Original Article

Allergic rhinitis and bronchial asthma in preschool children: possibilities of modern therapy for comorbid diseases

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Abstract

The article presents modern views on the problem of bronchial asthma and allergic rhinitis as a comorbidity in children. The concept of single chronic allergic respiratory syndrome is considered. Following international and national recommendations for the management of patients with bronchial asthma and allergic rhinitis, the impact of leukotriene receptor antagonists in the treatment of this comorbidity is determined. The compliance in the treatment of children with bronchial asthma and ways of its optimization are given. The use of montelukast sodium in the treatment of the persistent forms of allergic rhinitis and bronchial asthma in children is scientifically substantiated. The treatment outcomes for the control therapy of mild persistent forms of bronchial asthma and allergic rhinitis in children aged 2–6 years with such leukotriene receptor antagonists as montelukast sodium are shown.

Keywords: Allergic rhinitis, bronchial asthma, children under 6 years old, therapy, montelukast sodium

Introduction

Allergy is the rapid reaction of the body to allergens, by which the individual's immune system is stimulated [1]. Nowadays, allergies are a global problem causing significant medical, social, and economic losses. Thus, allergic diseases and sensitivity reactions are diagnosed in more than 50% of the European population, more than 30% of which are diagnosed in children. Among 15000000 disabled people around the world, the ratio of patients with bronchial asthma (BA) is 1% [2]. Asthma ranks fourth in the structure of causes for general disability of children aged 10-14 [3-6]. Allergic rhinitis (AR) is diagnosed in about 40% of children, occasionally occurs in children of the first two years of life, and the greatest incidence is in children of school-age [7, 8].

A specific allergic pathology feature today is the close correlation between atopic diseases: thus, in 20-60% of patients with atopic dermatitis (AD), BA develops in 30-45% of patients - AR [9]. Based on the epidemiological studies, 15-40% of patients with AR have BA and 76-80% of patients with BA have AR. Considering the statistics, it becomes clear that AR is a predictor for BA development. Unfortunately, very often, a child is diagnosed with AR too late - at the age of 6-7, although its first manifestations can be seen in 2-3-year-old children. This is confirmed by the results of the epidemiological study (BAMSE) carried out in Sweden, which examined the development and combination of the most common allergic diseases in children (AD, BA, and AR) from the date of baby's birth to age 12.

In the first year of life, isolated AR and isolated BA occurred in 2% of children, and their combination was diagnosed in 1% of cases among all children, i.e. BA and AR developed simultaneously [9, 10].

This work aimed to establish clinical and epidemiological features of bronchial remodeling in patients of school age with bronchial asthma and comorbid allergic pathology to optimize case follow-up and treatment.

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Materials and Methods

The analysis of the scientific literature written by Russian and foreign scientists devoted to the problem of allergic rhinitis and bronchial asthma in children of pre-school age, as well as the possibilities and prospects to apply modern comorbid disease therapy over the period from 2004 to 2019 was carried out. The following methods were included in the methodological grounds of the study: theoretical (analysis and generalization of scientific literature and sources, empirical material analysis), formal-logical, structured system, analysis, synthesis, abstraction, comparison, induction, deduction, etc.

Results

The AR disease makes BA and other ENT-organ diseases more severe, increases the risk of otitis media with perforation, relapsed and/or chronic sinusitis. AR has been proven to disrupt the child's sleep and daily activity. Patients with AR experience problems with falling asleep, night awakening events, feelings of sleep loss and feeling tired after having rest [3].

One of the frequent respiratory allergy symptoms is cough, but often not enough attention is paid to it. As a BA symptom, the cough may indicate inadequate asthma control, when not having wheezing syndrome - in the coughing BA form. Typically, such patients respond well to administered broncholytic and anti-inflammatory therapy.

Allergic rhinitis can also be accompanied by coughing as a result of postnasal mucus drip and larynx and pharynx irritation. In such patients, coughing relieves or disappears after the offending allergen elimination and use of histamine or glucocorticoid (intranasal glucocorticosteroids) H1 receptor blockers. With the AR and BA combination, coughing can often be considered not as a manifestation of common and comorbid states, but as a monodisease sign [11].

Coughing aggravates the BA severity and indicates its incomplete control. Undiagnosed AR in a patient with BA can lead to the increased basic asthma therapy to the use of systemic glucocorticosteroids, so children with AR need to be examined for BA and those with asthma - for AR [12].

The correlation between the two nosologies is due to a single morphological substrate (upper and lower respiratory tracts), common triggers, and pathogenetic mechanisms.

