Pediatr Allergy Immunol 2008
DOI: 10.1111/j.1399-3038.2008.00749.x

PEDIATRIC ALLERGY AND IMMUNOLOGY

ADHD as a (non) allergic hypersensitivity disorder: A hypothesis

Pelsser LMJ, Buitelaar JK, Savelkoul HFJ. ADHD as a (non) allergic hypersensitivity disorder: a hypothesis.
Pediatr Allergy Immunol 2008.

Research data concerning the causal association between attention deficit hyperactivity disorder (ADHD) and allergies are conflicting. Allergic disorders, like asthma and eczema are clinical syndromes in which both genetic predisposition and environmental factors (pets, pollen and foods) contribute to its development. The hypothesis of ADHD, in some children also being an allergic disorder, is postulated based on comparison of the mechanisms underlying the development of ADHD and allergic disorders. According to the accepted terminology, ADHD may comply with the criteria of hypersensitivity, allergy and atopy. This hypothesis has to be thoroughly tested by randomized controlled trials using environmental triggers and immunologic research. As genes related to the immune system may be associated with ADHD, further genetic research is compulsory. Immunotherapeutic approaches, using immunotherapy and probiotics, can subsequently be implicated in the treatment of ADHD. If hypersensitivity to environmental stimuli like foods contributes to the development of ADHD, the assessment and treatment of ADHD will have to be reconsidered, thereby improving the quality of care for these patients.

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Key words: ADHD; allergy; children; food; hypersensitivity

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Accepted 25 March 2008

Attention deficit hyperactivity disorder (ADHD) is a highly heritable psychiatric disorder that affects 2–12% of children worldwide (1, 2). It is as yet unknown whether the prevalence of children with ADHD is increasing. Several environmental influences are known that raise the risk for ADHD development (1), but the exact aetiological pathways are still largely unknown (3). Medication and psychosocial intervention are the most frequently used methods of treatment (4). As our knowledge about the cause(s) of ADHD remains speculative (5), it is important not only to unravel the genetic architecture of ADHD, but also to determine to what extent environmental factors can be regarded as risk factors for developing the disorder. Psychosocial and biological environmental influences like foetal distress, hypoxia and family dysfunction are considered to have aetiological importance (1), and a complete assessment needs to take account of all these influences (6).

To date, clinicians do not consider environmental factors such as exposure to foods or inhalants of much importance and do not pay much attention to them in the current diagnostic process of ADHD. These environmental factors, however, do play a major role in other complex genetic diseases, like asthma and eczema (7, 8). Here we argue that exposure to foods and inhalants and subsequent hypersensitive mechanisms can be important in the multifactorial causation of ADHD and this should have consequences for diagnosis and treatment of this disorder.

The old hypothesis: ADHD being engendered by allergic disorders

Eventually ADHD was hypothesized being a side effect of allergic disorders: allergic reactions engendering cholinergic/adrenergic activity imbalances in the central nervous system, leading to ADHD symptoms in some children (9). Other

studies suggested the possibility of a causal relationship between allergies and ADHD (10, 11), based on a surprisingly high proportion of children with ADHD having associated symptoms of allergic disorders. Recently, children with ADHD were found to display skin prick test results to common aeroallergens consistent with allergic rhinitis (12). However, there is increasing evidence that neither asthma nor its treatment are causing behavioural or school problems in school-age children, yet lingering concerns regarding this issue persist (2, 13). When comparing atopic and non-atopic children for the prevalence of ADHD no association between immunoglobulin E (IgE)-mediated atopic responsiveness and ADHD was found (14–16). Biederman et al. (13) found no substantial aetiological or pathophysiological relationship between asthma and ADHD. The risk for asthma did not meaningfully differ between ADHD and control children (13). Despite the range of diverse studies that attempt to understand the co-morbidity of asthma and psychiatric diagnoses (17), the controversy whether or not ADHD and asthma are causally linked still exists in the literature.

Asthma is a leading cause of childhood chronic medical illness, affecting 7–15% of children and the prevalence rates have dramatically increased by 74% between 1980 and 1994 (2). In addition, a rising prevalence of food hypersensitivity and severe allergic reactions to food has been reported the last decade (18). Thirty-nine per cent of all children in the United Kingdom have been diagnosed with one or more atopic conditions and 11% with more than one atopic disorder (19). These data imply that there is a significant chance that asthma and ADHD can occur in the same individual, so co-morbidity of ADHD and allergic disorders should not be very surprising (20). Furthermore, from various studies it is concluded that asthma and ADHD show an independent transmission within families (2, 13, 16). This is consistent with the notion that although ADHD and asthma or eczema might occur simultaneously, these disorders need not be causally related with each other (2, 13, 16). Therefore we reject the old hypothesis, ADHD being caused by allergic disorders, replacing it by a new hypothesis, ADHD being a (non)allergic hypersensivity disorder itself.

