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Is prediction of the allergic march possible on the basis of nasal cytology?

Abstract

Introduction: The term allergic march has been used to describe natural evolution of the atopic disease in children, accompanied by the change in organ manifestation with time.

The aim of the study was to analyze the role of the cellular components of the nasal cytology as a tool for prediction of atopic diseases and clinical symptoms preceding allergic march.

Material and methods: In a retrospective manner out of a group of 1620 children, 146 symptomatic children (60 girls and 86 boys) meeting inclusion criteria (age below 4 years at first visit, symptoms suggesting allergy, nasal cytology performed at the beginning of observation, observation of at least 4 years) were included in analysis.

Results: Mean age of children at time of enrollment was 27 months (SD 10 months). After 4 years allergic rhinitis (AR) was diagnosed in 85 children (58.2%), atopic eczema/dermatitis syndrome (AEDS) in 51 (34.9%) and asthma in 48 (32.9%). Non-allergic etiology was identified in 36 patients (22.5%). All patients with asthma suffered from AR.

Significant differences between groups were found in number of eosinophils ($p < 0.001$), neutrophils ($p < 0.001$), and lymphocytes ($p = 0.028$) in cytological examination of nasal mucosa. In children with AR (alone or combined with other comorbidities) nasal eosinophilia was higher than in children with AEDS (18% *v.* 3%; $p = 0.004$) or non-allergic disease (18% *v.* 4%; $p < 0.001$). Nasal eosinophilia of at least 8% was predictive for development of AR (sensitivity 80%, specificity 95%).

Conclusions: In children below 4 years nasal eosinophilia ≥ 8% was predictive for AR development. Allergic march was observed in children with AEDS or/and gastrointestinal allergy symptoms present at the beginning of observation. Nasal eosinophilia in small children might be predictive for the risk of allergic march.

Key words: nasal cytology, allergic march, allergic rhinitis, asthma

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Introduction

Atopic eczema/dermatitis syndrome (AEDS), asthma, and allergic rhinitis (AR) are common atopic conditions in the first years of life. Cutaneous manifestations and food allergy are often the first symptoms of allergic disease. Asthma and AR usually develop between the third and the sixth year of life and are much more common in children who have previously had cutaneous manifestations and/or food allergies. This natural evolution of atopic disease is referred to as the "allergic march". Manifestations of atopic disease appear at a specific age, persist for years, and — with time — tend to

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remit or change the organ manifestation. An example of the allergic march may be the development of asthma in a child with AEDS or AR. So far, research projects investigating the allergic march have been unable to unequivocally confirm which factors affect its appearance, which patients will develop it, and with which disease it will end. It is also unclear which of the diagnostic tests can predict the allergic march. There have been unsuccessful attempts to select children predisposed for atopic diseases right after birth based on blood and/ /or umbilical cord blood parameters [1, 2].

The method of examining the nasal mucosa was first described by Hansel in 1934 [3]. The first cytological examinations in small children were performed by Matheson et al. [4]. The nasal mucosa is the most accessible part of the respiratory tract epithelium, and the picture resulting from cytology accurately reflects all the ongoing processes in the mucosa. Nasal cytology is, however, rarely performed in practice despite its simplicity and experts' recommendations [5, 6].

The aim of our study was to assess the usefulness of nasal cytology as a prognostic criterion facilitating prediction of the allergic march in small children. Another aim was to determine which symptoms at the beginning of the observation were associated with the risk of allergic disease.

Material and methods

This was a retrospective study in which, out of 1620 children managed at the Allergy and Paediatrics Specialist Practice in Kraków, Poland, we identified those who met the following study enrolment criteria:

— age from 1 month to 4 years inclusive at presentation;
— presence of signs and symptoms suggestive of allergic disease;
— performance of nasal cytology within the first 4 weeks of the first visit;
— remaining under observation for at least 4 years.

A total of 1322 children did not meet the enrolment criteria. Another 57 children were excluded due to interrupted observation period, and in a further 95 children various chronic conditions were identified by diagnostic tests. We therefore included a total of 146 children meeting the enrolment criteria (86 boys and 60 girls). At the beginning of the observation the age ranged from 1 to 42 months (mean 27 months, SD 10 months). With respect to the initial diagnosis (based on the present signs and symptoms) made after the first visit, the children were divided into three groups. Group A (n = 62) comprised children with AEDS, Group B (n = 98) comprised those with recurrent respiratory infections accompanied by bronchial obstruction (children with at least 3 episodes of bronchial obstruction were included), and Group C (n = 26) comprised children with gastrointestinal symptoms. Symptoms qualifying to two or three groups were present in 37 children. All the patients included in the observation had nasal symptoms of varying severity (blocked nose, recurrent rhinitis, sneezing, nasal discharge), which were an indication for nasal cytology. Seventy-nine children had a family history of atopy.

