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Title: Allergic airway diseases in childhood: an update

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Abstract:

Complex multifactorial diseases such as allergic rhinitis and asthma are not only becoming an increasing burden to health care systems, but especially affect the life quality of children and families suffering from their allergic symptoms. Also physicians are challenged by the multifaceted diseases as their work involves not only the often difficult decisions on case-adapted diagnostics, treatment and monitoring, but also possible preventive measures. This review gives an outline of the latest scientific developments related to the aetiology, diagnosis and management of allergic airway

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diseases in childhood, as well as prenatal and early life risk factors and strategies for prevention.

Key words: airway, allergy, biomarkers, childhood, diagnostics, environment, life quality, prediction, risk factors, therapy.

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Allergic airway diseases in childhood: an update

Allergic airway diseases in childhood - a multifaceted enemy

It is widely known that the increasing prevalence of allergic airway diseases (1,2), such as allergic rhinosinusitis and asthma, present an important challenge to public health care systems(3). This development already starts to become manifest among young patients, as most of the allergic diseases diagnosed in childhood also persist into adulthood (4). It has also been shown that children at pre-school age suffer from a higher morbidity in asthma than any other age group and that the management of early wheezing is a fundamental challenge for physicians all over the world (5). Overall, the main defiance is not only the high prevalence of allergic diseases, but also the great diversity of phenotypes and patients' needs. This variety makes the development of general recommendations for diagnostic procedures and treatment, as well as possible prevention strategies difficult. Luckily, the high scientific interest permanently results in new findings. In the following, the latest achievements in the assessment of risk factors, the interrelation of genetic predisposition and environmental factors, the evaluation of diagnostic tools, the improvement of live quality as well as novel treatment and preventive strategies will be outlined.

Prenatal and early postnatal risk factors

The risk of developing asthma or allergic rhinitis throughout a lifetime is believed to be determined, at least partially, already before birth (6). Apart from complex genetic factors (7,8), which will be discussed later in this review, a variety of environmental factors (9) during pregnancy and in early childhood may affect the incidence of allergic diseases in childhood (10). Especially the nutrition of mothers during pregnancy has been a focus to various studies showing that dietary patterns (11-13), selective supplementation (14) as well as levels of iron (15), Vitamin D (16), folic acid (17) and other nutrients (18) may have protective as well as adverse effects on the evolution of atopic diseases in the offspring. An Australian prospective cohort study (19) among asthmatic pregnant women showed that twelve-month-old infants whose mothers had confirmed viral infections during pregnancy reported more frequent wheeze (40% had 4-12 wheeze attacks compared with 0%), sleep disturbances, beta agonist treatment, prolonged colds and eczema, compared to infants whose mothers had no laboratory-confirmed viral infection. But not only respiratory infections during pregnancy may change the offspring's fate, as it has been shown by a study on febrile and gynecological infections among pregnant women (20). These and other infections often require the use of specific drugs, but also temporary discomforts of other causes result in the intake of medication. Although the use and prescription of any drug should be carefully re-evaluated during pregnancy, some substances have become over-the-counter-drugs for pregnant women even if their exact impact on the unborn has not been precisely evaluated before (21). Although a possible teratogenic effect of a drug needs to be accurately ruled out by the manufacturer before its prescription during pregnancy, the intake of various pregnancy-approved drugs may nevertheless affect the prevalence of allergic diseases in the offspring (22). Accordingly an observational study from the Netherlands discovered a relationship between the maternal intake of acid-suppressive drugs (such as proton pump inhibitors and Histamine 2-antagonists) and the development of multiple allergic diseases in their children (23). In parallel, the intake of antibiotics in pregnant women has been shown to increase the risk of asthma in a Danish national birth cohort and a Swedish study group found a statistical association between maternal intake of many drugs, including paracetamol, and childhood asthma (24). But not only pharmacological aspects may affect the atopic future of the unborn. The exposure to maternal stressful events, such as mourning, divorce or the loss of job, has been shown to moderately increase the risk of wheezing, asthma, eczema and allergic rhinitis during childhood (25,26). After the course of pregnancy, the mode of delivery has been identified to influence the prevalence of atopic diseases and asthma in childhood. Nevertheless, the results of different studies are conflicting. While some investigations during the last years resulted that a caesarian section is a risk factor for the later development of allergic diseases (27,28), recent findings underline that this may only be the case for emergency caesarian sections (29). On the contrary, other studies could not confirm any adverse effect (30, 31). Factors as the mode of delivery as well as the number and order of siblings (32) may also have an impact on childhood asthma and allergic disease. Once a child is born, it may be affected by neonatal jaundice. This common condition can be treated easily and early, nevertheless it has been shown in various studies to increase the rate and severity of childhood asthma (33), as well as allergic rhinitis (34). In some cases, a neonate's condition requires the application of antibiotics very early in life. If this becomes necessary as early as within the first week of life, it may increase the risk of allergic rhinitis at school age as it has been shown within a Swedish birth cohort (35). But not only the very early contact with antibiotics (36) may affect the patient in his or her future development of atopic diseases. Also at later time

