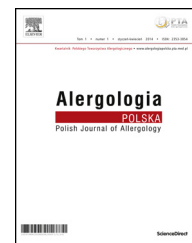


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Original research article/Artykuł oryginalny

Nasal allergen challenge in clinical practice – A real life study



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ABSTRACT

Nasal allergen challenge represents, together with skin tests and specific IgE, one of the basic diagnostic tools used in allergology. The goals of the study were to evaluate types of allergens used, the clinical picture of the challenge, and its safety in our daily clinical practice. In total 136 challenges in 109 patients were analyzed. The study group included 60 women and 49 men, with an average age of 34 years. In 15 patients (13.8% of the study group), apart from allergic rhinitis, bronchial asthma was also diagnosed. Eighty-two patients (75.23%) were challenged with 1, and 27 subjects (24.77%) with 2 allergens. The majority of challenges were performed with house dust mites (58 challenges, 42.6%), followed by *Alternaria*, mugwort, grasses, birch, hazel, and alder. The clinical picture mimicked the symptoms reported after the natural exposure to the specific allergen. The mean score after the allergen challenge in the group with the positive result was 154.95 points ($p < 0.05$ vs control solution), and in those with negative challenge 36.67 points. Side effects after the challenge, including itchy throat, cough, dyspnea and facial pruritus, were reported by 21 patients. None of side effects was serious or required any medical intervention. Among evaluated factors only female sex (OR 3.59, 95% CI 1.33–9.68, $p = 0.012$), but not diagnosis of asthma, 2 challenges per day or the type of allergen used, was associated with a higher risk of adverse events. In conclusions, nasal allergen challenge represents safe and valuable diagnostic tool in our clinical practice.

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Introduction

Controlled allergen exposure tests represent, together with skin tests and specific IgE levels, one of the basic diagnostic

methods used in allergology. We can distinguish specific challenges (exposure to suspected allergen, symptoms develop typically in IgE dependent mechanism) and non-specific challenges (e.g., with histamine, methacholine, capsaicin and other stimuli). Due to the way of exposure, we distin-

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guish nasal, conjunctival, bronchial, oral and intravenous challenges. It seems that due to the simplicity of implementation into the clinical practice, the nasal challenge is the most common. The standards, the mechanisms and the rules of the evaluation of the challenge results are broadly presented in the guidelines of the Polish Society of Allergology [1] and the European Academy of Allergology and Clinical Immunology [2]. The primary indications for nasal challenge with allergen include: confirmation of clinical diagnosis in case of interpretation difficulties and discrepancies in other tests results and in comparison to clinical picture, qualification for specific immunotherapy, monitoring of pharmacotherapy [3] and specific immunotherapy [4], and in scientific research. An interesting modification of the controlled exposure trial is the chamber exposure challenge (e.g. Vienna chamber [5]) in which patients are exposed to a specific type and dose of allergen. The basis for evaluating the challenge is the presence of typical clinical symptoms. In the case of nasal provocation, the most typical symptoms include itching, sneezing, the appearance of secretion and swelling of the nasal mucosa. The point or analog scales represent the main tool for symptom evaluation. It seems that the assessment of clinical symptoms is sufficient in daily practice. It is recommended to add the assessment of objective parameters such as rhinometry, acoustic rhinometry [6], assessment of peak inspiratory flow (PNIF). Other studies, including the assessment of cell influx into nasal washings, levels of proinflammatory mediators [7], the measurement of nitric oxide in the exhaled air are of importance in scientific research.

The purpose of the study was to evaluate the course of nasal challenges with specific allergens, the analysis of the types of allergens used, the clinical picture of the challenge and its safety in our daily clinical practice.

