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Profile of immune response during nasal challenge with *dermatophagoides pteronyssinus* in subjects with allergic airway diseases

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Abstract

Background T lymphocyte helper (Th) 2 plays the main role in pathogenesis of allergic airway diseases (AAD). Recent studies showed that interleukin (IL) 33, Th17 and Th22 also may be involved in allergic inflammation. The aim is to evaluate cytokine level before and after nasal challenge with *Dermatophagoides pteronyssinus* in patients with AAD.

Methods Patients with persistent allergic rhinitis (AR) with or without allergic asthma (AA) allergic to house dust mite and healthy individuals underwent nasal challenge with *Dermatophagoides pteronyssinus*. Measurements of IL-13, IL-17, IL-22 and IL-33 in serum and nasal lavage were performed before, 2 and 22 h after nasal challenge by ELISA.

Results . Ten patients with AR only, 6 patients with AR and AA and 7 healthy individuals were involved in the study. Serum IL-22 level significantly increased in patients with AR and AA and nasal lavage IL-22 tended to increase in patients with AAD after nasal challenge. Serum IL-13 level tended to increase in patients with AR and AA. IL-13 level in nasal lavage fluid decreased at 22 h after nasal challenge in patients with AR only. IL-17 level in serum and nasal lavage decreased in patients with AAD. Serum IL-33 tended to increase after nasal challenge whereas IL-33 in nasal lavage significantly decreased.

Conclusion Cytokine profile differs between local and systemic compartments and between patients with allergic rhinitis only and patients with allergic rhinitis and asthma after nasal challenge.

Keywords Allergy, Rhinitis, Asthma, Interleukin, Nasal challenge, House dust mite

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Background

Prevalence of allergic airway diseases – allergic rhinitis (AR) and allergic asthma (AA) – is high and still increasing worldwide [1–5]. AR and AA are very often diagnosed together, that is why the hypothesis of united airway disease was proposed. AR is one of the most common phenotypes of chronic rhinitis and one of the most prevalent allergic diseases worldwide [5–8]. It is estimated that this disease affects almost 20% of population [6]. Asthma affects 1–18% of the population in different countries [9]. This disease have many phenotypes, but one of the most common is allergic [9]. AR and AA usually affect children and young adults and are highly associated with poorer quality of life, disturbed social life, daily activity and increased leave day at school or work [10, 11]. However, the exact mechanisms and prognostic markers of these diseases are still not fully investigated.

It is known that in allergic airway diseases the main role belongs to T lymphocyte helper (Th) 2 producing interleukin (IL) 4, IL-5 and IL-13 (type 2 immunity) [1, 7, 12]. Recent studies showed that newly described IL-33 may be important in inducing Th2 inflammation [13]. Moreover, there is increasing evidence that not only Th2, but other subtypes of T lymphocytes, such as recently discovered Th17 and Th22, which are important in the development of autoimmune disorders or chronic non-allergic airway inflammation may be involved in the pathogenesis of allergic airway diseases [12, 14].

AR and AA are heterogenous diseases and have variety of symptoms which severity and respond to treatment differs. Moreover, AR and AA are very often diagnosed together, that is why the hypothesis of united airway disease was proposed [15, 16]. It is known that during allergic airway diseases both local and systemic inflammation develops. There is lack of clinical studies where cytokine profile is investigated in local (nasal lavage) and systemic (serum) compartments before and after challenge with allergen and their link with clinical data is assessed. This is crucial for understanding the role of cytokines in immune response to specific allergen and for perceiving differences between local and systemic inflammation.

The aim of this study is to evaluate local and systemic cytokine profile (level of IL-13, IL-17, IL-22, and IL-33) before and after nasal provocation with *Dermatophagoides pteronyssinus* allergen in patients with allergic airway diseases.

Methods

Study population

Study was performed in Department of Immunology and Allergology of Hospital of Lithuanian University of Health Sciences. The study was approved by the Kaunas Regional Biomedical Research Ethics Committee (No. BE-2-28). Subjects gave their written informed consent.