Nasal cytology was performed in all the children at the Allergy and Immunology Laboratory of the Non-Public Healthcare Establishment "Alergo-Med" in Krakow, Poland. The children were not on any elimination diet and/or undergoing any challenge test. Before cytology all the medications that might affect the result were discontinued: antihistamines, antileukotrienes, nasal decongestants, local cromones, and ipratropium bromide (given to some small children in an inhalation through a nasofacial mask) were discontinued at least 5 days before cytology; local glucocorticosteroids 14 days before; ketotifen 4 weeks before, and systemic glucocorticosteroids at least 6 weeks before cytology. Samples for exfoliative cytology were collected with an inoculation loop from the medial surface of the inferior nasal concha, 1 cm away from its anterior margin. Samples were collected twice from each of the nasal meatus. In the first smear, which was stained by the Papanicolaou method, the percentages of particular epithelial cells were determined (columnar, goblet, basal, and squamous cells). In the second smear, which was stained by the Wright method, relative counts of the following infiltrating cells were determined: neutrophils, lymphocytes, macrophages, eosinophils, and metachromatic cells (basophils, mast cells). The sampling method and the further processing of the samples were based on the methodology and norms prepared by Sanokowska and Miszke, as modified [7–9].

During the following visits, standard procedures were performed (history, physical examination) and an individual strategy of diagnostic investigations and specialist consultations was established. Particular emphasis was placed on the symptomatology of allergic diseases and response to treatment. The IgE-dependent mechanism associated with aerogenous allergens was verified by skin tests or by specific IgE determination. Four years after the initial nasal cytology, the final diagnosis

was established based on the course of the disease and ancillary investigations performed during that period. The diagnosis of AR was based on the recommendations of the international expert group and the ARIA report [5, 6]. The diagnosis of AEDS was based on the United Kingdom Working Party criteria [10], while that of asthma was based on the recommendations of the National Heart, Lung, and Blood Institute (NHLBI) expert group and the World Health Organisation (WHO), of 1995, as modified [11]. In accordance with these recommendations, when the diagnosis of asthma was made and its severity has been established, pulmonary function test results were taken into account, if available, in addition to the history and physical examination. In some of the children, peak expiratory flow (PEF) measurement was an additional diagnostic element, particularly results confirming a significant improvement in bronchial patency following short-acting β_2-agonists.

For the purposes of statistical analysis the study population was divided into six groups depending on the final diagnosis (AR, AR + asthma, AR + asthma + AEDS, AR + AEDS, AEDS, and non-allergic diseases). The mean counts and medians for each type of infiltrating and epithelial cells were calculated. A non-parametric Kruskal-Wallis ANOVA test was performed to check for the differences in the distribution of cells. The cells with respect to which the analysis showed statistically significant differences ($p < 0.05$) between the groups were further analysed by multiple comparison tests. In order to optimise the threshold values of the test and visualise the statistical relationships, receiver operating characteristics (ROC) curves were constructed. The threshold values were established on the basis of the minimum distance of the ROC curve points from the "ideal point". For the established threshold percentage of cells of a given type, the sensitivity, specificity, confidence interval (CI), and likelihood ratio (LR) were calculated. The likelihood ratio (for a positive result) is the ratio of the likelihood of a positive test result in patients with the disease to the likelihood of a positive test result in patients without the disease. The ROC curves were constructed for the patient subgroups identified by age, family history, and initial symptoms (Groups A, B, C).

Statistical analysis was performed using the STATISTICA 7.0 software package at the significance level $p < 0.05$. The graphs were drawn using OriginPro 7.0 and STATISTICA 7.0, and the remaining calculations were performed using Microsoft Excel.