Methods

The study was performed at the Department of Internal Diseases, Asthma and Allergy, Medical University of Lodz and medical histories of all patients who had nasal allergen challenge performed in 1 year (2012) were analyzed. The allergen type, symptoms (collected using the analog scale, VAS (Fig. 1)), symptoms variability depending on the applied allergen and potential side effects reported by the patient within 30 min after the challenge were studied. Clinical manifestations usually include watery, runny nose, blockage and itching of the nose, sneezing, runny discharge on the back of the throat, and itchy eyes. Symptoms after challenge were assessed using the analog scale (VAS). The score for each symptom on the analog scale is 0–100. The maximum possible score is 600 points. At the same time, the patient was encouraged to add, if needed, the presence of other symptoms, not reported on the scale (e.g. dyspnea).

Methodology of performing intranasal challenge

Intranasal challenge was performed in line with the standards of the Polish Society of Allergology [1]. Patients qualified for challenge by the referring physician, after

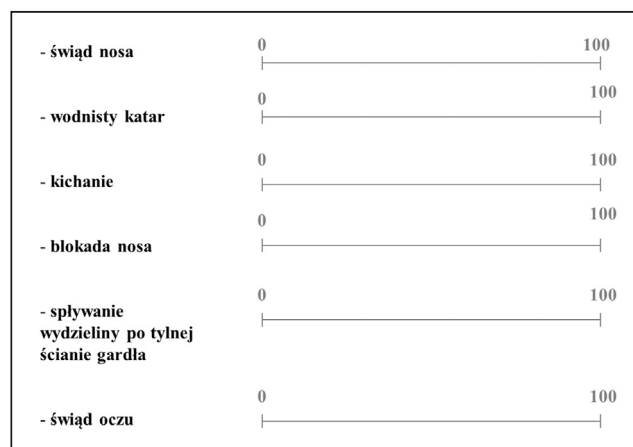


Fig. 1 – Visual analog scale (in Polish) used for the determination of the symptoms after the challenge

discontinuation of drugs that affect nasal mucosa reactivity, after 10–20 min of adaptation to environmental conditions, had performed a rhinoscopic examination and baseline clinical evaluation using the VAS scale. The control fluid solution (allergen carrier) was administered to both nostrils, followed by re-assessment of VAS symptoms after 15–20 min. The allergen was administered with a standardized atomizer. Volume of the administered dose equal to 0.2 ml of the allergen solution. The standard allergen extracts (Allergopharma-Nexter, Przyszowice, Poland) were used at the concentration of 5000 SBE/ml. In the case of suspected severe allergy to a given allergen, it was possible to reduce the dose by preparing further dilutions. The allergen application was performed after deep inspiration when the patient was holding on his breath. This procedure is recommended to reduce the risk of aspiration of the allergen to the lower respiratory tract. After 15–20 min, symptoms were reassessed with the VAS scale. A positive test result was defined as an increase in symptom severity by at least 20% compared to the value after administration of the control solution. In case the symptom severity after administration of the control solution was over 20% compared to placebo, the further allergen challenge was abandoned. In selected cases, due to medical indications, 2 challenges were performed on 1 day, only when the result of the first attempt was negative. After the challenge patient was observed for 30 min. In case of any distressing symptoms after the challenge from the upper or lower respiratory tract, rescue drugs were available.

Statistical analysis

Descriptive statistic was used to analyze the study results. Wilcoxon's test was used for paired data. To study factors potentially associated with risk of adverse events after the allergen challenge odds ratios (OR) and relative risk (RR) in univariate analysis were calculated. Chi-square test (or Fisher's exact test wherever appropriate) was applied. Multivariate logistic regression model including all potential predictors was built and adjusted for sex, age and asthma

diagnosis. SPSS version 17.0 software (SPSS Inc., Chicago, IL) was used for the statistical analysis. $p < 0.05$ was considered a statistically significant difference for all tests.