Study groups:

- patients with persistent AR diagnosed according to the guidelines of Allergic Rhinitis and its Impact on Asthma (ARIA) [5] and having symptoms for at least 2 years;
- patients with AR and well controlled mild to moderate AA diagnosed according to the guidelines of Global Initiative for Asthma (GINA) [9] and having symptoms for at least 2 years;
- healthy individuals without AR and AA or other diseases that can negatively impact the results.

The inclusion criteria were:

1. age 18–60 years,
2. hypersensitivity to HDM diagnosed by skin prick test or/ and allergen specific Ig E test (for patients with allergic airway diseases),
3. no use of local or systemic glucocorticoids or other immunosuppressant drugs for at least 1 month before the study,
4. no use of antihistamines for 1 week before the study and.
5. no respiratory infection for at least 1 month before the study.

Exclusion criteria were:

1. relevant hypersensitivity to other inhaled aeroallergens,
2. malignant diseases and systemic autoimmune diseases,
3. treatment with allergen immunotherapy,
4. pregnancy,
5. severe asthma or asthma exacerbation.

Evaluation of allergic sensitization

Allergic sensitization was determined by skin prick test or allergen specific IgE test.

Skin prick test was performed according to the standard protocol with standard inhalant allergens (Diater, Spain) on the inner forearm. Drop of different allergen solution was placed at 3 cm distant from each other. Histamine solution 10 mg/ml was used as a positive control and diluent was used as a negative control. The skin was pricked through the drop using the tip of a lancet (separate lancet was used for all allergen drops). Skin reaction was assessed after 15 min. Wheal was measured using ruler. The test was assumed as a 'positive' if diameter of the wheal was at least 3 mm.

Measurement of allergen specific IgE was performed using standard immunoblot analysis according to the

manufacturer's instructions (Euroimmun, Germany). Total IgE in serum was measured using enzyme immunoassays (AIA-FAC IgEII Tosoh Bioscience, Japan).

Nasal challenge with dermatophagoideus pteronnysinus

Nasal challenge was performed according to EAACI recommendations [17]. Patient 15 min acclimated to room conditions. Then nasal function measurement (total nasal resistance (TNR)) using rhinomanometer (Ganshorn Spiroscout, Germany) was performed. For patients with asthma spirometry was performed. Patient evaluated nasal symptoms using Total nasal symptom score (TNSS) [17]. The permission to use validated questionnaires (Lithuanian versions) was received. Two puffs of control solution were applied into both nostrils. After ten minutes patient evaluation of nasal symptoms using TNSS and rhinomanometry were performed. If there were no significant changes in the results, actual allergen challenge was performed.

Dermatophagoideus pteronnysinus allergen (Inmunotek, S.L., Spain) for provocation was prepared according to manufacturer's recommendations. During allergen application, the patient had to hold his breath to avoid inhaling the allergen into the lower airways. The applicator of the delivery device was inserted into the nasal vestibule and pointed upward and laterally toward the medial canthus of the eye to deposit allergen on the inferior and the middle turbinate mucosa when spraying the solution into the nose. Ten minutes after allergen application, clinical signs according to TNSS were reassessed, and rhinomanometry was repeated. The procedures were repeated after a period of additional 20 min, 5 h, and 22 h. After 2 and 22 h after nasal challenge peripheral blood and nasal lavage fluid were collected.

Peripheral blood collection and processing

Peripheral vein puncture was performed for all subjects. Blood samples were drawn into KEDTA tubes for investigation for complete blood count. Blood samples were also drawn into serum tubes. Serum tubes were stored at room temperature for 30–60 min. and centrifuged at 3500 rpm for 10 min, and serum was separated and frozen at -80°C for further analysis.

