaviors in children, while a Mediterranean diet was negatively associated (111). Folic acid supplementation during pregnancy protected offspring from internalizing and externalizing behaviors and the development of ASD (112, 113). These results indicate that the maternal diet during pregnancy affects neurodevelopment and thus the risk of developing ASD or ADHD. Therefore, future research should

not exclusively be focused on nutritional interventions in postnatal development but should also aim at beneficially directing neurodevelopment via maternal diets.

Conclusion

In this review, we addressed the findings of (food) allergic diseases and food-based therapies in ASD and ADHD. Based on clinical and preclinical observations, it seems feasible to hypothesize that allergic reactions to foods indeed trigger or worsen the manifestation of neurodevelopmental disorders in at least a subset of pediatric patients. In children with ASD, these allergic reactions could be both IgE as non-IgE-mediated, while in ADHD, it is more likely that non-IgE-mediated, cell-mediated, or non-allergic responses to foods are involved. We hypothesize that both prenatal and postnatal allergic immune activation regulate complex, but critical, neuroimmune interactions and therefore affect neurodevelopment and brain function. Pathways involved in allergy-mediated effects on neurodevelopment and behavior could include neuroimmune interactions induced by mast cells and cytokines such as IL-6, as these mediators have been shown to induce behavioral deficits in preclinical models and are enhanced in ASD patients. Changes in the microbiome and subsequent signaling to the brain could also be involved in the behavioral consequences of an allergic response. Nevertheless, very little preclinical research is conducted on the prenatal and postnatal effect of an allergic response on neurodevelopment and behavior related to ASD and ADHD. Untangling the mechanisms underlying the effects of hyperallergenic foods and food-allergic reactions on neurodevelopmental impairments could lead to new targets for the treatment of children with ASD or ADHD.

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