Nutrition, immunological mechanisms and dietary immunomodulation in ADHD

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Abstract Attention-deficit hyperactivity disorder (ADHD) etiology is not completely understood, but common comorbid dysfunction of the gastrointestinal and immune system suggests that these systems may be affected by a common genetic background and molecular mechanisms. For example, increased levels of specific cytokines were observed in ADHD. Moreover, ADHD has a high comorbidity with both Th1- and Th2-mediated disorders like ear infections, eczema and asthma. A common pathophysiological mechanism was suggested to underlie both asthma and ADHD, while several genes that are linked to ADHD have immune functions. Furthermore, immunological recognition of food provoking ADHD-like behavior was suggested. An immune imbalance, probably requiring a predisposing genetic background, is therefore suggested to contribute to ADHD etiology, with immune dysregulation being more likely than a single subcellular defect. However, next to allergic mechanisms, also pharmacological mechanisms (especially in case of food additives) might be involved. In addition, though cellular (cytokine-related) rather than antibody-mediated immune mechanisms seem involved, specific immune-inflammatory markers other than antibodies have not been systematically studied in ADHD. Substantial alterations implicated in ADHD apparently occur in the immune system and epigenetic regulation of gene expression. As a result, chronic inflammation and oxidative stress could develop, which can lead to ADHD symptoms, for example by chronic T-cell-mediated neuroinflammation. If immune pathways contribute to ADHD, both its diagnosis and treatment should be reconsidered. Modulation of immune system activity might have potential in ADHD treatment, for example by nutritional approaches providing safe and low-cost ADHD therapy, but further research in these fields is implicated.

Keywords ADHD · Dietary intervention · Immune mechanism · Immunomodulation · Nutrition

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common neurocognitive behavioral disorder with childhood onset. Currently ADHD has a prevalence of 8–12 % worldwide [1]. The core symptoms of this disorder are hyperactivity, impulsivity and inattention, associated with impaired dopaminergic and noradrenergic transmission [2]. ADHD is a major public health problem since it affects several aspects in the life of affected subjects, both in childhood and adulthood [1]. In addition, ADHD is frequently associated with other psychiatric disorders, such as oppositional defiant disorder (ODD), conduct disorder (CD), depression and anxiety. Moreover, affected subjects are at higher risk for substance abuse and criminal behavior [1, 3]. Therefore, this disorder represents a heavy (financial) burden for patients, as well as for their family and society [4].

Since ADHD is prevalent around the world, available epidemiological characteristics of populations can provide a clue into the distribution and etiology of this disorder [1].
A recent article indicates a clear effect of geographical location on ADHD prevalence: solar intensity explained 34–57% of the variance in ADHD prevalence, with an apparent preventative effect of high solar intensity [5]. However, also other aspects of this disorder should be evaluated to be able to explain its variability and heterogeneity.

Currently, the main treatment for ADHD is pharmacological, using stimulant drugs such as methylphenidate (MPH) and dexamphetamine and the non-stimulant drug atomoxetine, which reduces symptoms in the majority of children and adolescents. Research indicates that the combination of pharmacological treatment with behavioral therapy may be the most beneficial form of therapy for children diagnosed with ADHD [1]. MPH is the primary choice of medication for ADHD and although the benefits, until now, outweigh the risks, this medication has potentially serious side effects. The most common side effects of MPH are headaches, sleeping disturbances and loss of appetite [6]. Severe adverse effects, like psychotic symptoms and mood disorders, are reported in 0.25% of children treated with MPH [7]. In addition, also cardiovascular concerns regarding the use of MPH were raised. In adults, initiation of MPH is for example associated with an increase in risk of sudden death or ventricular arrhythmia [8]. As MPH increases heart rate and blood pressure in all age groups, great caution is advised regarding its use, especially in those with a family history or other known risk factors for cardiovascular disease [9,10]. Consequently, parents are disinclined to use MPH and non-adherence to therapy is rather high. In addition, until now full symptom reduction in ADHD patients is yet to be achieved and the burden of ADHD associated consequences has not been diminished [6,11–13]. More research is therefore needed to explain the etiology of this complex neurobiological disorder, while benefits of alternative therapies should be explored.