Nasal smear and nasal lavage fluid specimen collection and processing

Nasal smears of patients were obtained by gently swabbing the nasal inferior turbinate with a cotton-tipped swab. The sample was then placed on a surface of glass microscope slide and stained with Giemsa stain for eosinophil detection. All specimens were examined by qualified pathologist.

Nasal lavage fluid was collected for all subjects using 5 ml isotone saline per nostril with reclined neck (about 30°C from the horizontal) and closed soft palate. After 30 s the subject flexed the neck draining lavage fluid into a sterile vessel. Nasal lavage fluid was frozen at -80 °C for further analysis (cytokine measurement).

Laboratory evaluation of cytokines

Measurements of IL-13, IL-17, IL-22 and IL-33 in serum and nasal lavage were performed by ELISA using commercial kits (Elabscience Biotechnology Inc., USA) with Euroimmun Analyzer I (Germany). Intra-assay precision coefficients of variability for IL-10 was 5.42%, for IL-13–5.58%, for IL-17–5.04%, for IL-22–5.51%, for IL-33–4.99% and for IFN-γ – 4.89%.

Results

Twenty-three subjects (13 women and 10 men, mean age 32.17 ± 10.32) underwent nasal challenge with *Dermatophagoideus pteronnysinus*. Sixteen patients were with allergic airway diseases (10 with AR only and 6 with AR and AA) and 7 healthy individuals. Blood eosinophil count and serum IgE level were higher in patients with allergic airway diseases than in control group. There was a tendency that eosinophils ($p=0.06$) in nasal secretion were higher in patients with allergic airway diseases than in healthy patients. All patients were allergic to *Dermatophagoideus pteronnysinus* allergen. Eleven patients also had hypersensitivity to other allergens (birch, grass and/or mugwort pollen). Nasal challenge was performed during winter when there is no exposure to pollens. Subjects' demographic data are shown in Table 1.

Nasal symptoms according to TNSS and TNR were evaluated before and after nasal challenge at different time points. TNSS significantly differed between patients with allergic airway diseases and control group during all measuring points and a tendency was seen that TNR was higher in patients with allergic airway diseases than in healthy individuals during all measuring points (Table 2). Significantly higher TNR results in patients with AR and AA than in healthy individuals were observed at 22 h after nasal challenge. Moreover, significant increase of nasal symptoms severity after nasal challenge was found in patients with allergic airway diseases (Table 2).

Level of IL-13, IL-17, IL-22, and IL-33 was measured in serum and nasal lavage fluid before and at 2 and at 22 h after nasal challenge with allergen. A tendency was observed that levels of IL-13, IL-17, IL-22 and IL-33 in serum and IL-17 and IL-33 levels in nasal lavage fluid before nasal challenge were higher in patients with allergic airway diseases than in healthy individuals ($p<0.15$).

Serum IL-22 level significantly increased after nasal challenge in patients with AR and AA at 2 and 22 h after nasal challenge (Fig. 1). A tendency was observed that nasal lavage IL-22 in patients with AR only and in

Table 1 Subjects' who underwent nasal challenge demographic data

	Patients with AR only($n=10$)	Patients with AR and AA ($n=6$)	Control group ($n=7$)
Male/ female, N	7/3	2/4	1/6
Age, years, mean ± SEM	29.63 ± 3.27	34.25 ± 5.89	33.71 ± 3.62
Duration of rhinitis symptoms, years, mean ± SEM	17.33 ± 5.79	10.40 ± 3.61	N/A
Duration of asthma symptoms, years, mean ± SEM	N/A	6.00 ± 3.67	N/A
Blood eosinophils, x10/9	0.28 ± 0.08*	0.19 ± 0.03*	0.07 ± 0.03
Blood eosinophils, %	4.43 ± 1.17**	2.36 ± 0.68	1.16 ± 0.31
Serum IgE, kU/l	211.36 ± 83.75*	388.43 ± 133.88**	27.99 ± 10.08
Eosinophils in nasal secretion, %	11.50 ± 7.90	6.50 ± 3.67	4.43 ± 2.73
Allergy to other allergens than HDM, N (%)	6 (60.00%)	5 (83.30%)	N/A