points within early childhood, the administration of antibiotics increases the risk for atopic respiratory diseases at school age (37, 38) and even the dosage could be related to the child's outcome. This effect may possibly be explained by the alteration of the colonic microbiome which has been observed in murine models (40). As the diversity of the gut microbiota is considered an important factor in the development of atopic disease (41), a special focus is to be set on the alimentation of infants, especially the role of breastfeeding. For the latter, an evaluation of two Greek cross-sectional studies (42) has shown in a total of 3755 children that exclusive breastfeeding is associated with a reduced prevalence of wheezing in preschoolers. No significant changes in these findings could be observed according to differences of length of the exclusive breastfeeding periods from 2 months to 6 months. However, the protective effect seems to diminish in older children.

Evolution, genes and the environment

The long existing concept of TH2 responses, being held responsible for macro-parasite defense and allergic diseases, has recently been challenged by Palm et al.(43) who propose a fundamentally different view on the role of the TH2 pathway. In their reasoning, an acute IgE-mediated response may have evolved to protect the organism against a great variety of environmental toxins, irritants and venoms which results in symptoms also typical for allergic diseases. Thus, acute symptoms like sneezing, coughing, overshooting production of tears and nasal secretion, diarrhea, vomiting and itching are all aimed at the expulsion of a possibly threatening matter. As all of these symptoms are associated with a pronounced discomfort of the host, they automatically cause a beneficial avoidance of their inducer. By this, the authors propose that allergic reactions are not an unintended reaction of the immune system, but a beneficial defense against noxious antigens. Nevertheless, it is not disclaimed that a mistargeted reaction to truly innocuous allergens may exist. This sheds new light on the definition and diversity of allergens. Although substantial data underline the role of genetic predisposition in complex, multifactorial diseases, such as atopy (44,45), asthma (46,47) or allergic rhinitis (48,49), this evidence alone does not fully explain their aetiology. Moreover, genetic variations have to be evaluated in combination with numerous environmental factors and cellular stressors, which have been shown to alter gene transcription even throughout various generations (8,50). In the search for specific agents causing DNA methylation changes, tobacco smoke could recently be identified in various studies as modifying factor (51-53).

Hew at al. (54) analyzed in 256 subjects the impact of early exposure to ambient polycyclic aromatic hydrocarbons on the impairment of immunity in atopic children. The results show that the exposure to higher PAH levels is significantly associated with an increased methylation of FOXP3 ($p<0.05$), a key locus involved in atopic diseases. This impact was higher among atopic children and resulted in a Treg dysfunction as well as increase in total serum IgE levels. The possible role of local IgE production in the course of allergic airway diseases (55), lead a Canadian study group to the comparison of methylation profiles in peripheral blood mononuclear cells (PBMCs) and airway epithelial cells (AECs) (56). Although no significant differences could be found between atopic and healthy subjects, the analysis resulted in cell specific DNA methylation patterns for AECs compared to PBMCs which underlines the importance of differentiation between local and systemic immunity.

Diagnostic tools and monitoring

Especially in small children, the accurate clinical diagnosis of allergic asthma versus other distress phenotypes may pose a challenge even to experienced physicians. In order to facilitate the distinction of allergic versus infectious symptoms in toddlers, Ranciere et al.

(57) grouped 2084 children between 1 and 3 years of age in a "cough phenotype" and a "dyspnea phenotype", evaluating their symptoms in the categories: wheezing, dry night cough, dyspnea with sleep disturbance and breathlessness. While infants of the cough phenotype showed more often allergic features, the dyspnea phenotype was mainly associated with infections. Within the same birth cohort, dry night cough could also be identified as a marker of allergy in preschool children (58). Once the clinical history is assessed, diagnostic procedures such as skin prick testing and/or specific IgE determinations are usually initiated.