Etiology of ADHD

ADHD is considered a heterogeneous, complex and multifactorial disorder, influenced by both genetic and environmental factors (Fig. 1). However, the exact pathophysiology of this disorder remains unclear. In addition, factors involved in ADHD causation are interchangeable and no individual factor is either necessary or sufficient to trigger ADHD [1,14,15]. In fact, heterogeneity might be a central factor in the clinical variability of the disorder, illustrated by the multiplicity of involved genes and associated environmental factors [16]. It is also unclear whether distinct ADHD subtypes and ADHD with and without certain comorbidities have a distinct etiology [14].

Genetic factors

Genetic factors play a dominant role in ADHD etiology, as illustrated by studies exploring the familial transmission of ADHD, which indicated that the heritability of ADHD is approximately 75% [1,17]. ADHD is often comorbid with for example personality disorders and obesity. Due to a potentially heritable nature of these disorders, their genetic framework may contain common risk-modifying genes [18,19]. Still, only a limited number of genes with small effect sizes have been repeatedly identified by genome scans to be associated with ADHD. None of these individual genes has substantial effects, indicating that genes with a large effect probably do not exist [14]. Moreover, specific ADHD susceptibility genes are still missing and also genome-wide significant results were not found in genome-wide association studies (GWAS), e.g., in German children with ADHD compared to controls [20]. The Cross-Disorder Group of the Psychiatric Genomics Consortium executed a GWAS focusing on the identification of risk loci with shared effects on five major psychiatric disorders, including ADHD. The results provide evidence relevant to the disease cause [21,22]. However, such interpretation ignores the possibility that there are secondary adaptive or compensatory mechanisms alongside primary pathophysiological processes. Future research thus has to distinguish between genetic alterations related to core psychopathological processes and those related to putative secondary adaptive mechanisms.

Environmental factors

The contribution of environmental factors to ADHD is estimated to be 20–30% [14]. Environmental factors that have been linked to ADHD are low socioeconomic class, foster placement and family dysfunctions. In addition, several studies show that pregnancy-related factors, such as low birth weight, delivery complications, prematurity, dysmaturity, and prenatal alcohol and/or tobacco smoke exposure, may be considered environmental risk factors for ADHD [1], presumably by inducing epigenetic effects. Epigenetic effects on gene activation and inactivation are increasingly understood to be important in phenotype transmission and development. The level of gene expression and epigenetic factors can be modulated by environmental factors, indicating that gene-by-environment studies will be promising for the future [15,23,24].

Stress

Perinatal stress can cause disturbances in the endocrine and immune system involved in the hypothalamus–pituitary–
adrenal (HPA) axis activity, associated with the major stress hormone cortisol [25]. As is widely accepted, cortisol acts by its nuclear receptor on antigen-presenting cells to suppress the production of interleukin (IL)-12 and IL-18, thereby inhibiting type 1 T-helper cell (Th1) responses (characterized by immunoglobulin (Ig) G3 antibodies and the cytokines tumor necrosis factor (TNF)-α, interferon (IFN)-γ and IL-2), while increasing IL-4 mediated type 2 T-helper cell (Th2) activity (with IgG4 antibodies and IL-4, IL-10 and IL-13) [26]. As a result, cortisol affects the Th1/Th2 balance and high physiologic concentrations of cortisol shift the immune response from pro-inflammatory Th1 predominance to a more balanced pro-inflammatory Th1/anti-inflammatory Th2 cytokine profile, most likely due to increased numbers of regulatory T-cells (Treg)—an important autoregulation mechanism in the control of inflammatory responses [25–27]. In children suffering from ADHD, cortisol production is found to be relatively deficient [28], and we hypothesize that their concentrations of Th1-derived pro-inflammatory cytokines are elevated while the Th2-derived anti-inflammatory IL-10 is depressed at the expense of generating sufficient numbers of Treg [27]. The resulting defective down-regulation of inflammation and lack of balanced immunoregulation may thus contribute to an enhanced pro-inflammatory cytokine synthesis, which has a major role in the pathophysiology of brain white matter damage, as chronic elevation of TNF-α and IL-6 prime cells to undergo apoptosis or necrosis [26]. Under ADHD conditions, this low cortisol level could therefore promote defective Treg immunomodulation and enhanced Th1 (neuro)inflammation and thereby stress-related impairments in children’s self-regulation at the emotional, cognitive and behavioral levels [26–28]. In some ADHD children, this decrease in Treg formation could be very profound, which could then result in a Th2-driven inflammation making the child “allergy-prone” by inducing activated B-cells, mast cells and eosinophils [26]. Based on this notion, an additional, but controversial, theory is that dietary factors and inhalants can contribute to ADHD via Th2-like hypersensitivity reactions, either by exacerbating symptoms or by being part of the causation etiology [29, 30].