*$p<0.05$ compared with control group

**$p<0.01$ compared with control group

Table 2 Changes of TNSS and TNR before and after nasal challenge with Dermatophagoideus pteronnysinus[1]

	Patients with AR only	Patients with AR and AA	Control group
TNSS			
Before challenge	1.00 (3.00)*	1.5 (1.00)*	0.00 (1.00)
10 min after challenge	1.00 (5.00)$^{\pm}$**	4.5 (3.00)*	0.00 (1.00)
20 min after challenge	1.50 (7.00)**	4.5 (5.00)$^{\pm}$*	0.00 (0.50)
5 h after challenge	2.00 (3.00)$^{\#}$**	1.5 (1.00)*	0.00 (0.50)
22 h after challenge	1.00 (4.00)**	2.5 (1.00)*	0.00 (0.50)
TNR (kPa*s/L at 150 Pa)			
Before challenge	0.27 (0.55)	0.52 (0.81)	0.19 (0.11)
10 min after challenge	0.26 (0.79)	0.68 (0.43)	0.18 (0.13)
20 min after challenge	0.25 (0.58)	0.33 (0.06)	0.19 (0.15)
22 h after challenge	0.27 (0.36)	0.55 (0.24)*	0.21 (0.11)

[1]Data are presented as median (range)

*$p<0.05$ compared with control group

**$p<0.01$ compared with control group

$^{\#}p<0.01$ compared with before challenge in current group

$^{\pm}p<0.05$ compared with before challenge in current group

patients with AR and AA increased after nasal challenge ($p=0.09$).

IL-13 level in serum tended to increase after 2 and 22 h compared with baseline only in patients with AR and AA ($p=0.09$). IL-13 level in nasal lavage fluid decreased at 22 h after nasal challenge compared with baseline data in patients with AR only.

IL-17 level in serum significantly decreased after nasal challenge in patients with AR only and AR and AA (Fig. 1). Nasal lavage IL-17 tended to decrease in patients with AR only ($p=0.06$) and significantly decreased in patients with AR and AA.

Serum IL-33 tended to increase after nasal challenge in patients with allergic airway diseases whereas IL-33 in nasal lavage fluid significantly decreased in patients with AR only and in patients with AR and AA (Fig. 1).

It was also found that total IgE level before nasal challenge was positively significantly related to serum IL-22 at 2 and 22 h and IL-13 level at 2 h after nasal challenge in patients with AR and AA (rs=0.95, $p<0.05$; rs=0.90, $p<0.05$, rs=0.89, $p<0.05$, respectively). Blood eosinophils count before nasal challenge was positively significantly related to higher serum IL-33 at 2 h after nasal challenge in patients with AR and AA (rs=0.98, $p<0.01$).

TNR at 22 h after nasal challenge positively correlated with serum IL-22 and IL-13 at 2 h after nasal challenge and with IL-17 in nasal lavage fluid at 2 h after nasal challenge in all patients with allergic airway diseases (Fig. 2). Correlations between cytokines and TNSS after nasal challenge were not found.

Discussion

This study revealed that novel cytokines such as IL-17, IL-22, and IL-33 together with IL-13 may play a significant role in the pathogenesis of allergic airway diseases – AR and AA. However, there are differences in immune response between local and systemic compartments and between patients with allergic rhinitis only and patients with asthma and rhinitis.