Especially the latter make blood withdrawals necessary, which may be difficult in small children. Therefore, recent developments in allergen microarray diagnostics deserve special attention, as they allow the simultaneous assessment of antibody profiles towards up to 170 allergenic molecules (59) using only minute amounts of serum. This method is a useful tool for a precise assessment of allergic sensitization (60), especially in polysensitized patients (61), but also for its monitoring (59). Still, the obtained IgE results always need to be interpreted in combination with the clinical history of the patient as it does not necessarily imply allergic symptoms (62) and any method based on the assessment of IgE antibodies remains invasive, as blood withdrawal is inevitable. In order to identify new, non-invasive diagnostic tools, Vyhldal et al. (63) tested the assessment of gene expressions in the buccal mucosa of asthmatic and non-asthmatic patients. This test turned out to be a reliable, non-invasive method to detect changes in the gene expression related to atopy, especially in children. As such, it may become a valuable tool for diagnosis as well as for the evaluation of therapeutic responses. Another important instrument for the monitoring of allergic airway diseases are questionnaires which evaluate the control of allergic rhinitis and asthma, as well as the patient's quality of life. Thanks to careful testing and repeated adjustments of the monitoring tools CARATKids (64) and RHINASTHMA-Adolescents (65), standardized questionnaires for both assessments are now ready to be used in clinical practice.

Living with asthma and rhinosinusitis: psychosocial factors and life quality among children

Children living with a chronic disease, such as asthma or rhino-sinusitis, have to face continuous challenges in everyday life adjustment, despite their young age (66). Especially adolescents seem to be affected strongly by psychosocial adaptive difficulties which may result in depression and anxiety. A recent meta-analysis (67) showed among 8 eligible studies, that the prevalence of depressive and anxiety symptoms among 3546 asthmatic teenagers were significantly higher than among 24 884 healthy controls (depression, 0.27; 95% CI, 0.18-0.39 vs. 0.13; 95% CI, 0.09-0.19; anxiety, 0.33; 95% CI, 0.19-0.52 vs. 0.21; 95% CI, 0.12-0.33). This trend was also repeated for both, when analyzing the risk of developing either one of the two conditions. Braig et al. (68) analyzed the data of two prospective population-based cohort studies in southern Germany in order to assess the quality of life among adolescents suffering from a wheeze. Interestingly their results show that especially late-onset wheezers seem to be vulnerable for aggravations in psychosocial aspects of health-related quality of life. But not only asthma is the driving factor for mood impairment in youth, as a recent Italian study shows among 1283 subjects aged 10 to 13 years (69). According to the administered health respiratory questionnaire as well as tests for depression and anxiety, the likelihood among the teenagers to be depressed increased from 11.2 to 17.7% ($p <$

0.0001) in the presence of rhinitis. Interestingly, in this study, asthma was not directly associated with a depressive mood, but their relation was mediated through rhinitis.