**Nutrition and behavior**

The occurrence of adverse physical reactions to foods (e.g., eczema, asthma, gastrointestinal (GI) disturbances) in
combination with the high comorbidity of behavioral and physical complaints, stimulated speculations that foods might not only affect organs like the skin, the GI tract and the respiratory system, but might also have an impact on the brain, resulting in adverse behavioral effects [2, 30–33].

Currently, there is evidence to support the theory that nutrition plays a role in hyperactivity and attention disorders, as cited by the editor of the American Academy of Pediatrics Ground Rounds: “The overall findings (…) require that even we, skeptics, who have long doubted parental claims of the effects of various foods on the behavior of their children, admit we might have been wrong” [34]. However, despite the evidence, this theory remains a controversial issue in the scientific community [32].

Adverse reactions to specific foods and food additives, exposure to toxic food contaminants and suboptimal levels of micronutrients such as essential fatty acids (FA), zinc, magnesium and iron have been described in children with ADHD [2, 31]. In addition, in some patients, a genetic impairment in fatty acid metabolism was described [32].

Behavioral reactions related to food

The controversy regarding the association between ADHD symptoms and hypersensitivity or intolerance to certain food additives (FA) begun in the 1970s when Feingold published the Kaiser-Permanente (K-P) diet, which aims at eliminating naturally occurring salicylates, artificial food colors (AFC) and flavors, and the preservative butylated hydroxytoluene. Through the years, many studies have been performed to test this diet [2, 31, 35]. Though results have been inconsistent, a meta-analysis of double-blind placebo-controlled trials concluded that there is evidence to support the theory that AFC promote hyperactivity in hyperactive children [35]. Bateman et al. [36] performed a population-based study with 277, 3-year-old children to evaluate the effect of AFC and a benzoate preservative on hyperactivity symptoms. Children were divided into four groups: (1) children with hyperactivity and atopy (n = 36), (2) without hyperactivity but with atopy (n = 79), (3) with hyperactivity but without atopy (n = 75) and (4) without hyperactivity or atopy (n = 87). The effect of FA on hyperactivity was substantial and occurred independently of pre-existing hyperactivity or atopy. In addition, there is enough evidence to support that a subgroup of children with ADHD can noticeably improve on an AFC-free diet, though this group may be small (about 10 %) [37]. Overall, the effect of FA seems mediated by a pharmacological mechanism, as for example dose–response effects and effects on a general population of children were observed, but regarding specifically adapted diets (e.g., Feingold diet, gluten-free diet, or diets excluding products like sugar), statistically significant and clinically relevant studies are lacking [36, 38, 39].

Alternatively, besides eliminating or restricting certain foods or components like FA, dietary supplementation is an intervention with potentially beneficial outcomes in ADHD. Clinical and biochemical evidence suggests that deficiencies of polyunsaturated fatty acids (PUFA) could be related to ADHD, as these are considered important for brain development and function [40]. Significantly lower plasma and blood concentrations of PUFA and especially lower levels of omega-3 PUFA have been shown in children and adolescents with ADHD, suggesting that PUFA supplementation may reduce the attention and behavior problems associated with ADHD [40]. In general, however, no statistically significant differences in ratings of overall ADHD symptoms were found in placebo-controlled PUFA supplementation studies, although results are not always consistent. Future research should address current weaknesses in this area, including small sample sizes, variability of selection criteria and supplementation type and dosage, and short follow-up periods [40].

ADHD patients often display lower zinc levels in serum, erythrocytes, hair, urine and nails, and zinc supplementation has proven beneficial, especially in combination with MPH [41]. Likewise, evidence of iron deficiency in children with ADHD was presented, while improvements in attention and behavior were reported following iron supplementation [42]. Other researchers, however, did not find such deficiencies or beneficial effects of micronutrient supplementation, so that further controlled trials are indicated [31, 32].