The new hypothesis: ADHD being an (non)allergic hypersensitvity disorder

The lack of a causal correlation between asthma and ADHD does not exclude the presence of a common pathophysiological mechanism underlying the development of asthma and/or ADHD when exposed to similar environmental triggers. Such a mechanism can exist without a direct causal relationship between both diseases.

According to the nomenclature of allergy, allergic disorders are clinical syndromes each defined by a group of symptoms and signs in target organs, in which genetic predisposition and exposure to environmental factors (dust mites, pets, tobacco smoke, foods) both contribute to its development (21).

ADHD and asthma are both highly hereditary diseases. Polymorphic variants in several genes involved in regulation of the dopamine, and related neurotransmitter pathways are reported to be associated with ADHD (22). Not only the dopaminergic system, but also the noradrenergic and histaminergic systems can be involved with ADHD (23).

The term 'hypersensitivity' should be used for allergic and non-allergic reactions for which environmental triggers are held responsible (21). Hypersensitivity is an 'umbrella' term to cover for allergic hypersensitivity, i.e. with a defined or strongly suspected immunological mechanism, and for non-allergic hypersensitivity, i.e. with an immunological mechanism excluded. Eighty per cent of childhood asthma has been reported to be allergic, resulting from immunological reactions, being IgE- (extrinsic) or non-IgE-mediated (intrinsic) (21). It has been suggested that eczema can be differentiated into an atopic and non-atopic eczema form. Only atopic eczema might follow the distribution and risk pattern that have been ascribed to asthma and hay fever. As the immunological mechanism underlying the development of eczema and the role of IgE antibodies in the aetiology of the disease are less well known, the term IgE-associated is used, the word 'associated' being provisional (24).

From this, it is clear that the different types of allergic diseases are heterogeneous with respect to the role of the immunopathology underlying the cause of these diseases. Although ADHD has never been postulated as an allergic disorder itself, we are of the opinion that ADHD symptoms may be caused or 'triggered' by several heterogeneous factors, reflecting different mechanisms underlying the disorder, as has been stated before (25). Some of these mechanisms may represent allergic immunopathology.

Strengthening the new hypothesis

According to the revised and widely accepted terminology of allergies, ADHD meets the criteria

of hypersensitivity. Displaying asthma symptoms after exposure to dust mites reflects a hypersensitive reaction in which the dust mite is the defined stimulus. Equally, showing ADHD symptoms after eating normal amounts of certain foods (10, 15, 26–30), or after pollen exposure (31), can be a matter of hypersensitivity, in which the foods and pollen reflect the defined stimulus which is tolerated by normal subjects (Fig. 1). More research is needed to determine whether such a hypersensitivity reaction is allergic or non-allergic with respect to its underlying cause. Recent research has shown that the effect of food additives on behaviour may occur independently of the presence of an atopic status or the presence of hyperactive behaviour, probably via a non-IgE-dependent histamine release from mast cells and basophilic granulocytes (32). Some children can react to food components, including additives, with the development of atopic symptoms (33), or ADHD-like symptoms (34), while only seldom children will react to an isolated additive component alone (26). Some degree of hyperactivity when exposed to food additives and benzoate preservatives may be applied to all children, not exclusively to hyperactive or atopic subgroups (32, 35). Recently, it has been described using outgrowth of murine neuroblastoma cells *in vitro* that specific combinations of common food additives show synergistic effects to inhibit neuronal cell differentiation (36). These food additives show their effect at concentrations theoretically achievable in plasma by ingestion of foods or drinks that are typically consumed by children.

When ADHD symptoms develop in response to food components, and when an immunological mechanism can be defined which underlies this development, then the ADHD is a consequence of an allergic response. The immune mechanism can be related to the induction of IgE antibodies or be a consequence of other mechanisms. This is in accordance with the revised allergy nomenclature. Subsequently, if the child has the atopic constitution, it may be called 'atopic' ADHD. As yet, we do not know to what extent these mechanisms take place, whether they are limited to a subgroup or affect the majority of children with ADHD.

