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The influence of allergens on the development of selected ENT diseases in the pediatric population

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Abstract
There is substantial evidence that allergies are a significant factor triggering and exacerbating many ENT diseases. The problem is particularly visible in the pediatric population, of which as many as 20% suffer from some form of atopy. Moreover, the course of these conditions is more complex than previously thought. The aim of the study was to collect information on the most common diseases in otorhinolaryngology and their link with hypersensitivity to allergens. The literature review included allergic rhinitis, adenoid hypertrophy, otitis media and sinusitis. Owing to a better understanding of the pathogenesis of these diseases, pediatricians can effectively treat and prevent their development.

keywords : allergy, sinusitis, otitis media, allergic rhinitis

Introduction
Our immune system plays a vital role in homeostasis and host defense. Its imbalances are of great importance because they can lead to allergy. Allergies affect patients' quality of life but also generate high costs for healthcare systems around the world. The prevalence of allergic diseases is increasing in Eastern and Asian countries and has become a major health concern.[1] In recent decades, the incidence of allergic diseases increased, affecting around 20% of the worldwide population, especially children.
Cross-sectional studies indicated that allergic diseases occur in order, from atopic dermatitis and food allergy in infancy into allergic asthma and allergic rhinitis in childhood. This phenomenon is called the 'allergic march'. This progression of atopic disease involves anatomical structures in classical sequence skin-gastrointestinal tract-respiratory tract.[2] However, recent studies challenge this pathway and indicate that it's more heterogenous than we thought. One of them observed that while 48.3% of children included in the study exhibited some form of allergic disease, only 7% followed the classic allergic march.[3] The mechanism underlying the phenomenon is not yet completely understood. Some of the diseases mentioned above resolve gradually to disappear with age, whereas others persist for many years.
Furthermore, it's important to consider the correlation between common allergens and ENT diseases, especially in children, because of the impact that the diseases have on physical and mental well-being. It is observed that physical development disorders, mental retardation, memory and cognition pathology are typical for children with ENT pathology. Mardiyan et al. came to the conclusion that schoolchildren with ENT pathology have a relatively high level of anxiety as compared to other schoolchildren and those levels increase with age. The data revealed that the ENT organ's dysfunction causes communication disorders, which in turn lowers the patients' socio-psychological and adaptation abilities.[4]

Having realized the importance of this topic, we decided to discuss and analyze the potential correlations between allergens and otolaryngological diseases in the pediatric population.

The aim of the work

The aim of the study was to evaluate the relationship between the occurrence of allergies and the development of ENT diseases in the pediatric population

Materials and Methods

The article presents a systematic review of scientific research focusing on the relationship between allergies and the occurrence of some of the laryngological diseases in the pediatric population, such as tonsillar hypertrophy, rhinitis, otitis media, and chronic sinusitis. For this purpose, a database analysis was performed - among others PubMed, Web of Science, and Google Scholar. Additionally, the bibliography of cited works was reviewed. Both Polish and English language literature were used. The review of the literature and article selection were carried out in March 2024.

Discussion

Allergic Rhinitis

Rhinitis is a diversified condition associated with an inflammatory response in allergic rhinitis (AR) but can also occur without it in a so-called 'idiopathic' rhinitis. Allergic rhinitis is the most common non-infectious rhinitis that is associated with an IgE-mediated immune response to environmental allergens in genetically predisposed sensitized individuals.[5] Depending on the study and the location of that study, allergic rhinitis has been reported in 5-50% of the population. More frequently in children.[6] Allergic rhinitis' symptoms include anterior or posterior rhinorrhea, nasal congestion/blockage, nasal pruritus and sneezing. Diagnosis may be challenging in the pediatric population but diagnostic clues include chapped lips from mouth breathing, fatigue, irritability, poor appetite and attention issues. [6]

The International Study of Asthma and Allergies in Childhood (ISAAC) revealed upward trends of rhinitis with an average prevalence of 8-15% in children. Studies of the natural history of rhinitis in children have shown a prevalence for allergic rhinitis of 3.4% at 4 years old and 27.3% at 18 years old.[5] Available evidence indicates that the prevalence of allergic rhinitis in children increases with age into young adulthood. Children with parental history of atopic disease are more likely to develop symptoms and at a younger age.[5] About 80% of individuals diagnosed with allergic rhinitis develop symptoms before age 20.[7] This condition is essentially absent in infants and typically develops at school age. It is unlikely to manifest before 2 years of age because sensitization takes years to develop. Kulig et al. performed a multi-center longitudinal study in Germany consisting of 587 children from birth to 7 years of age and concluded that two periods of seasonal allergen exposure are typically required to develop clinically significant allergic rhinitis. In their cohort, no one was diagnosed with seasonal allergic rhinitis by the age of 1.[6]

Common allergens are mainly proteins and glycoproteins found in airborne particles. Important allergens vary in different parts of the world, with grass pollinosis in the UK, ragweed in North

America and *Parietaria* in Mediterranean areas.[5] In Europe, the principal major burden allergens are birch or ragweed.