One of the best investigated Th2 produced inflammatory biomarker IL-13 is associated with eosinophilic lung inflammation, airway epithelial cell hypertrophy, goblet cell metaplasia, mucus hypersecretion, subepithelial fibrosis, and airway hyperresponsiveness [18, 19]. IL-13

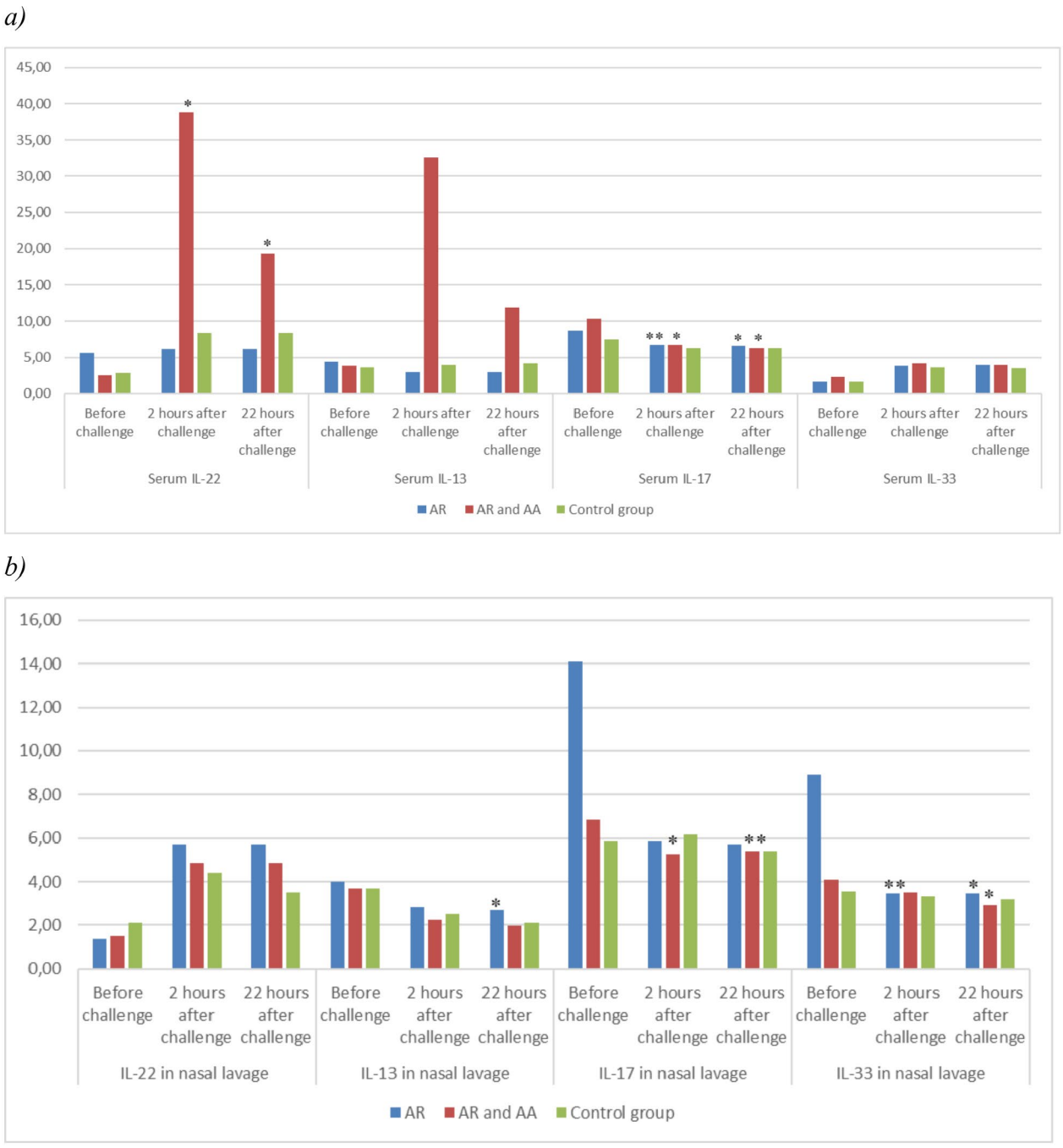

Fig. 1 Cytokines level before and after nasal challenge with Dermatophagoideus pteronnysinus in serum (**a**) and nasal lavage fluid (**b**)[1]
[1]Data are presented as median.
[**] $p < 0.01$ compared with data before challenge in certain group.
[*] $p < 0.05$ compared with data before challenge in certain group.