Recently, the concept of a "single chronic allergic respiratory syndrome" has been considered referring to rhinitis manifestations and transient wheezing to the manifestations of the same disease in the upper and lower respiratory tracts. The common mechanism for the development of the immediate-type allergic reaction has two phases for both diseases: early (or classical way) and late. Mastocytes (mast cells) and basophils to which reagent antibodies are attached are involved in the early phase of the response. Eosinophilic inflammation has a major role in late-phase development and, to a lesser extent, neutrophilic inflammation influences it [13].

During the early immune response phase, after having been attached to reagent antibodies (specific to certain allergens immunoglobulin molecule E (IgE) of the corresponding allergens), inflammation mediators are released from the mast cells: histamine, which increases vascular permeability and causes smooth muscle spasms, eosinophilic and high molecular neutrophilic chemotactic factor, thrombocyte activating factor, stimulates thrombocyte aggregation and release histamine and serotonin from them. Eosinophils activated by mediators release secondary mediators: diamine oxidase and arylsulfatase; neutrophils release the thrombocyte activating factor and leukotrienes. Thus, as a result of the mediator inflammation released into the acute phase, there is a smooth bronchial muscle contraction, an increase of blood circulation in the respiratory tract, and an increase in the vascular permeability, swollen mucosa develops, mucus secretion increases, which disrupts the respiratory function [14].

Macrophages, eosinophils, and thrombocytes, to which antibody reagents are also attached, are involved in the late phase of the response. When combined with the corresponding allergen, mediators are released from these cells, which cause tissue damage and inflammation: mastocytes release cytokines and chemokines which initiate proliferation, differentiation, and chemotaxis of eosinophils and T-lymphocytes of 2 type helpers (Th2). Th2 lymphocytes, releasing cytokines, support chronic inflammation. So, a large number of mediators are involved in BA and AR development, histamine being the most important.

However, blocking histamine receptors does not prevent the leukotriene release by activated macrophages, eosinophils and thrombocytes [14].

Lipid allergy mediators - leukotrienes - play an extremely important role in AR development. Leukotrienes are critical to the pathogenesis of a wide range of inflammatory diseases, including BA, AR, and allergic conjunctivitis, AD, urticaria fever, atherosclerotic cardiovascular diseases, inflammatory bowel diseases, disseminated sclerosis, cancer, etc. [15]. The source of leukotrienes is arachidonic acid, which is formed from the cell membrane phospholipids by the effect of the A2 phospholipase enzyme as a result of the influence of various damaging agents on the cell membrane. Their formation occurs during the subsequent arachidonic acid metabolism in a lipooxygenase way involving inflammation cells (neutrophils, basophils, mast cells, eosinophils, macrophages) [9].

For the last few decades, an inflammatory concept was one of the opinions on the allergic disease pathogenesis, including AR and BA, based primarily on the Minimal Persistent Inflammation. This concept is one of the key concepts in allergology. Based on it, patients with allergies who directly contact with causal allergens have a permanent allergic inflammatory process, even if there are no symptoms. The

lightest persistent inflammation level is manifested as infiltration being impacted by inflammatory cells (eosinophils and neutrophils), as well as adhesion molecule expression [16]. Clinically, there is an allergic symptom - it is only an "allergic iceberg peak".

Diseases such as BA, AR, and AD, even during the period of clinical well-being (remission), are characterized by the chronic inflammatory process. In the case of AR, cysteinyl leukotrienes (CysLT) including LTC4, LTD4, LTE4, and LTB4 more than histamine contributes to hyperplasia of a bronchial mucous membrane and a nasal cavity [17].

These lipid substances forming from arachidonic acid by the effect of 5-lipooxygenase are powerful pro-inflammatory mediators that cause bronchoconstriction, hypersecretion of mucus and its clearance disruption, stimulate the influx of eosinophils and other inflammatory cells, increase the blood vessel permeability 100 times more effective than histamine, stimulate myofibroblast proliferation and differentiation causing subepithelial fibrosis [7]. The mechanism that develops nasal blocking in AR is associated with the CysLT1 receptor activation [7] and significant nitric oxide release, which leads to blood vessel expansion and mucus accumulation in the nasal cavity followed by mucosa hyperplasia. Therefore, patients should be treated by anti-inflammatory therapy not only during acute clinical manifestations but at the rehabilitation phase as well [18].

Taking into account the unity of BA and AR pathogenesis, it becomes clear that in order to treat and prevent the inflammatory process in allergic diseases, anti-inflammatory therapy is required to administer, which is capable to block both histamine and leukotriene receptors.