Results

At the end of the four-year observation period the most common disease in the study group was AR, affecting 85 children (58.2%), including 54 boys and 31 girls. Asthma was diagnosed in 48 children (32.9%), including 34 boys and 14 girls. Sporadic asthma was diagnosed in 30 children (62.5%) and chronic asthma in 18 children (37.5%), including 9 cases of mild, 7 of moderate, and 2 of severe asthma. All the children with asthma were also diagnosed with AR. AEDS was diagnosed in 51 children (34.9%). Asthma, AR, and AEDS were diagnosed in 15 children (10.2%). The presence of AR and AEDS was a prognostic factor for asthma. Non-allergic diseases were diagnosed in 36 children (22.5%).

Family history of atopy was associated with an increased risk of an atopic respiratory disease during the observation. Allergic rhinitis was diagnosed in 77% of children with, and in 36% of children without, a family history of atopy ($p < 0.001$). For asthma the respective percentages were 47% and 16% ($p < 0.001$) and there were no differences for AEDS (38% *v.* 36%, *NS*).

Only the incidence of asthma was sex-related. The disease was diagnosed in 40% of boys ($n = 34$) and 23% of girls ($n = 14$, $p = 0.04$). There were no significant differences in the incidence of AR (63% *v.* 52%, respectively, for boys and girls, $p = 0.18$).

The differences between the diagnostic groups in neutrophil, eosinophil, and lymphocyte counts were statistically significant ($p < 0.05$) (Table 1). There were also considerable differences in metachromatic cell counts ($p = 0.035$), but due to the rare occurrence of these cells in the study population (they were only identified in 15 children) it was not possible to construct the ROC curves and to perform the remaining analyses. No significant differences were observed in the epithelial cells of the nasal mucosa in children with atopic diseases. The non-parametric Kruskal-Wallis ANOVA test demonstrated that the cells with the highest prognostic value were eosinophils.

Multiple comparisons for eosinophil counts showed that there were statistically significant differences between the AR group (isolated AR or with asthma or AEDS) and the group with non-allergic diseases ($p < 0.001$) and the AEDS group ($p < 0.01$).

After comparing the cytology reports it was found that in children who had developed AR (isolated or with co-morbidities) the mean relative eosinophil count at the beginning of the observation was significantly higher than that in children with isolated AEDS (18% *v.* 3%, $p = 0.004$) or with

Table 1. The Kruskal-Wallis test statistics for each cell type

Cell type	H statistic	Type I error
Neutrophils	**H = 31.05**	**p < 0.001**
Metachromatic cells	H = 11.95	p = 0.035
Eosinophils	**H = 68.47**	**p < 0.001**
Lymphocytes	**H = 12.54**	**p = 0.028**
Macrophages	H = 7.53	p = 0.184
Columnar cells	H = 6.51	p = 0.259
Goblet cells	H = 7.22	p = 0.205
Basal cells	H = 5.52	p = 0.356
Squamous cells	H = 5.20	p = 0.392

non-allergic diseases (18% *v.* 4%, p < 0.001). There were no differences in eosinophil counts between the children with isolated AR or AR with other atopic diseases (Fig. 1).

The ROC curve (Fig. 2) for AR deviated from the y = x line the most and was closest to the "ideal" point (0.1). The ROC curve for asthma was below the ROC curve for AR. The analysis of the ROC curve showed that an initial nasal eosinophil count of at least 8% was characterised by the highest prognostic value for identifying children in whom AR would eventually be diagnosed (sensitivity 80%, specificity 95%; Table 2).

In the group of children with cutaneous manifestations at the beginning of the observation (Group A), 35 (56.5%) developed AR, and 15 of these (24.2%) were diagnosed with asthma. AEDS continued to be present in 48 children (77.4%) after 4 years of observation. This group was characterised by the highest LR for AR (21.20).

In the group of children with recurrent bronchial obstruction (Group B), 59 children (60.2%) developed AR, and 44 of these (44.9%) also developed asthma. There were 15 children (15.3%) with AEDS. The initial bronchial obstruction in the majority of the children (55.1%) was not associated with the development of asthma.

In the group of children with gastrointestinal symptoms (Group C), 16 children (61.5%) developed AR, and 8 of these (30.8%) also developed asthma. There were 6 children (23.1%) with AEDS. In Group C, LR for AR was high (9.38), and nasal cytology was characterised by the highest sensitivity (0.94) at a specificity of 0.90 (Table 2).

Analogous analyses were performed for neutrophils and lymphocytes. It was revealed, however, that the relative neutrophil and lymphocyte counts in nasal cytology had no prognostic value for AR, asthma, or AEDS.