promotes mast cells and B cell proliferation and induces class switching to IgE and IgG4, also promotes survival, activation, and recruitment of eosinophils and stimulates eosinophil trafficking from the peripheral blood to the site of inflammation by inducing the production of IL-5 and eosinophil chemokines such as eotaxins [20]. Clinical studies show increased serum, nasal lavage fluid, sputum and BAL IL-13 concentration in children and adults having atopic diseases including AA and AR [19, 21–26]. In our study, a tendency was observed that serum IL-13 level was increased after nasal challenge with *Dermatophagoideus pteronnysinus* in patients with AR and AA,

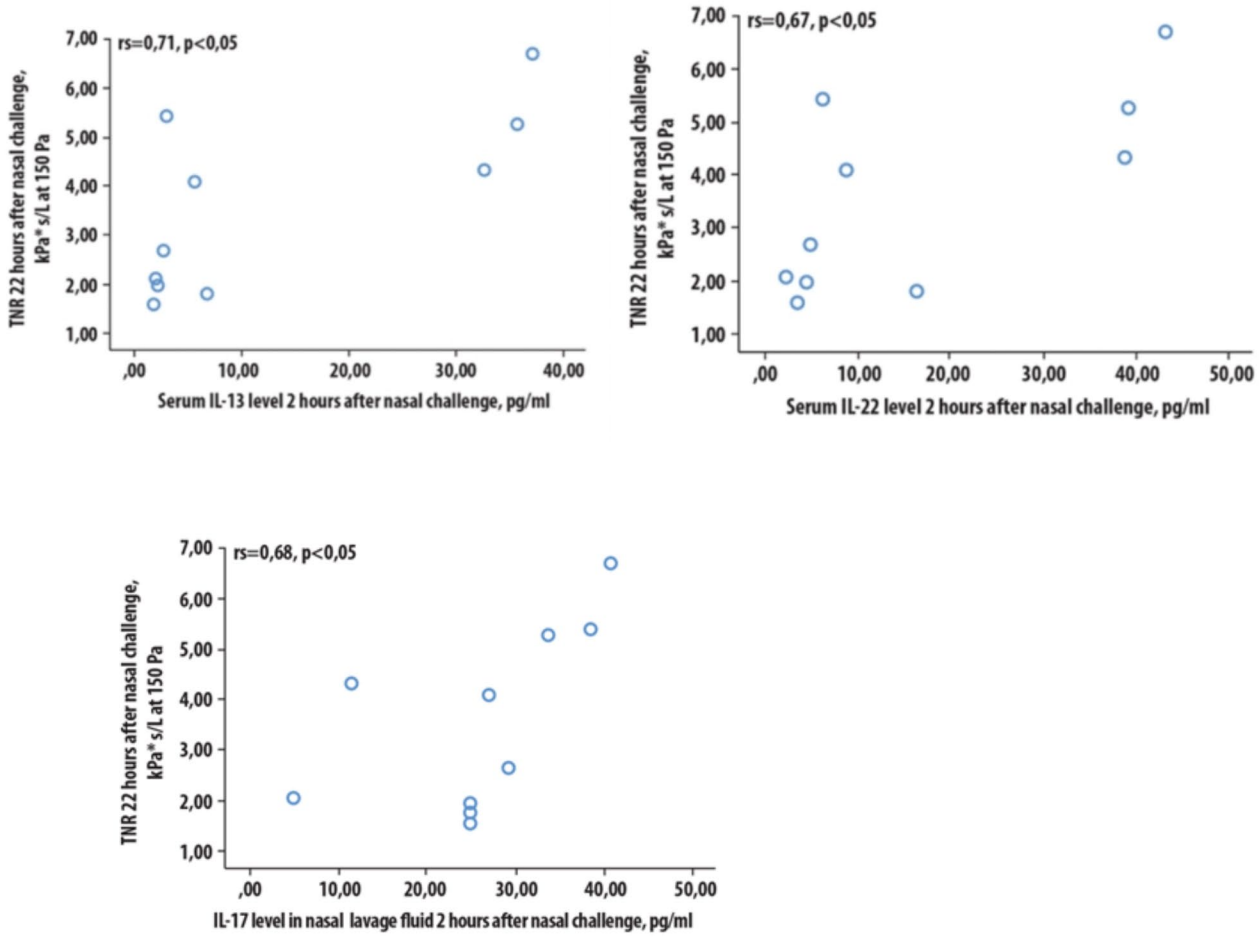

Fig. 2 Correlation between TNR 22 h after nasal challenge and cytokines after 2 h after nasal challenge in patients with allergic airway diseases

but 22 h later IL-13 in nasal lavage fluid decreased significantly in patients with AR only. According to the other authors, serum IL-13 increased significantly in patients with AA after bronchial challenge *with Dermatophagoideus pteronnysinus* [27], but Baumann et al. showed that IL-13 serum levels did not change at 5 and 24 h after nasal challenge with pollen allergen compared to baseline data, whereas IL-13 in nasal secretions rose moderately 2 h after nasal challenge and was more pronounced 5 h later but felt to low levels after 24 h [23]. Our study revealed that higher serum IL-13 level at 2 h after nasal challenge was related with higher TNR at 22 h after nasal challenge in all patients with allergic airway diseases. According to Baumann et al., link between IL-13 level in nasal secretions with obstruction was observed 5 h after nasal challenge with pollen allergen [23]. Campion et al. performed challenge with birch pollen allergen for birch pollen-allergic patients and found high IL-13 levels 2 to 8 h after allergen provocation for 8 of 20 provoked participants [28]. This group also showed significant changes in clinical parameters, with a secondary drop in nasal airflow and increased symptoms of nasal obstruction. These findings