Results

In total 136 challenges performed in 109 patients were analyzed. The study group consisted of 60 women and 49 men with an average age of 34 years (median 31 years, min 13, max 79 years). In 15 patients (13.8% of the study group), apart from allergic rhinitis, bronchial asthma was also diagnosed. Eighty-two patients (75.23% of the group) were challenged with 1 allergen, and 27 patients (24.77%) with 2 allergens. The primary indication for provocation was qualification for specific immunotherapy and selection of vaccine composition in cases of doubts, or in case of polysensitization.

Type of allergen used

The most challenges were performed with the house dust mite allergens (58 challenges, 42.6% of provocation, including 30 challenges with *Dermatophagoides farinae* and 28 with *Dermatophagoides pteronyssinus*), followed by mold (*Alternaria*, 36 challenges), mugwort (19 challenges), grasses (10) birch (10), hazel (2 challenges) and alder (1 test) (Fig. 2). The most commonly used allergens during the second challenge were mites (12 tests), followed by grass (4 tests), hazel (2 tests) and mugwort (1 test).

Clinical picture

The mean overall score of the initial symptoms (before challenge) was 32.36 points (min 0, max 210) and summed up to 32.7 points (min 0, max 230) after administration of the control solution (placebo). After administration of the tested allergen, the severity score for the whole study group increased more than 2.5 times, to 90.35 points (min 0, max 470). In 61 cases, on the basis of the severity of symptoms, the allergen challenge test was found positive. The mean

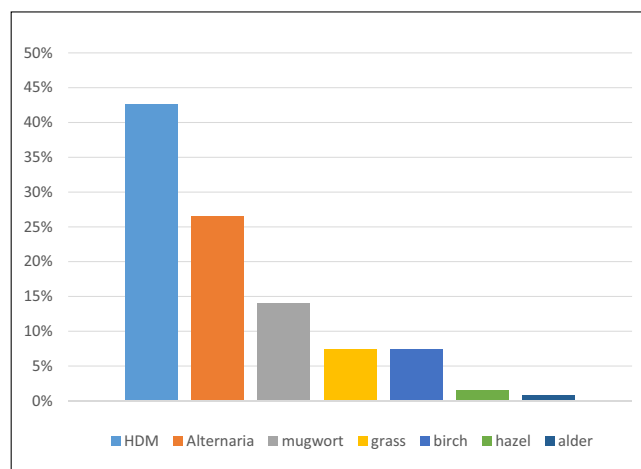


Fig. 2 – Allergens used in the nasal allergen challenge in the study cohort

score after allergen exposure in the group with positive challenge was 154.95 points (min 40, max 470) ($p < 0.05$ vs control solution), and in the group with negative challenge scored up to 36.67 points (min 0, max 300) ($p > 0.05$ vs control solution). The mean increase in VAS symptoms compared with the placebo was almost 5-fold in the group with positive challenge and summed up to 122.49 (min 25, max 410). In the group with negative challenge results, the increase in symptoms was 0.19 (min -40, max 90).

In the clinical picture after the house dust mite challenge symptoms included, nasal obstruction, followed by runny nose or runny discharge on the posterior wall of the throat (Fig. 3). After *Alternaria* challenge runny nose, followed by rhinorrhea and sneezing dominated (Fig. 4). After challenge with pollen allergens (grass, mugwort, birch) the clinical picture was clearly dominated by runny nose, blockage and itchy nose (Fig. 5).

Safety of provocation

In addition to symptoms reported on the analog scale, any other complaints reported by patients were monitored. At baseline (before challenge) 5 patients reported cough, 3 – pruritus, obstructive or dry throat, 3 – dyspnea, 2 facial or skin pruritus, and 1 patient – dark circles under eyes. After administration of placebo, 5 patients reported pruritus or throat irritation, 4 cough, 2 dyspnea, and 1 patient reported itching, rhinorrhea and severe headache. After the allergen test, the most common complaints included itchy throat (8 patients), cough (5), dyspnea (3), facial pruritus (2), swelling, sinus pain, and tearing (1 patient). All reported symptoms were described as benign. In none of presented cases any emergency treatment was needed.