Allergy and food intolerance

Though most children with ADHD symptoms reacted to FA in the study of Egger and colleagues [43], no child reacted to these alone. The few food diet, also known as oligoantigenic diet, aims to eliminate the most commonly sensitizing allergens from the diet, such as cow’s milk, wheat, eggs and nuts. This diet is supported by the theory that, at least in some children, hyperactivity can be (caused by) a form of food allergy. Food hypersensitivity, including true allergy, and ADHD may share common etiologic pathways, as a behavioral response to food often occurs in ADHD children [30, 43–45]. Specifically, cell-mediated hypersensitivity, rather than an IgE or IgG antibody-mediated allergic response, seems involved, which will result in chronic T-cell stimulation, thereby contributing to the development of a neurologic inflammation [26, 30, 33, 46, 47]. Furthermore, host-mediated inflammation disrupts intestinal microbial composition and such a reaction may contribute further to aberrant responses to foods and
supports the high comorbidity of functional GI and psychiatric disorders through the gut–brain axis [48, 49].

Only a few double-blind studies have evaluated the effect of dietary restrictions and, although characterized by small numbers of participants, their results show a reliable and significant benefit from an elimination diet in a subgroup of ADHD patients [33, 43, 45]. At least in specific subgroups, diet may thus contribute to behavioral problems, probably with involvement of a hypersensitivity mechanism [30, 33, 45, 47]. Therefore, despite the fact that the diagnosis of food sensitivity is complex, in selected patients who are willing and committed to make the effort, a 2–3 week restricted elimination diet (RED) is justified [32, 33]. We have previously hypothesized that a (non-)allergic hypersensitivity disorder can trigger ADHD-type symptoms in some children, sharing mechanisms with immunological reactions: mast cells are activated and cytokines and histamine are released by exposure to triggering foods [30]. Nevertheless, if ADHD symptoms are triggered by food allergies in a subgroup of patients, these reactions do not seem to follow the typical IgE implication as most food allergies do, and also IgG measurements are not proven to be useful [33, 46]. In addition, a RED, involving a totally changed diet, still remains a controversial dietary intervention [2, 31–33].

Possible immunological aspects of ADHD

ADHD has a high comorbidity with both Th1- and Th2-mediated disorders. As compared to controls, ADHD patients have a higher incidence of stomach aches and ear infections, which are Th1-mediated conditions [50], as well as of hypersensitivity and atopic diseases like eczema, asthma and rhinitis, which are Th2-mediated conditions [51, 52]. In recent years, there has therefore been an interest in the potential role of atopy and allergic immunopathology in ADHD. In addition, indications of immunological dysregulation leading to chronic Th2-cell-mediated inflammation (see above), including an increased cytokine profile and eosinophilic activity, support the theory that there is an immunological background that can be part of the causation cascade of symptoms or partly responsible for symptom exacerbation in a subgroup of patients diagnosed with ADHD [50–53]. Since the 1980s it has been hypothesized that allergic reactions implicating an imbalance in adrenergic activity in the central nervous system lead to ADHD symptoms in a subgroup of children [54]. In addition, immunological recognition of provoking foods, rather than a direct biochemical or pharmacological pathway, was suggested, based on the diversity of agents causing a similar response in different children [55, 56]. Dietary proteins can provoke immune reactivity resulting in GI inflammation that may be partly associated with an aberrant innate immune response against endotoxin, a product of gut microbiota [57, 58]. This dysregulated immune response in children with ADHD has been further corroborated by more frequent episodes of physical illness [50] and elevations in pro-inflammatory cytokines with four times higher concentrations of IL-1 and IL-6 [53], which support a chronic immune-mediated neurological inflammation [26, 53, 54]. This overproduction of cytokines can lead to chronic inflammation in brain tissue, which is consistent with findings of gray matter heterotopia and reduced cortical volume and folding in ADHD, and behavioral effects [26–28, 53–55, 59].