support the theory that IL-13 is involved in late phase allergic inflammation and in nasal secretions appears between 4 and 8 h after nasal allergen challenge [29]. Serum IL-13 level more increases in patients with AR and AA than in patients with AR only and is related to higher total IgE level in patients with AA suggesting that asthma is more related with systemic inflammation than AR.

The main function of Th17 cells is to clear extracellular and intracellular pathogens [30, 31] and to protect mucosal homeostasis and to enhance neutrophil response [30]. IL-17 is usually associated with development of chronic non-allergic airway inflammation and neutrophilic inflammation [12, 14, 32]. Studies provide evidences that IL-17 contributes to type-2 low asthma [33], and high level of IL-17 is found in patients with severe asthma [34–36]. However, a number of studies have found high levels of serum IL-17 in patients with AR [37–39]. Our

study showed that nasal challenge with *Dermatophagoideus pteronnysinus* significantly decreased IL-17 after 2 and 22 h compared with baseline in patients with AR only and in patients with AR and AA. On the contrary, Baumann et al. showed that IL-17 A level in nasal secretions increased after nasal challenge with pollen allergen, but it was measured 5 h after provocation [40]. Research which investigated changes of IL-17 level before and after nasal challenge with HDM were failed to find. Decrease of IL-17 level after nasal challenge in our study may be explained by the evidence that this cytokine is more related with neutrophilic inflammation and more severe form of allergic diseases, especially, asthma. However, we have found positive correlation between TNR and IL-17 in nasal lavage fluid after nasal challenge in all patients with allergic airway diseases. There is evidence that IL-17 causes a significant disruption of the epithelial barrier in chronic rhinosinusitis [41]. Other experimental research revealed that IL-17 can exacerbate airway inflammation and cause airway hyperreactivity in some asthmatic endotypes with hypersensitivity to HDM [42].