The modern program and algorithm of rational BA and AR pharmacotherapy include drugs similar to their mode of action and origin - inhalation and glucocorticosteroids [19], leukotriene receptor blockers. The only difference is that the control AR therapy applies second-generation H1-antihistamines and their active metabolites, which are not so efficient in BA, and to eliminate the BA exacerbation, bronchodilators are administered, and in the case of AR - decongestants and elimination irrigation therapy agents [14, 20].

To date, drugs - leukotriene receptor blockers, and histamine H1 receptor blockers - have been developed and successfully introduced into clinical practice [21].

The international guide for the management of patients with AR - ARIA - provides recommendations [14, 20] on treatment, which vary depending on the symptom evidence. Intranasal corticosteroids are shown in all AR options except for mild seasonal rhinitis, while oral non-sedative second-generation H1-blockers (loratadine, cetirizine, desloratadine, fexofenadine, levocetirizine) are considered to be the frontline therapy in mild AR [22], except for the cases of persistent AR with severe or moderate severity. These drugs are quick (for less than 30-60 minutes) and safe (even in long-term administration in children) in eliminating nasal and ocular symptoms, they are moderately effective in case of nasal stuffiness [2]. It is noted that regular H1-blocker administration is more effective than administration on-demand [23].

Rational AR therapy can significantly improve the course of BA by reducing the need for bronchodilators, reducing the aggravation rate, and improving pulmonary function (GINA, 2014-2017). Second-generation H1 blockers are effective in reducing post-loading bronchospasm, cough in children with mild pollen asthma and AR [24, 25]. H1- antihistamine prescription improves pharmacological control over BA virus-challenged aggravations [26] due to its anti-inflammatory effect (influence on an adhesion molecule expression - ICAM1) epithelial cells [27].

Conclusion

In recent years, the scientific medical literature has increasingly discussed the issues of polypathia - a combination of many diseases and pathological conditions in particular patients. Thus, in 1921, the works of Pfaundler M., VonSeht L. proposed the following concepts, which are now commonly used: syntrophy - the two or more pathogenetically related diseases, which naturally develop and have mutual interference (influence) on each other, dystrophy - conditional mutual "incompatibility" of many nosologic diseases.

From this point of view, allergic pathology in children, in particular, the so-called "atopic march", is a classic example of syntropy and comorbidity, since etiopathogenetic patterns of allergic disease development and persistence in child partially indicate general allergy mechanisms regardless of the target organ localization [24].

Among the general characteristics of allergic diseases in children is the familial atopic pathology aggregation, which emphasizes the importance of the genetic component in asthma phenotype formation, and the basis of comorbidity, in particular the respiratory allergic pathology, is morphofunctional similarity and systemic mechanisms of chronic allergic inflammation development [3].

During the period of intensive growth and development, a child overcomes the so-called "atopic march" [22] characterized by changes in target organs (gastrointestinal tract, skin, respiratory organs), and reflects the environmental factor influence on the course of allergic pathology. The process ends with the formation of respiratory hyperresponsiveness to specific and non-specific trigger factors in the form of so-called "asthma phenotype". At the same time, certain nosological disease forms influence the incidence and nature of bronchial hyperresponsiveness and vice versa, and the results of numerous long-term

epidemiological surveillance reveal the correlation and mutual aggravation of the course of allergic pathology [28].

