Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

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Allergy

EDITORIAL

# Itches and scratches – is there a link between eczema, ADHD, sleep disruption and food hypersensitivity?

DOI:10.1111/j.1398-9995.2011.02705.x

Attention-deficit/hyperactivity disorder (ADHD) – characterized by the core symptoms impaired attention, increased impulsivity and motor hyperactivity – has repeatedly been discussed to be associated with or induced by immunological mechanisms while other findings relate to the potential effects of nutrition on behavioural symptoms. In this context, ADHD has been suggested to constitute a hypersensitivity disorder implying allergic or nonallergic mechanisms as response to environmental allergens or nutritional components (1). Recent findings suggest that a subgroup of ADHD cases may be triggered by infant eczema (syn. atopic dermatitis) (2).

## Is ADHD triggered by food?

ADHD is a frequent multifactorial disorder with onset in early childhood and a worldwide prevalence of around 5%. ADHD leads to considerable psychosocial impairment and causes substantial economic burden (3). Family studies indicate a substantial genetic component, but the exact molecular mechanisms of ADHD are still incompletely understood (4). Even though there is a body of evidence indicating that ADHD is a valid diagnostic entity with neurobiological specifics, there is a public discussion whether ADHD may be diagnosed too often and pharmacological treatment may be prescribed without the necessary care and diagnostic accuracy. Furthermore, the discussion whether ADHD may be caused, induced or exacerbated by food or food components has recently been fuelled by a randomized controlled trial that suggested that in some children with ADHD, a restrictive elimination diet may have beneficial effects and may reduce ADHD symptoms (5). As immunoglobulins did not mediate the effect, the study supports the notion that ADHD symptoms may be regarded as a nonallergic hypersensitivity reaction at least in a subsample of patients with ADHD, although the specific mechanisms underlying the assumed hypersensitivity remain hypothetical (1).

Previous hypotheses and dietary therapies had proven to display at best low effect sizes in meta-analyses (6). Even though novel investigations have tried to overcome previous methodological shortcomings, to date the clinical relevance of the findings of ADHD in general remains controversial, in particular given study limitations such as incomplete blinding and potential referral bias (5). Further, it appears unlikely that various specific nutritional components – only some of which are known to induce allergic or pseudo-allergic reactions – may uniformly affect the behaviour of different children and that highly individualized elimination diets may be subsumed in a common pathophysiological pathway leading to ADHD symptoms. Accordingly, a previous study had provided only limited evidence for an effect of food additives on ADHD symptoms in healthy children, being present only at low concentrations at a defined age range (7). This finding has been comprehensively assessed by the European Food and Drug Administration, concluding that the clinical relevance of the proposed effect is considered small, if at all present (8).

Despite these limitations, it may be concluded that there is some evidence for an effect of nutrition on problem behaviour in a subgroup of patients with ADHD, and further research is required to quantify and qualitatively assess this phenomenon and its underlying biological mechanisms. In contrast to well-known allergic reactions to food components causing eczema, the existing literature does not confirm classical allergic or atopic mechanisms to mediate the effects of nutrition on ADHD symptoms (5).

## Eczema is a risk factor for ADHD

Notably, recent population-based cohort studies indicate an association of ADHD with eczema. These studies consistently suggest that childhood eczema – even when not persistent beyond the age of 2 years – increases the risk of occurrence of ADHD later in life by the factor 1.5 (9–12). If the findings with regard to food effects on ADHD symptoms are true, eczema should be considered as a potential confounder or modifier of the association in future studies.

Eczema is highly prevalent (around 20%) in early childhood, and the associated symptoms (e.g. itchy rash) considerably impact the quality of life of affected individuals and their families and cause increased levels of stress (13). Interestingly, the observed association between ADHD and eczema appears to be independent of comorbid atopic disorders such as allergic rhinitis or allergic asthma (2). Considering that only a proportion of all children with eczema are atopic, i.e. display increased levels of total and allergen-specific IgE, atopy per se is unlikely to be a risk factor for ADHD and classical atopic mechanisms are unlikely to play a major role in the observed association.