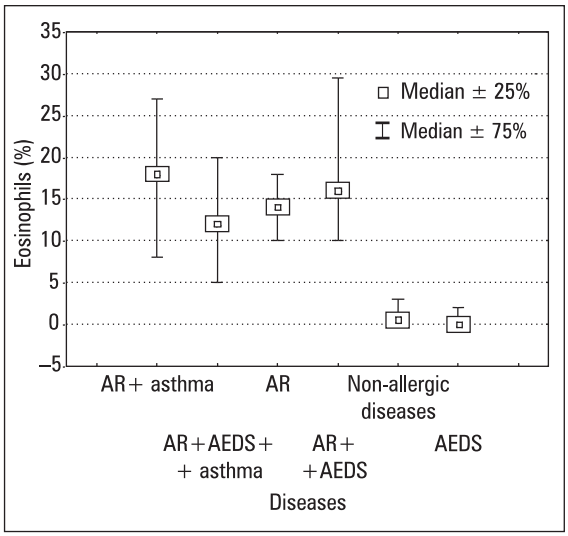

Figure 1. Medians of eosinophils in nasal cytology in children with different final diagnoses. AR — allergic rhinitis; AEDS — atopic eczema/dermatitis syndrome

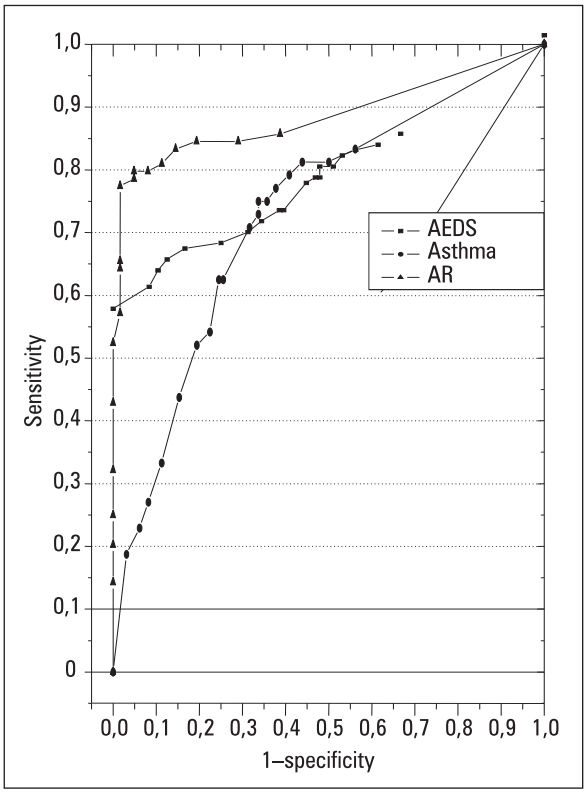

Figure 2. Value of eosmophils for final diagnosis — ROC curves. ROC curves for final diagnosis — eosinophilis

Discussion

Current epidemiological data and studies assessing inter-disease relationships show that AEDS usually precedes the development of AR and asthma [11], and that the development of food allergy

Table 2. Sensitivity, specificity, confidence interval, and likelihood ratio (LR) for eosinophils in various final diagnoses (AR, asthma, AEDS)