One patient (31-year-old woman diagnosed with rhinitis without bronchial asthma) just a few minutes after the challenge with *D. pteronyssinus* reported pruritus, facial flushing, erythema, dizziness, “light” tinnitus. On examination no skin lesions, no redness, no obstructive features on auscultation were found. RR 135/70, HR 88/min. Intravenous

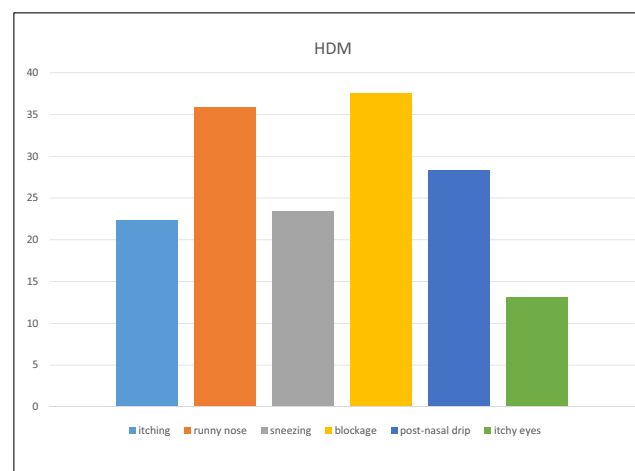


Fig. 3 – Clinical symptoms reported by patients with the VAS after the challenge with house dust mites (HDM, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*)

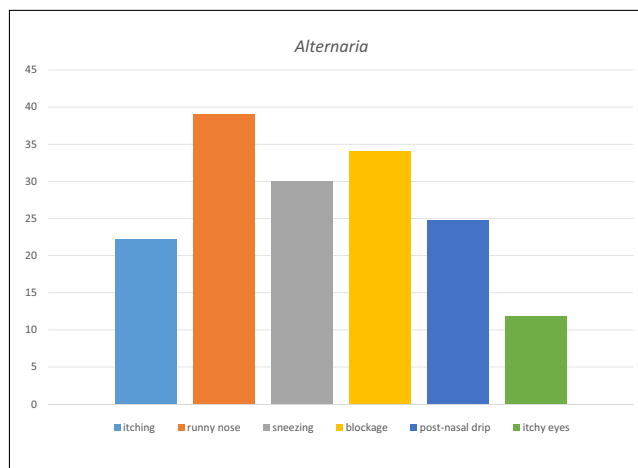


Fig. 4 – Clinical symptoms reported by patients with the VAS after the challenge with *Alternaria*

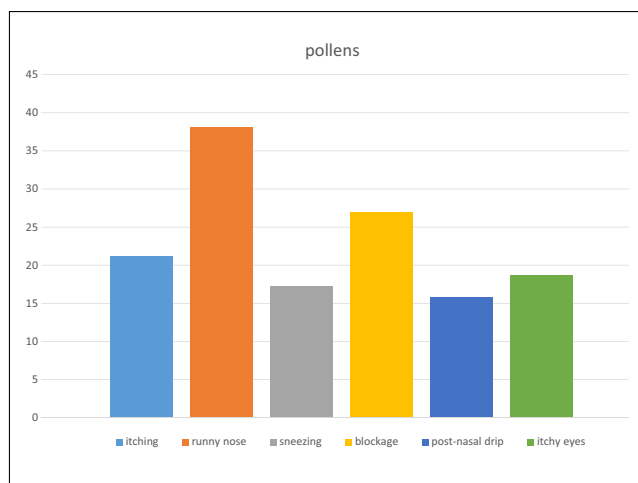


Fig. 5 – Clinical symptoms reported by patients with the VAS after the challenge with pollens (mugwort, birch, hazel, alder, grass)

port was secured, RR and HR monitored. Symptoms disappeared within minutes without any medication.