Therapy of allergic airway diseases in childhood

Most allergic children do not only experience one specific type of symptoms caused by a clearly identified allergen, but in fact suffer from a complex pattern of comorbidities (70), as well as reactions to many different allergenic molecules (71). Thus, patients need an individually adapted scheme of therapy, which fits and controls the course of disease. Up to now, specific immunotherapy is the only available disease-modifying approach in respiratory allergy (72), nevertheless it is not the approach most commonly opted for. A cross-sectional study among 1.275 children suffering from allergic rhinitis, recruited from 271 centers in Spain, showed that the most frequently used therapeutics are oral antihistamines (76%), nasal corticosteroids (49%) and a combination of both (45%), while only 21% of the patients received a specific immunotherapy (73). A recent review on the efficacy of sublingual immunotherapy for allergic rhinitis and rhinoconjunctivitis in children concluded that it is a feasible and safe medication for allergies to grass and ragweed pollen (74). On the other hand, data on sublingual immunotherapy in subjects allergic to house dust mites, are very controversial (75-78) and more information is still needed. Apart from this, Paino et al. showed that the adherence to sublingual treatment, especially among preschoolers, is rather poor (79) which makes regular visits to the physician for subcutaneous immunotherapy probably more feasible. Nevertheless, sublingual applications are less invasive and currently also evaluated as a possible method for a preventive approach among pre-school children. Szépfalusi Z et al. (80) showed in a double-blinded, randomized, placebo-controlled pilot study with 31 children who were sensitized to house dust mite or grass pollen that the preventive application of SLIT is safe for children aged 2-5 years. Although no significant difference in the IgE sensitization profiles could be noted after 12 and 24 months, an induction of IL-10 and IgG antibodies was observed as regulatory mechanisms. Another option within the therapeutic strategies are monoclonal anti-IgE-antibodies, known as Omalizumab. Particularly for patients suffering from severe allergic asthma, its efficacy and safety have been confirmed in various trials (81, 82). A French 1-year real life survey on Omalizumab (83) as add-on therapy even concluded in better results than the clinical trials, showing a reduction in exacerbation and hospitalization rates of 72% and 88.5%. Additionally, the 104 observed children suffering from severe allergic asthma, showed an improvement of 4.9% ($p=0.023$) in their forced expiratory volume after twelve months and the inhaled corticosteroid dose decreased by 30% ($p<0.001$). A German randomized, double-blind, placebo-controlled, multicenter trial (84) obtained similar results among 114 patients aged 11-46 years. Omalizumab or placebo therapy was started two weeks before specific immunotherapy. After 18 weeks of parallel treatment, only SIT was continued. During the add-on therapy, patients from the Omalizumab group reported fewer symptoms of seasonal allergic rhinitis and asthma, but no significant difference could be observed between the groups for the time of specific immunotherapy only. However, patients treated with omalizumab/SIT in combination, showed a slight increase in lung function (FEV1). Another favorable feature of the therapy with Omalizumab is that it may as a pre-treatment increase the safety of specific immunotherapy for patients with severe allergic asthma (85). Simultaneously to the success story of monoclonal anti-IgE-antibodies, other therapeutic options are also

evolving, such as epicutaneous immune modulation (86,87), the application of gastrointestinal parasites (88,89) or the manipulation of complement components (90).

Biomarkers and prediction

The earlier a disease can be treated, the better. Therefore, it is of great interest to identify children at high risk of developing an allergic airway disease as early as possible. A Dutch study group demonstrated in a cohort of 230 children, that 5 year old children who suffer from persistent wheezing, already had elevated inflammatory markers in exhaled breath condensate at pre-school age (91). The same could not be found in children with a temporary or no wheeze at the same age. As wheezing alone is not necessarily related to atopy, Kulkarni et al. investigated the grade of eosinophilic airway inflammation in asthmatic children with and without food allergy, resulting in a significantly higher percentage of sputum eosinophils and fractional exhaled nitric oxide in allergic children (92). Another approach for early diagnosis of an allergic airway disease is the assessment of specific IgE in combination with bronchial hyperresponsiveness to metacholine provocation testing and exhaled levels of NO. As shown by Schulze et al. (93), this combination is a useful and safe tool for the early assessment of house dust mite allergy and could be confirmed as reliable predictor in 350 patients. Additionally, exhaled NO values acted as an indicator of early asthmatic responses. But not only asthma, also allergic rhinitis has been shown to increase the level of oxidative stress (94) in children. Interestingly, the co-existence of the two diseases does not further increase the levels of malondialdehyde, assessed as a marker of oxidative stress. For a less invasive approach, several prediction scores have currently been developed to assess the individual risk of future asthma in symptomatic preschoolers (95,96) or to predict the course of allergic rhinitis in adolescence (97). A new approach in the area of monitoring and prediction is the development of short-term individual symptom forecasts based on electronic symptom records, which will be digitally assessed in real-time. Although this project is still in its pilot phase it could generate potentially interesting results about the use of e-Health technology (98). While all the aforementioned predictive tools are applied among symptomatic children, a study among 820 children of the German Multicenter Allergy Study cohort showed that parental hay fever in combination with elevated specific IgE antibody levels are strong preclinical factors and may serve as a useful predictive tool for the future development of seasonal allergic rhinitis, even before the occurrence of the first symptoms. Although all of the aforementioned predictive tools have their particular strength, they only represent a small part of the possibilities (99, 100) enriched also by new research areas such as genomics, proteomics, metabolomics, and the analysis of the microbiome. Integrative approaches (101) will require multifaceted analysis strategies as well as the handling of immense data sets, but may result in promising new insights.

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