	Total n = 146	Boys n = 86	Girls n = 60	Family history n = 79	No family history n = 67	A n = 62	B n = 98	C n = 26
Allergic rhinitis								
Cutoff parameter (eosinophil count)	8	8	6	5	8	10	5	8
Sensitivity	0.8	0.83	0.77	0.82	0.88	0.85	0.83	0.94
Confidence interval (0.95)	0.69–0.91	0.73–0.93	0.62–0.92	0.72–0.92	0.75–1.01	0.73–0.97	0.73–0.93	0.82–1.06
Specificity	0.95	0.94	0.9	0.86	0.95	0.96	0.87	0.9
Confidence interval (0.95)	0.91–0.99	0.86–1.02	0.79–1.01	0.71–1.01	0.88–1.02	0.88–1.04	0.74–1.00	0.71–1.09
LR	16	13.83	7.7	5.86	17.6	21.25	6.38	9.38
Asthma								
Cutoff parameter (eosinophil count)	8	10	10	12	8	12	8	10
Sensitivity	0.75	0.68	0.64	0.62	0.82	0.73	0.77	0.75
Confidence interval (0.95)	0.63–0.87	0.52–0.84	0.39–0.89	0.46–0.78	0.59–1.05	0.51–0.95	0.65–0.89	0.45–1.05
Specificity	0.66	0.75	0.7	0.66	0.76	0.72	0.74	0.56
Confidence interval (0.95)	0.57–0.75	0.63–0.87	0.57–0.83	0.52–0.80	0.65–0.87	0.59–0.85	0.61–0.87	0.43–0.89
LR	2.21	2.72	2.13	1.82	3.42	2.61	2.96	1.69
Atopic eczema/dermatitis syndrome								
Cutoff parameter (eosinophil count)	7	7	10	7	7	7	7	10
Sensitivity	0.52	0.61	0.41	0.59	0.43	0.51	0.8	0.67
Confidence interval (0.95)	0.38–0.66	0.43–0.79	0.20–0.62	0.41–0.77	0.22–0.64	0.37–0.65	0.60–1.00	0.29–1.04
Specificity	0.52	0.465	0.63	0.38	0.66	0.47	0.55	0.5
Confidence interval (0.95)	0.42–0.62	0.34–0.59	0.48–0.78	0.25–0.51	0.52–0.80	0.2–0.74	0.43–0.67	0.28–0.72
LR	1.08	1.14	1.11	0.95	1.26	0.96	1.78	1.33

and/or AEDS in childhood considerably increases the risk of AR and/or asthma [12, 13]. In children with AR there is an increased risk of developing asthma later in life [11, 14].

In our study, children with AEDS at the beginning of the observation (Group A) or with gastrointestinal symptoms (Group C) were characterised by a high incidence of AR (56.5% and 61.5%, respectively). This was probably associated with the allergic march. In these children, gastrointestinal symptoms and symptoms of AEDS preceded the development of a full-blown AR.

In Group B, bronchial obstruction at the beginning of the observation was more often associated with other diseases (55.1%) than asthma (44.9%).

Our results suggest that elevated eosinophil counts on nasal cytology may be a marker of an incipient (or already ongoing) allergic march. However, no statistically significant difference was observed in eosinophil counts between children with isolated AR and children in whom AR coexisted with other atopic diseases. Therefore, based on the elevated eosinophil count in the nasal cytogram, it could not be predicted whether the child would develop AR or AR and asthma. Nevertheless, nasal cytology may be used indirectly to define the group of children at risk of asthma, because asthma always coexisted with AR in the study group. Ciprandi et al. found similar changes in the nasal mucosa in patients with sporadic and mild

asthma and in patients with isolated AR. This finding confirms that AR might be an initial phase of asthma [15]. In a similar study, Gaga et al. found eosinophilic infiltrates in the noses of patients with AR unaccompanied by AR-related signs or symptoms [16]. Illi et al. followed up 1315 children with AEDS and found that the allergic march most commonly took the form of asthma 3 years after developing AEDS [17]. Bergmann et al. followed up children with AEDS and found that about 40% of children with AEDS in early childhood (at the age of 3–5 years) had symptoms of asthma [18].

It is currently believed that the previous approach to the allergic march in childhood was too much of a simplification of the natural history of allergic disease, as children with AEDS and wheezing have been shown to have much poorer pulmonary function than children with either AEDS or wheezing alone [19]. This suggests the existence of two phenotypes of atopic disease rather than an evolution of AEDS towards asthma. According to Wahn et al. [20], rather than using the word "march" the word "marathon" should be used, as it would define the broad interactions between the involvement of genes and exposure to allergens in addition to other facilitating factors such as infection.

The contribution of genetic factors is estimated at about 60%, which suggests a significant role of environmental factors. As a result, different patients develop different "allergic phenotypes" with or without clinical symptoms [11]. This hypothesis was confirmed by Berg et al. who demonstrated that while as a result of elimination diet the incidence of AEDS in early childhood markedly decreased, this was not paralleled by a decreased incidence of asthma and AR later in life [21].