Genetic implication of ADHD as an allergic disorder

ADHD, as asthma and other atopic diseases, is highly hereditary [1, 30]. Significant associations between risk factors for ADHD and six ADHD candidate genes were described, i.e., the dopamine and serotonin transporter genes DAT1/SLC6A3 and 5-HTT/SLC6A4, the DRD4 and DRD5 dopamine receptor genes, the HTR1B serotonin receptor gene and the SNAP-25 gene [15, 16, 60]. In ADHD, not only polymorphic variants in specifically identified genes related to the regulation of dopamine, but also noradrenergic and histaminergic receptor systems are involved [14, 30], supporting involvement of the neuroendocrine–immunological network [61]. SNAP-25, a presynaptic plasma membrane protein that is highly expressed in the nervous system, is important in the regulation of synaptic vesicle membrane docking and fusion of exocytotic released neurotransmitters. Furthermore, SNAP-25 modulates several voltage-gated ion channels and is suggested to be involved in histamine release from mast cells [16, 61]. In animal studies, mice with a reduced expression of SNAP-25 presented ADHD-like symptoms and associated striatal dopamine and serotonin deficiencies [60]. In addition, STAT6 (signal transducer and activator of transcription 6, a transcription factor in Th2 cells and thus important for immune regulation)-deficient mice exhibited increased locomotor activity and decreased expression of striatal dopamine transporter, both typical of ADHD [62]. Moreover, the idea that MHC (major histocompatibility complex)-linked genes play a role in the development of immune responses in ADHD was based on significant correlations between ADHD and presence of HLA-DRB1 and HLA-DR4 [63, 64]. Nevertheless, genetic loci for ADHD have not yet been identified by GWAS [20–22].

Epigenetic programming in ADHD

Abnormal intrauterine development and placental insufficiency are considered fetal environmental factors
Asthma is less clear: though most studies found a positive association between ADHD and streptococcal infection and a causative role for otitis media require further confirmation [24, 68]. Indeed, imaging studies in humans have associated abnormal dopaminergic mechanisms within mesocortical and frontostriatal pathways with impairments in attention and ADHD [1, 55]. Such prenatal infections result in enhanced IL-6 signaling, which alters fetal brain (e.g., dopaminergic) development and which can cause long-term brain abnormalities [69, 70]. These imbalances in maternal/fetal cytokines with a shift toward pro-inflammatory cytokine signaling may thus be relevant for prenatal immune activation and link these gene-by-environment interactions to dopamine-associated neuropsychiatric disorders. In addition, also maternal nutrient restriction or specific dietary patterns change placental gene expression, though this can be reversed by supplementation with for example folate, a methyl donor. Specific non-coding RNA is also associated with chromatin modifying activity, resulting in a functional GABA-dependent neuronal development [23]. With respect to stress-related maternal epigenetic induction and resulting childhood modulation of ADHD severity, glucocorticoid production and receptor expression and signaling are all crucially important mediators. This epigenetic process of dynamic DNA methylation in brain neurons (e.g., the hippocampal GR promoter, the serotonin receptor and the nerve growth factor-inducible protein A) is thus likely to be involved in the etiology of mental and behavioral disorders [23].

Atopic diseases and ADHD

Eczema, asthma and rhinitis are often grouped as “atopic diseases”, with 1 in 4 children being affected with one or more of these [30, 71]. The association between atopic diseases and ADHD has been subject of controversy for some time, but a number of studies have reported a significant association between both conditions. For example Schmitt et al. [51] analyzed 1,436 patients with atopic dermatitis and found a significant association with ADHD when compared to controls, while a population-based study reported that pediatric patients diagnosed with an allergic disorder had a significantly increased risk of ADHD [72]. More specifically, various studies reported a positive association between eczema and ADHD or mental health problems [51, 73, 74]. The association between ADHD and asthma is less clear: though most studies found a positive association between both conditions [75–78], the majority did not correct for comorbidity with eczema. Nevertheless, a common pathophysiological mechanism was suggested to underlie both asthma and ADHD [30]. No association has been found between rhinitis and ADHD [75]. Nevertheless, pollen caused neurobehavioral regression in ADHD patients [79].

Both eczema and asthma are inflammatory conditions frequently associated with IgE-mediated hypersensitivity [75]. However, since atopic diseases, in particular eczema, can be mediated by various mechanisms, no information on the atopy mechanism affecting ADHD risk could thus be identified from these findings [30, 80]. In addition, behavioral reactions to food components occur independently of atopy, perhaps by a non-IgE-dependent histamine release from mast cells and basophilic granulocytes, as behavioral hypersensitivity reactions to foods occur in both allergic and non-allergic children [30, 36, 43, 61]. Consumption of offending foods in food allergy can result in increased gut permeability, as measured by the ratio of absorption of mannitol (a marker of normal monomer passage) and lactulose (a marker of macromolecule exclusion), which is consistent with bowel inflammation. Food allergy or hypersensitivity can thus induce an immune dysregulation in the gut, leading to chronic inflammation in the bowel, which can spread throughout the body [81, 82]. Why these hypersensitivities occur, as well as the mechanisms underlying the association between ADHD and atopic diseases, thus remains unclear, but these reactions have been shown to involve components of the immune system and are apparently independent of a family history of atopy and lifestyle factors such as breastfeeding and early day care exposure [30, 50, 72, 74, 75, 78]. In addition, though the relationship between psychological problems and allergic diseases could be bidirectional [83], suggesting a reciprocally causal relationship, the “chicken or egg” debate on this relationship is still ongoing in literature [84, 85]. Nevertheless, it might be no coincidence that ADHD often remits with age [1]. The “atopic march”, the natural history of allergic manifestations, is characterized by a typical sequence of IgE antibody responses and concurring clinical symptoms. The onset of atopic diseases generally tends to be early in life and may therefore be related to the maturation of the immune system. While they persist over years or decades, atopic diseases often remit spontaneously with age [86].