### Is disturbed sleep the link?

As both childhood eczema and ADHD are frequently accompanied by impaired sleep patterns, we recently hypothesized that disturbed sleep may be a modifying factor for the association between the two disorders (14). This assumption was supported by epidemiological data showing a strong association between eczema and ADHD in children with disrupted sleep, but not in children without sleeping problems (12). The relevance of sleep for mental and behavioural development has been emphasized by numerous studies showing that sleep disruption in infancy is linked to disruptive behaviour and psychological problems in later life such as increased irritability or difficult temperament (15, 16). Theories involving disturbed vigilance in the pathophysiology of ADHD have a long history, and recent methodological advances in functional imaging and neurophysiology corroborate a relevant contribution of disturbed arousal in the phenotypic variance of ADHD (17, 18). Accordingly, some investigations indicate that reduction in ADHD symptoms induced by restrictive elimination diets is accompanied by improved sleep patterns in patients with ADHD, one potential explanation being that sleep disruption may mediate food effects on behaviour (19, 20).

### Immunological effects on behaviour

With regard to these converging and overlapping findings, it is tempting to speculate that ADHD symptoms, eczema, food hypersensitivity and sleep disruption may be linked by shared pathophysiological factors and that these impairments are characterized by a relevant developmental interplay, especially in early infancy and childhood. Maternal exposure to stress during pregnancy may be an early unspecific factor triggering both allergic inflammation and alterations in neural development via prenatal programming of the hypothalamus–pituitary–adrenal axis (21). Disturbed sleep, as characteristic feature of both ADHD and eczema, may be one mediating factor in the observed associations. However, other mechanisms may as well be involved such as genetic or neuro-immunomodulatory pathomechanisms. Allergic sensitization and chronification is accompanied by the activation of the typical TH2 response followed by interleukin and cytokine release; however, typical atopic mechanisms are unlikely to play a causal role in the observed phenomena. Instead, nonallergic activation of TH1 and TH17 cells, thus mediating inflammatory processes, may be of relevance in this context (22). Excessive cytokine release may impact on the central nervous system in the light of the capability to pass the blood–brain barrier, possibly affecting both neurotransmission and brain circuits known to be involved in ADHD symptomatology or affecting the sleep–wake rhythm (23). While these considerations of the impact of immunological processes on cognition and behaviour are largely derived from cell and animal models, there is increasing evidence that autoimmune reactions following bacterial infections (especially group A β-haemolytic streptococcus) may lead to neuropsychiatric symptoms including tics, obsessive–compulsive symptoms and hyperactivity that are generally referred to as paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (24). These clinical observations provide further evidence for a potential impact of immunological mechanisms on behaviour.

### Conclusion

The question why different disorders co-occur in an individual is amongst the most challenging questions in aetiological research owing to the high heterogeneity underlying multifactorial conditions such as eczema or ADHD. Comorbidity may be explained by complex theoretical models that have been reviewed elsewhere (25, 26). The identification of aetiology-based subtypes of complex phenotypes may facilitate improved prevention and treatment and provide the basis for individualized medicine. We hypothesize that there may be a specific subphenotype characterized by the comorbid association between eczema, sleep disruption and ADHD. We furthermore speculate that the subgroup of patients with ADHD responsive to nutrition may reflect our proposed phenotype.

Future studies aiming to disentangle these converging observations require distinct complementary approaches. First, the temporal and developmental aspects of the phenotypic expression of ADHD symptoms, eczema, allergic sensitization, sleep disruption and food hypersensitivity need to be characterized by longitudinal clinical studies. Second, we propose excessive cytokine release and consequent functional alterations and/or stress-related effects in ADHD-relevant brain circuits and structures as promising aetiopathomechanisms for future research efforts. Third, genetics, epigenetic programming, proteomic as well as metabolomic characteristics may provide insight into shared aetiological underpinnings. Fourth, interventional studies may clarify whether treatment of one condition may provide therapeutic or preventive effects on the other(s).

To conclude, there is cumulating evidence for a relevant functional interplay between immunological and behavioural symptom dimensions. Behavioural neuropsychiatric disorders and somatic disorders cross the borders of our current disease classifications, which rely on phenomenological grounds and categorical concepts and may require interdisciplinary therapeutic and research approaches. Our previous systematic review indicates that almost 10% of the risk of ADHD may be attributable to eczema (2). These novel insights into the interrelationship between somatic and psychiatric disorders raise further questions on the potential effect of early preventive measures.

### Authors' contributions

M.R. drafted the manuscript. All authors contributed to and approved the final manuscript.

### Conflict of interest

The authors declare no conflict of interest.

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