A situation where symptoms are confined to the lower respiratory tract and the pathological changes in the nose may not manifest clinically is a completely different problem [22]. Many authors recommend that the severity of the allergic reaction in adults with AR should be measured objectively in addition to symptom score (visual analogue scale [VAS], total nasal symptom score [TNSS]). Such objective methods include measurement of the eosinophil count in nasal secretions [23], facial thermography [24], and/or measurement of nasal inspiratory peak flow rate (NIPFR) [25]. In children below six years of age these techniques cannot be applied due to the low repeatability of measurements. In this age group, observation of nasal symptoms is difficult because the symptomatology of AR in small children differs significantly from that in older children and adults. This is especially true in children with adenoid hypertrophy [26]. Our results relating to the diagnosis of asthma must be analysed in two different groups of children. The first group consisted of children with bronchial obstruction at the beginning of the clinical observation and the second group included children who developed symptoms of asthma during the four years of observation. The allergic march occurred in the second group. In a similar study, Gustafsson et al. followed up 94 children with AEDS aged 0–7 years for 8 years. After this period, asthma was diagnosed in 43% and AR in 45% of the children, although remission of AEDS (or perhaps the allergic march) was observed in 87%. In addition, asthma was more common in children diagnosed with a severe forms of AEDS [27, 28].

The common prognostic factors for atopic diseases of the respiratory tract (asthma, AR) were a family history of allergic diseases and, for asthma, male sex. In the study group, during the 4-year observation, boys were nearly twice as frequently diagnosed with asthma than girls (40% vs. 23%). These findings are consistent with the literature, indicating that asthma in childhood is more often seen in boys. This sex-related risk is most probably associated with the lower diameter and increased tone of the bronchi and the increased IgE concentration in boys [11].

In our study group, more than 80% of children with asthma had a family history of atopy. Burke et al. conducted a meta-analysis of studies assessing the value of family history for predicting the development of asthma and observed a sensitivity of 4–43%, which was not high [28].

In our study, based on the elevated eosinophil count in the cytogram, we could not predict whether the child would develop AR or AR and asthma. It seems, however, that nasal cytology may be used indirectly to identify the group of children at risk of developing asthma because asthma in the study group always coexisted with AR. Sale et al. demonstrated a correlation between bronchial hyperreactivity and the presence of eosinophils in the nasal mucosa, thereby proving the unity and/or interrelationship of these phenomena. Unfortunately, this observation was conducted in a very small group of 11 children [29].

In conclusion, none of the risk factors discussed above allowed us to fully identify the children who would develop one or more allergic diseases, and for this reason nasal cytology should be performed as one of the many other tests used in the evaluation of allergy. The European Academy of Allergy and Clinical Immunology (EAACI) therefore emphasised that only a positive result of na-

sal cytology may be helpful in determining the cause, while the absence of eosinophils in the cytogram is not conclusive to the diagnosis [30]. Treating elevated eosinophil counts on cytology as a marker of the risk of allergic march may be a completely novel application of this diagnostic method. In our study, changes in the composition of infiltrating cells in the form of an increased relative eosinophil count were the element of the highest prognostic value. This suggests an exceptional possibility of identifying a group of children who are likely to develop the allergic march.

Conclusions

1. The allergic march (development of respiratory tract allergy) was observed in children with atopic eczema/dermatitis syndrome and/ /or food allergy symptoms in whom nasal cytology revealed relative eosinophil counts of at least 8%.
2. In children below 4 years of age, relative eosinophil counts of at least 8% were associated with a high risk of allergic rhinitis.
3. Elevated eosinophil counts on nasal cytology in small children may be treated as a marker of the risk of the allergic march and may, therefore, be helpful in identifying children at risk of an allergic disease of the respiratory tract.