Proposed immune-mediated mechanisms in ADHD

Developmental plasticity in utero can enable the fetus to be functionally resilient to maternal stressors, but at the same time, these adverse early experiences can contribute to stress-sensitive neuroendocrine immune reactivity,
The pathophysiology of atopic disease is hypersecretion of IgE, increased eosinophilic and basophilic activity, increased IL-4 and IL-5-mediated Th2 expression and reduced regulatory T-cell-mediated IL-10 secretion [88, 89]. Therefore, children suffering from an atopic disease present an increased level of pro-inflammatory cytokines, like mast cell-derived IL-6 and TNF-α [87], which may pass the blood–brain barrier and affect neuroimmune mechanisms involving behavior and emotion [90]. In addition, ADHD patients are reported to have a cerebrospinal fluid cytokine profile intermediate to that of patients with obsessive–compulsive disorder (characterized by a skewing to pro-inflammatory cytokines) and schizophrenics (skewing to anti-inflammatory cytokines), with elevated concentrations of the innate pro-inflammatory cytokine TNF-β and reduced levels of anti-inflammatory cytokine IL-4, as well as of IL-2 and IFN-γ [91]. Though more research is required, it is suggestive that this profile is reminiscent of the altered immune regulation in the gut caused by maternal stress, whereby a chronically activated innate immune compartment leads to pro-inflammatory cytokine production, which is insufficiently counteracted by anti-inflammatory cytokines from epithelial cells, lamina propria dendritic cells and Treg [92]. These cytokines determine the chronicity of the inflammatory process and affect neuroimmune mechanisms involving brain circuits important for behavior and emotions [53–55]. Along with IFN-α, IFN-γ, IL-2 and IL-10, cytokines like IL-1, IL-6 and TNF-α can pass the blood–brain barrier, bind to receptors on vagal sensory nerves and stimulate the HPA axis. However, chronic and persistent elevation of cortisol levels can, as a consequence of negative feedback, cause a HPA output below normal levels resulting in increased neuroinflammation and impaired cognitive functions [25–28, 53–55, 90]. Moreover, plasma levels of the C4b complement protein, important in the defense against viral and bacterial infections, were decreased in ADHD patients [93]. Antibodies against glutamic acid decarboxylase (GAD65, important for inhibitory neurotransmission) have been detected in the serum of ADHD patients, as well as reactions of serum antibodies with cells in the cerebellum, suggesting direct effects on brain function [94].

Cellular immunity could contribute to ADHD by injuring neuronal cells [95], e.g., by chronic T-cell-mediated inflammation, but this has not been systematically studied in ADHD. Nevertheless, various results suggest involvement of a cell-mediated immune mechanism in ADHD etiology, at least in a subgroup of patients. For instance, as compared to controls, ADHD patients had increased activity of adenosine deaminase, an enzyme important in T-cell maturation and function [95]. Moreover, dopamine transporters, causally implicated in ADHD and targets for drugs like MPH, are abundant on human T-cells, activate STAT6 and trigger selective secretion of immune-regulatory cytokines (e.g., IL-10) [30, 96, 97]. In addition, there is a significant increase in tolerance toward provoking foods following EPD (enzyme-potentiated desensitization) treatment was observed as compared to placebo. EPD reduces cellular responsiveness to antigens, including food additives, instead of giving rise to some form of immunization [47]. Frequent co-occurrence of ADHD and allergic diseases and correlation between ADHD and streptococcus-mediated neuropsychiatric disorders also suggest the participation of the immune system in the ADHD pathogenesis [24, 50–52]. On the other hand, the lack of an association with asthma, IgE-dependent atopy and IgG levels, and the discussion on elevated anti-ganglia antibodies in ADHD deny a role of autoimmunity and IgE- or IgG-mediated reactions in ADHD pathogenesis [33, 46, 75, 78, 98–100].