According to the scientific literature, IL-33 is associated with Th2 inflammation [43]. After nasal challenge with *Dermatophagoideus pteronnysinus* serum IL-33 tended to increase after 2 and 22 h compared with baseline, but IL-33 level in nasal lavage fluid decrease in patients with AR only and in patients with AR and AA. According to Kalinauskaite-Zukauske et al. the serum level of IL-33 at baseline was significantly higher in the AA group compared with healthy subjects, but the bronhcial challenge with *Dermatophagoideus pteronnysinus* did not provoke an increase of this cytokine in any group after 24 h [27]. Baumann et al. also did not observed changes in IL-33 level after nasal challenge with pollen allergen [44]. Campion et al. revealed significant increases in the soluble IL-33 receptor serum stimulation 2 (sST2) in nasal secretions within minutes after challenge with birch pollen allergen compared with the placebo group [28]. There is lack data about changes of IL-33 before and after nasal challenge with HDM in scientific literature. However, decrease of this cytokine in nasal lavage fluid after nasal challenge could be explained by the theory similarly as in case of IL-13 decrease – IL-33 in nasal lavage fluid increases 4–8 h after nasal challenge, but in this study concentration at this time point was not investigated.

Despite the evidence that IL-22 can be important in the pathogenesis of AR and AA, it is unclear if this cytokine acts as pro-inflammatory agent or anti-inflammatory agent. Studies provide controversial data. There are data that IL-22-positive mice had a reduced number of eosinophils and a lower level of IL-13 in bronchoalveolar lavage (BAL) and mucus-producing cells in the airways after ovalbumin stimulation when compared with IL-22-negative mice [45, 46]. On the contrary, some experimental studies showed that ovalbumin-challenged and IL-22-deficient mice had a low level of eosinophils in BAL and lung tissue [47–49]. Clinical studies revealed that plasma or serum IL-22 level was higher in patients with AR and AA compared with control patients [38, 49–51]. Moreover, significantly increasing expression level of IL-22 was observed in nasal mucosa of patients with mild persistent allergic rhinitis and patients with moderate/severe allergic rhinitis in comparison with data from healthy nasal mucosa analysis [49]. Some studies revealed positive relation between IL-22 level and severity of AR and AA [49–52]. Our study showed that nasal challenge with *Dermatophagoideus pteronnysinus* increased serum IL-22 level after 2 and 22 h in patients with AR and AA and tended to increase nasal lavage IL-22 level in patients with AR only and in patients with AR and AA. Moreover, higher serum IL-22 level at 2 h after nasal challenge was associated with higher TNR at 22 h after nasal challenge. PubMed search of studies with investigation of IL-22 before and after nasal challenge with HDM failed to find them.

Conclusions

To sum up, nasal challenge with *Dermatophagoides pteronyssinus* allergen revealed differences of local and systemic cytokine profile in patients with AR only and AR patients with AA. Serum IL-13 and IL-22 tended to increase higher in patients with AR and AA than in patients with AR only after nasal challenge. IL-13 and IL-33 increased in serum but decreased in nasal lavage after nasal challenge whereas IL-17 levels decreased in both compartments in patients with AR only and AR patients with AA. More studies evaluating cytokine profile in local and systemic compartments and its relation with clinical symptoms before and after allergen challenge need to be performed in order to identify specific patterns of inflammation and phenotypes of these diseases.

Abbreviations

Th	T lymphocyte helper
AAD	Allergic airway diseases
IL	Interleukin
AR	Allergic rhinitis
AA	Allergic asthma
ARIA	Allergic Rhinitis and its Impact on Asthma
GINA	Global Initiative for Asthma
EAACI	European Academy of Allergy and Clinical Immunology
HDM	House dust mite
Ig	Immunoglobulin
TNR	Total nasal resistance
TNSS	Total nasal symptom score

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Author contributions
L.T. performed statistical analysis and prepared figures and tables. L.T. and B.G. wrote the main manuscript text. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Kaunas Regional Biomedical Research Ethics Committee (No. BE-2-28). Subjects gave their written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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