References

1. Borres M.P., Einarrson R., Bjorksten B. Serum levels of interleukin-4, soluble CD23 and IFN-α in relation to the development of allergic diseases during the first 18 months of life. Clin. Exp. Allergy 1995; 25: 543–548.
2. Kjellman N.I.M. Predictive value of high IgE levels in children. Acta Pediatr. Scand. 1976; 65: 465–471.
3. Hansel F.K. Observations on the cytology of the secretions in allergy of the nose and paranasal sinuses. J. Allergy 1934; 5: 357–366.
4. Matheson A., Rosenblum A., Glazer R., Dacanay E. Local tissue and blood eosinophils in newborn infants. J. Pediatr. 1957; 51: 502–509.
5. van Cauwenberge P., Bachert C., Passalacqua G. et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy 2000; 55: 116–123.
6. Bousquet J., Khaltaev N., Cruz A.A., Denburg J. et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008; 63 (supl. 86): 8–160.
7. Miszke A., Sanokowska E., Chomiak E. Cytologia zdrowej błony śluzowej nosa. Otolaryngol. Pol. 1985; 39: 25–31 .
8. Miszke A., Sanokowska E. Nowe normy cytologiczne dla śluzówki nosa. Otolaryngol. Pol. 1994; 47: 44–47.
9. Miszke A., Sanokowska E. Wartość diagnostyczna cytologii błony śluzowej nosa. Otolaryngol. Pol. 1999; 53: 253–256.
10. Williams H.C., Burney P.G., Pembroke A.C., Hay R.J. The UK Working Party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. Br. J. Dermatol. 1994; 131: 406–416.
11. The Global Strategy for Asthma Management and Prevention (GINA 2008). Available at: http:www.ginasthma.org.
12. Gustafsson D., Sjoberg O., Foucard T. Sensitization to food and airborne allergens in children with atopic dermatitis followed up to 7 years of age. Pediatr. Allergy Immunol. 2003; 14: 448–452.
13. Eichenfield L.F., Hanifin J.M., Beck L.A. et al. Atopic dermatitis and asthma: parallels in the evolution of treatment. Pediatrics 2003; 111: 608–616.
14. Papadopoulos N.G., Borres M., Gern J., Nieto A . New visions in respiratory allergy (asthma and allergic rhinitis): iPAC summary and future trends. Pediatr. Allergy Immunol. 2008; 19 (supl. 19): 51–59.
15. Ciprandi G., Milanese M., Tosca MA., Cirillo I., Vizzaccaro A., Ricca V. Nasal eosinophils correlate with FEV1 in patients with perennial allergic rhinitis associated to asthma. Eur. Ann. Allergy Clin. Immunol. 2004; 36: 363–365.
16. Gaga M., Lambrou P., Papageorgiou N. et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. Clin. Exp. Allergy 2000; 30: 663–669.
17. Illi S., von Mutius E., Lau S. et al. Multicenter Allergy Study Group. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J. Allergy Clin. Immunol. 2004; 113: 925–931.
18. Bergmann R.L., Edenharter G., Bergmann KE. et al. Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. Clin. Exp. Allergy 1998; 28: 965–970.
19. Piippo-Savolainen E., Remes S., Kannisto S., Korhonen K., Korppi M. Asthma and lung function 20 years after wheezing in infancy: results from a prospective follow-up study. Arch. Pediatr. Adolesc. Med. 2004; 158: 1070–1076.
20. Wahn U., Marenholz I., Nickel R et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. J. Allergy Clin. Immunol. 2006; 118: 866–871.
21. von Berg A., Filipiak-Pittroff B., KraÅNmer U. et al. Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). J. Allergy Clin. Immunol. 2008; 121: 1442–1447.
22. Ciprandi G., Cirillo I., Vizzaccaro A., Milanese M., Tosca M.A. Airway function and nasal inflammation in seasonal allergic rhinitis and asthma. Clin. Exp. Allergy 2004; 34: 891–896.
23. Droszcz W. Badania dodatkowe i konsultacje w chorobach układu oddechowego — zarys postępowania w pracy lekarza. Alergia 2004; 3: 16–17.
24. Passalacqua G., Canonica G.W. A review of the evidence from comparative studies of levocetirizine and desloratadine for the symptoms of allergic rhinitis. Clin. Ther. 2005; 27: 979–992. Erratum in: Clin. Ther. 2005; 27: 1669.
25. Blomgren K., Simola M., HytoÅNnen M., PitkaÅNranta A. Peak nasal inspiratory and expiratory flow measurements — practical tools in primary care? Rhinology 2003; 41: 206–210.
26. Tarchalska-Kryńska B., Modrzyński M. Ocena cytologiczna błony śluzowej nosa u dzieci z przerostem migdałka gardłowego. Cz. II. Pol. Merk. Lek. 2001; 60: 408.
27. Gustafsson D., Sjoberg O., Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis — a prospective follow-up to 7 years of age. Allergy 2000; 55: 240–245.
28. Burke W., Fesinmeyer M., Reed K., Hampson L., Carlsten C. Family history as a predictor of asthma risk. Am. J. Prev. Med. 2003; 24: 160–169.
29. Sale R., Silvestri M., Battistini E. et al. Nasal inflammation and bronchial reactivity to methacholine in atopic children with respiratory symptoms. Allergy 2003; 58: 1171–1175.
30. Fokkens W., Lund V., Bachert C. et al. EAACI position paper on rhinosinusitis and nasal polyps executive summary. Allergy 2005; 60: 583–601.