Dust mite fecal particles, cockroach residues and animal danders are common perennial allergens. Sensitization to allergens may be identified on the skin or in vitro testing which assesses the presence of allergen-specific IgE (sIgE).

The data on in utero or early exposure to mites, pollen, animal dander and fungal allergens is inconclusive. Exposure levels less than 2 mg dust mite allergen per gram of house dust may be a 'safe' level for atopic children for primary allergic disease prevention. When it comes to pet exposure as a protective factor for the development of the condition, there is conflicting evidence. Pet exposure, especially to dogs in non-allergic families in early childhood, may be protective. A 2020 systematic review and pooled analysis of five cohort studies found a protective effect for early life exposure to cats and dogs. Furthermore, early cat ownership in the first 2 years of life has been associated with a significantly lower risk of allergic rhinitis compared to non-ownership (OR 0.51; 95% CI 0.28-0.92). A prospective birth cohort study in Finland revealed that having a dog in the first year of life seemed to have protective properties by the age of 5 years (OR 0.72; 95% CI 0.53-0.97).[6] However, both of these studies did not make a firm conclusion about the protective effect of pet exposure. Several studies have demonstrated that the development of pollen sensitization in early life is associated with allergic rhinitis in later childhood. With environmental changes associated with global warming, such as the increased length of pollination season, we are starting to see higher rates of pollen sensitization in young children which will probably lead to higher rates of allergic rhinitis in adolescence and adulthood. A few studies posited that early life exposure to fungal allergens or dampness is a risk factor for allergic rhinitis. Unfortunately, available studies have not established a dose-response relationship for mold exposure. Although more and more in-depth reviews appear, no definitive conclusion can be drawn on early inhalant allergen exposure.[6]

According to the World Health Organization, food allergy concerns 4-10% of children (6-8% of infants and 3-5% of children up to 8 years old).[8] Although maternal diet restrictions while the child is in utero, such as limiting cow's milk, eggs, peanuts and fish, is not a contributing factor to the reduced development of allergic rhinitis, food allergy during childhood is a risk factor. However, a maternal diet high in oily fish or tree nuts has been reported to reduce the risk of allergic rhinitis. A meta-analysis of high-risk infants found that food sensitization at the age of less than 24 months increased the risk of allergic rhinitis during childhood. In a subgroup meta-analysis of observational studies, introduction of fish before 6-12 months was associated with a reduced risk of allergic rhinitis at 4 and 14 years.[6] Patients sensitized to pollen may present cross-reactivity with certain foods. The birch pollen major allergen (Bet v1) is mainly involved in the development of cross-reactive IgE antibodies to apple, celery and hazelnut.[8]

Although allergic rhinitis might seem to be a not-so-serious illness, it is important to further deepen our understanding of this condition because it underlies many complications, for example, is a major risk factor for poor asthma control.[7] We also have to take into consideration how it negatively affects quality of life and productivity at work or school.

Inflammation of the middle ear

Middle ear inflammation is one of the most common pediatric ENT diseases. It is the leading cause of medical consultations, surgical interventions, and intake of antibiotics among young children. It is estimated to occur in 95% of youth under the age of 7. [9]
Middle ear inflammation covers three main separate diseases that may overlap one another: acute otitis media (AOM), otitis media with effusion, and chronic purulent inflammation.
AOM is usually an infection originating in the nasopharynx, from which it spreads through the eustachian tube. It can be caused by viruses (adenoviruses, influenza viruses, and rhinoviruses) and bacteria (Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae). Children affected by the disease complain of severe, throbbing ear pain, hearing impediments, and frequently have a fever. [10] In turn, otitis media with effusion occurs without acute symptoms of inflammation. They are characterized by the accumulation of exudative fluid behind the eardrum, and one of the most typical symptoms include conductive hearing loss. [11]
Predispositions to the development of conditions mentioned above include third tonsil, genetic predisposition, immunological background, and eustachian tube dysfunction. More and more research confirms the controversial connection between allergies and the development of middle ear diseases, including a meta-analysis conducted based on 24 research papers in 2014 [12]. The authors concluded that people with allergies have more predispositions to the development of upper respiratory tract diseases and, consequently, otitis media. This happens through various mechanisms, the most important of which seem to be: eustachian tube dysfunction and dysregulation of the immune system.
The Eustachian tube is an opening connecting the middle ear cavity with the nasopharynx. It drains secretions, and equalizes the pressure between the tympanic cavity and its surroundings, when functioning properly, it forms a barrier for pathogens in the upper respiratory tract. Type 1 allergic reaction causes the nasopharyngeal mucosa to become excessively hyperemic and have increased permeability. The patency of the eustachian tube is impaired, generating negative pressure in the middle ear. Such mechanisms lead to inflammation. An allergic reaction also impairs the body's protective abilities and makes it easier for pathogens to colonize the epithelium. [13] Therefore, it can be concluded that children with atopy are more prone to otitis media.
Similar conclusions were drawn during a study of a group of 206 children with recurrent otitis media with effusion. Researchers showed that as many as 89% of respondents suffered from allergic rhinitis, and as many as 36% had bronchial asthma. [14]
The presented literature shows that there is a link between allergic reactions and the development of otitis media. Therefore, it seems reasonable for laryngologists to cooperate with allergists when treating young patients to prevent the recurrence of the infection.