References

1. Dehghani R, Kassiri H, RezvanTalaee MS, Mesgari L, Chimehi E, Dehghani A. Studying Women's Allergy Rate to Cosmetics in Kashan, Central Iran. Entomol. appl. sci. lett. 2018;6(1):45-50.
2. Graziano R., Ilio C.D., Conti P. [et al.] Advances in Therapy with Antileukotriene Drugs. Annals of Clinical and Laboratory Science. 2004;34:379-387.
3. Zabololotny D.I., Lykov A.A., Okhotnikova A.N., Kosakovsky A.L. [et al]. Allergic rhinitis in children (monograph). Kiev: Logos, 2016.
4. Antipkin Yu.G., Umnica T.R., Lapshin V.F. [et al] Bronchial asthma combined with allergic rhinitis in children the role of antihistamines in treatment. Asthma and allergy. 2014;4:60-65.
5. Gurtovaya M.N., Grebneva N.N., Prokopyev N.Y. Allergic rhinitis and bronchial asthma: incidence, causes, clinic, and treatment. Young scientist. 2014;2:318-326.
6. Malik M, Khan A, Hussain A, Hashmi A. Prevalence of Depression among Asthmatic Patients in Pakistan: Challenges for Integrated Team Care. Int. J. Pharm. Res. Allied Sci. 2017 Jan 1;6(4):8-16.
7. Ovcharenko S.I., Opalenova V.A. Allergic rhinitis, and bronchial asthma: Lordestin effectiveness assessment. Pharmateka. 2012;15. Pharmateca.ru/ru/archive/article/8594 [Online]. Available: [Accessed: 29 Feb, 2020].
8. Mohebbi A, Aghajanpour M. From Allergic Rhinitis to Spontaneous Cerebrospinal Fluid Leak: A rare Case Report of Sphenoid Sinus Defect. J. Biochem. Technol. 2018;9(1):70-3.
9. Namazova-Baranova L.C. Allergy in children - from theory to practice. Moscow, 2010.
10. Gentile D., Bartholow A., Valovirta E. [et al.] Current and Future Directions in Pediatric Allergic Rhinitis. J. Allergy Clin. Immunol: In Practice. 2011;1(3):214-226.
11. Brozek J.L., Bousquet J., Baena-Cagnani C.E. [et al.]. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision. J. Allergy Clin. Immunol. 2010;126:466-476.
12. Chawes Bo L. K. Upper and lower airway pathology in young children with allergic and nonallergic rhinitis. Dan. Med. Bull. 2011;58 (5):B4278
13. Bousquet J., Khaltaev N., Cruz A.A. [et al.] Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GALEN, and AllerGen. Allergy. 2008;63(86):8-160.
14. Canonica G.W., Compalati E. Minimal persistent inflammation in allergic rhinitis: Implications for current treatment strategies. Clin. Exper. Immunol. 2009;158:260-271.
15. Boulet L. Ph., Boulay M. Asthmarelated comorbidities. Expert Rev. Respir. Med. 2011;5(3):377-393.
16. Takemura M., Niimi A., Matsumoto H. [et al.] Clinical, Physiological and Anti-Inflammatory Effect of Montelukast in Patients with Cough Variant Asthma. Respiration. 2012;83(4):308-315
17. Abdallah A.M. Low dose inhaled steroid compared to leukotriene antagonist in children with mild persistent asthma. EAACI 2014, European Academy of Allergy and Clinical Immunology Congress, Copenhagen, Denmark, Jun 7-11, 2014. Abstr. 748.
18. Vasilevsky I.V., Skeptian E. The use of SINGULAR is a new strategy for allergic rhinitis treatment. ARS medica. 2011;3:159-172.
19. Geppe N.A., Ozerskaya I.V. The role of cromones in bronchial asthma and allergic rhinitis treatment in children. Pulmonology and allergology. 2009;1:11-14.
20. Burgess S., Sly P., Devadason S. Adherence with preventive medication in childhood asthma. Pulmonary Medicine. 2011.
21. Nenasheva N.M. Present and future of leukotriene receptor antagonists in the bronchial asthma and allergic disease therapy. Effective pharmacotherapy. Pulmonology and otorhinolaryngology. 2012;4:22-46.
22. Okhotnikova A.N., Gladush Yu.I., Bondarenko L.V. [et al]. Allergic rhinitis in children. Urgent issues of diagnosis and treatment. Clinical immunology. Allergology. Infectology. 2015;1(80):26-36.
23. Ciolkowska J., Mazurek H., Stasiowska B. Evaluation of stepdown therapy from an inhaled steroid to montelukast in childhood asthma. Allergol. Immunopathol. 2014;42(4):342-347.
24. Nedelskaya S.M., Yartseva D.A., Mazur V.I. [et al] Allergic rhinitis and bronchial asthma pollen etiology in children. Retrospective clinical course study. Modern pediatrics. 2013;1 (49):24-30.
25. Romanyuk L.I. Allergic rhinitis as a comorbide condition of bronchial asthma. Asthma and allergy. 2013;2:62-65.
26. Bulgakova V.A. Modification of bronchial asthma therapy. Possibilities to improve virus-induced asthma treatment efficiency in children. Pharmateka. 2015;4:6-12.
27. Umanets T.R. Bronchial asthma and allergic rhinitis: ways to optimize compliance and treatment efficiency. Asthma is allergy. 2015;1:61-64.
28. Artyuch A. Leukotriene receptor antagonists in bronchial asthma therapy. Time-proven efficiency. Clinical immunology. Allergology. Infectology. 2017;1(98):40-42.