When stepping beyond the borders of the brain we find preliminary studies on the effects of pollen and foods (defined stimuli) on ADHD symptoms which are in line with our hypothesis, and support the existence of a hypersensitive mechanism (10, 15, 25–31). All dietary studies, following the food dye-challenge research in the 1970s and unlike the challenge studies using an individually constructed elimination (few foods) diet (10, 15, 26–30), show evidence of efficacy for a properly selected subgroup (37, 38). In a nasal pollen challenge study (31), significant neurobehavioural regression was induced in children with ADHD. This regression occurred in both allergic and non-allergic children, and was not associated with the presence of respiratory symptoms. The results of these studies are consistent with our hypothesis, but far more research is needed to accept or reject our hypothesis.

Testing the hypothesis

This hypothesis has to be thoroughly tested by randomized controlled trials in unselected subjects by the following.

1. Genetic research: ADHD is a genetically complex disorder, including among others the involvement of multiple genes, gene–environment correlation, gene–environment

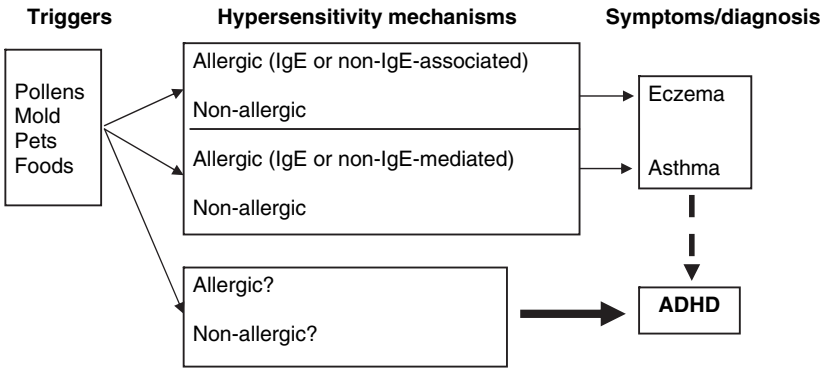

Fig. 1. Triggers and mechanisms of asthma, eczema and attention deficit hyperactivity disorder (ADHD) according to the old hypothesis (dashed arrow) and the new hypothesis (solid arrow). The underlying mechanisms of asthma, eczema and ADHD can be based on allergic sensitization, resulting in immunoglobulin E (IgE) or non-IgE-mediated mechanisms, or upon non-allergic mechanisms. Determining the underlying mechanism may have consequences for diagnosis and treatment of the disorder.

interaction and importance of developmental factors (39). Several genes are able to regulate the immune system and may be associated with development of the symptoms of ADHD (40, 41). Consequently the further unravelling of the genetic architecture of ADHD is very important.

2. Immunological research: Dopamine transporters are causally implicated in ADHD, and are targets for drugs like methylphenidate. These receptors are abundantly expressed on human T-cells, and trigger the selective secretion of immune-regulatory cytokines, like interleukin (IL)-10 (42). Furthermore these receptors react by activating STAT6, a pivotal transcription factor in Th2 cells of the immune system (43).
3. Blood tests: These tests are used to segregate between non-allergic or allergic mechanisms involved. This includes analysis of the role of IgE and IgG antibodies being specific for the food and inhalant components and the possible involvement of cell-mediated hypersensitivity (24). This enables us to understand the processes that initiate and regulate these responses. As a result of the poor prognostic value and reliability of food-specific IgE (44), a true allergy to a foodstuff is revealed by oral provocation tests or by improvement during an avoidance diet, being an essential tool in the diagnostic procedure (45).
4. The development of immunotherapeutic treatments: When allergic triggers are involved in ADHD, these will necessitate the development of new treatment strategies. Recently, children suffering from eczema symptoms, whether or not linked to a food allergy, are efficiently treated by the use of probiotics (46, 47). Moreover, when inhalant components are implicated in the development of ADHD symptoms, also allergen-specific immunotherapy might be useful. The potential use of these new anti-allergic strategies needs to be evaluated with children suffering from ADHD symptoms.
5. By determining the effects of environmental influences, using few food diets (10, 15, 26–30) and inhalant challenges, e.g. pollen (31), the number and features of children with ADHD in which a hypersensitive mechanism may be involved can be identified.

Implications for clinical practice

According to our hypothesis, hypersensitivity to environmental stimuli like foods and inhalants contribute to the development of ADHD, and thus the assessment and treatment of ADHD will have to be reconsidered. As allergic and non-allergic conditions may present with similar symptoms, an accurate allergy diagnosis is important in order to treat the patient most appropriately (48). Confirmation of this hypothesis will result in considering ADHD as two different entities: hypersensitive and non-hypersensitive ADHD, in accordance with the two variants of eczema depending on the determination of the effects of attributable risks (49). Determining and avoiding such triggers will reduce the predisposition to ADHD, and consequently reduce the use of medication. This new insight will improve the quality of care for ADHD patients in the future.

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