Chronic rhinosinusitis (CRS)

Rhinosinusitis is a group of diseases characterized by the simultaneous occurrence of inflammation and infection. The epithelium of the nasal mucosa and sinuses is the primary site of the inflammatory reaction, which, as it progresses, leads to local tissue damage. The diagnosis is made based on imaging tests and the clinical symptoms, such as nasal obstruction, nasal discharge, facial pain, or impaired smell. Endoscopic examination can reveal, among others: polyps, mucopurulent discharge, or obstruction, and a CT scan of the sinuses shows

changes in the mucosa. It was assumed that the classification based on the duration of symptoms includes acute inflammation (>4 weeks), subacute inflammation (4-12 weeks) and chronic inflammation (over 12 weeks). [15]

The chronic form of inflammation is considered one of the most common diseases in the pediatric environment. A study, which was carried out in 2013, found that 4%, or 1.7 million, children suffer from CRS every year. [16] Among the youngest children, the maxillary and ethmoid sinuses, which are present from birth, may be affected. With increasing age and the development of the sphenoid and frontal sinuses, these proportions change. It is worth emphasizing that in this group it rarely occurs as an isolated condition. Usually, coexisting and/or predisposing factors to the development of this disease include, for example: asthma, dental diseases, cystic fibrosis, adenoid hypertrophy, allergy, or immunodeficiency. [17]

Based on numerous studies, it can be concluded that the existence of allergies, especially allergic rhinitis, is a factor predisposing to the development of sinusitis. Atopy appears to be more common in patients with CRS than in the general population. Among the group of patients, increased concentration of IgE antibodies and the presence of interleukin 4, 5, and 13 were observed, which indicates the presence of an allergic inflammatory reaction. It is worth noting that avoiding exposure to allergens, antihistamines and immunotherapy used in the treatment of allergic rhinitis also brings improvement in the group of patients with chronic sinusitis. [18]

Among people suffering from allergy, mast cell degranulation leads to swelling of the nasal mucosa. In turn, an increase in the number of eosinophils impairs the movement of epithelial cilia, thereby disturbing mucus transport. Remaining secretions create a friendly environment for bacteria and other pathogens. All this promotes the development of chronic inflammation of the paranasal sinuses. Therefore, it seems reasonable to carry out allergy diagnostics in patients suffering from this disease.

Adenoid hypertrophy

The anatomical conditions of the adenoid make it constantly exposed to numerous pathogens or allergens. [19]

Kyu-Sup Cho et al. showed that in 70.6% of children with adenoid hypertrophy its tissue is sensitized to at least one allergen, and they assumed that this group of patients is at higher risk for concomitant allergies compared to the general population [20]. A study was also conducted, which results indicated a correlation between the size of adenoids in pediatric allergic patients and the pollen season. As much as 90% of the study group had an enlarged adenoid, however no significant changes in size were registered in the control group [21]. Zawisza and Modrzynski studied the frequency of adenoid hypertrophy in allergic children, where they found that among 436 children with allergic rhinitis, adenoid enlargement was statistically more frequently observed, compared to the control group (229 children without atopy). However, allergic rhinitis was not considered the main cause of adenoid hypertrophy, as other types of immune response are also capable of leading to it. [22]

In children suffering from obstructive sleep apnea, enlarged tonsils were studied, in which T lymphocytes showed increased amounts of cysteinyl leukotriene receptors 1 and 2, which could indicate their influence on tonsil enlargement. Nevertheless, the authors emphasize that for now, the presence of allergies should not be completely linked to their hypertrophy. [23]

In contrast, in a study conducted by Costa Junior et al. among children who breathe through their mouths, 46% had hypertrophy of the adenoid, but only 37% of them were allergic. While in patients without hypertrophy, 35% of the group turned out to be allergic. Statistical analysis showed no significant association between allergy and adenoid hypertrophy. [24]
Although we do not have concrete evidence of a correlation between the effects of allergens on adenoid hypertrophy, it seems reasonable to be open-eyed when diagnosing children who have this condition, especially if they have other atopic upper respiratory tract symptoms simultaneously.

Summary

According to the sources of information used, it appears that for some ENT disease entities there is a significant correlation between the influence of allergens and their occurrence. Such conditions will certainly be allergic rhinitis, otitis media or chronic sinusitis. However, in the case of adenoid hypertrophy, this correlation is still unclear and requires more studies to be conducted to clearly define the relationship.

DISCLOSURES

Author's contribution:

Conceptualization:
Methodology: Olga Snoch, Zuzanna Kalinowska, Weronika Matera
Formal analysis: Olga Snoch
Investigation: Olga Snoch, Zuzanna Kalinowska, Weronika Matera
Writing - rough preparation: Olga Snoch, Zuzanna Kalinowska, Weronika Matera
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