Future perspectives

Further research into the genetic background and gene-by-environment interactions of ADHD is implicated, as well as research into immunologic and dietary factors. This research should be performed in a multidisciplinary setting using proper immune biomarkers. Double-blind, placebo-controlled and possibly individualized interventions must focus on food components instead of whole food products, while in vitro tests for immune reactivity may provide fast and efficient identification of provoking substances. Further research should also focus on T-cell-mediated (or other) immunological mechanisms rather than IgE-mediated allergies. Since MHC involvement is likely to influence the development of an adaptive immune response in ADHD, the following steps have to be investigated: antigen presentation by antigen-presenting cells (APC), helper T-cell (Th) proliferation and regulatory T-cell and memory B-cell activation. Also the importance of breaking tolerance in ADHD, as in allergy, is interesting but not yet studied and could also provide a clue on the mechanism(s) underlying spontaneous remission of both atopic diseases and ADHD. Exposure to foods in ADHD diagnosis should be addressed, as well as the possible interconnection between oxidative and immune imbalances in ADHD, as both may contribute via neuronal damage and abnormal neurotransmission [95].

Properly selected patient groups with a valid and reliable ADHD diagnosis, as well as age- and sex-matched controls, should be included in further research. Efforts from international institutions should increase the standardization of epidemiological studies to obtain worldwide
comparable data, using acceptable sample sizes and methods and durations of behavior observation. Finally, using biological (e.g., serum) markers, patient subgroups should be defined based on ADHD causative and triggering factors to predict their responses to specific treatments [81].

Modulation of immune system activity might have potential in ADHD treatment. However, using food or nutrient supplementation in ADHD remains controversial with no consistent results or publications and further research in this field is warranted [2, 31, 32]. In this respect, the possibly improved nutritional composition of (elimination) diets, which might also contribute to behavioral improvement, should be investigated as well. Involvement of the gut–brain axis, as well as immune and behavior modulation via gut microbiota through pre- or probiotic supplementation, is also new and interesting concept [97]. Moreover, the recent finding relating ADHD prevalence to solar intensity and thus geographical location likely has major implications in the understanding of the etiology and possibly prevention of ADHD [5]. Further research should investigate whether this association is possibly mediated by immune factors [101], as exposure to ultraviolet B through sunlight enables the production of vitamin D3 in the body, which has immunomodulatory effects and which can prevent the development of allergic diseases by inducing Treg differentiation and by suppressing isotype switching to IgE in B-cells [102]. In addition, alternative treatments like EPD might increase insight into ADHD etiology. EPD may overcome difficulties with restricted diets in food-induced hyperactivity and might thus help to develop safe and effective treatments for food-induced hyperactivity, as it enabled patients to eat provoking foods without any adverse behavioral symptoms for some months [47]. Extensive modulation of the diet in ADHD (e.g., by RED) can contribute to major consequences for immune activity and functioning, like countering effects of increased infections and treatment (e.g., antibiotic) induced damage to gut epithelium and modifications of gut microbiota. Restoration of the Th1/Th2 balance and improved immunoregulation by regulatory T-cells (Treg) could avoid the ADHD genetically induced chronic immune dysregulation and neuroinflammation which can affect cognition and behavior and contribute to the development of ADHD [2, 31, 32, 53, 54, 81].

Conclusion

Although these have not yet been established as the main etiologic factor of ADHD, a large variety of foods and food components can provoke or exacerbate behavioral responses, though not every child responds to the same products in a similar manner. In addition, immunological mechanisms appear to contribute to ADHD, with a disturbed immune regulation being more likely than a single (sub)cellular defect and cellular mechanisms more likely than humoral. This chronic pro-inflammatory immune dysregulation probably requires a predisposing genetic background. If immune pathways contribute to ADHD development and/or manifestation, even if only in specific subgroups, ADHD diagnosis and especially treatment should be reconsidered to improve patient care. Nutritional approaches might have potential as efficacious, safe and low-cost ADHD therapy, for example by modulating immune system activity, and possibly also improve comorbid complaints. A thorough investigation of immune aberrancies in ADHD is thus required.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References


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