Factors associated with risk of adverse events during allergen challenge

Factors that may be potentially associated with higher risk of side effects of allergen challenge such as diagnosis of asthma, sex, type of allergen used (house dust mites, *Alternaria*), and 2 challenges per day have been evaluated. In univariate analysis only female sex was associated with higher risk of reporting any adverse events after the allergen challenge (OR 3.47, RR 2.57, $p = 0.01$). Other factors including asthma diagnosis (OR 0.54, RR 0.97, $p > 0.05$), house dust mites allergen challenge (OR 1.13, RR 1.10, $p > 0.05$), *Alternaria* allergen challenge (OR 1.79, RR 1.41, $p > 0.05$) and challenge with 2 allergens on the same day (OR 0.55, RR 0.63, $p > 0.05$) seem not to be associated with higher risk of

adverse events after the challenge. In the multivariate analysis model when corrected for possible confounding factors again only female sex but not asthma diagnosis, type of allergen used and number of allergen challenges remained associated with higher risk of reporting any adverse events after allergen challenge (OR 3.59, 95% CI 1.33–9.68, $p = 0.012$).

Discussion

Allergen provocation tests represent a valuable tool in the diagnosis of allergic diseases. As in this method we mimic the real life exposure to an allergen, the clinical relevance of an allergen for the severity of symptoms in the particular patient can be evaluated. This is of great value in cases of significant discrepancy between medical history and the results of skin prick tests or sIgE levels. When performed by well trained staff, with the use of standardized allergens, and in line with international guidelines [1, 2] allergen challenges are safe and well tolerated.

In our study, in a cohort of 109 patients, 136 allergen challenges were performed. Among allergens which were the most often used, as based on the clinical indications, house dust mites, followed by *Alternaria*, mugwort and pollens were found. What is of interest this is in line with the guidelines on allergen-specific immunotherapy in IgE-mediated allergic diseases of the German Society for Allergy and Clinical Immunology [8] which highly recommend an allergen challenge in all cases of perennial symptoms before the allergen immunotherapy is started. This is probably due to the fact that in case of perennial symptoms the evoking factor is less clear, and similar clinical picture may be due to non-allergic conditions including recurrent sinusitis, nasal polyps, drug-induced rhinitis, occupational rhinitis, hormonal rhinitis and senile rhinitis [9]. Symptoms reported after the allergen challenge with house dust mites and *Alternaria* included mainly nasal obstruction, followed by rhinorrhea, runny nose or runny discharge on the posterior wall of the throat whereas pollen challenge (grass, mugwort, birch) induced mainly rhinitis, blockade and itching. This clearly mimics the symptoms reported by patients after natural exposure to those groups of allergens. The degree of increase in symptoms evaluated with the VAS, in patients with positive challenge, was almost 5-fold higher as compared to placebo. This confirms previous recommendations [1, 2] suggesting that evaluation of outcome of the allergen challenge based on clinical symptoms collected with the use of visual analog scale is sensitive enough to be used in every-day clinical practice.

The allergen challenge in our study came out as a safe procedure as none of the reported adverse events was serious and none required any medical intervention. Twenty-one patients reported side effects after the allergen test. Among them the most common included itchy throat, cough, dyspnea and facial pruritus. Several factors that could be potentially associated with adverse events after allergen challenge, including diagnosis of asthma, sex, type of allergen used (house dust mites, *Alternaria*), and 2 challenges per day have been evaluated. In our study only female

sex, but not diagnosis of asthma, 2 challenges per day or the type of allergen used, was associated with higher risk of adverse events reported by patients. Association of female sex with the increased number of reported additional symptoms after allergen challenge may be due to higher level of introspection into own symptoms or willingness to share any findings that could be of importance for the medical staff. The pivotal findings of our study is that nasal allergen challenge is safe in patients with diagnosis of asthma, and that procedure including 2 challenges per day does not increase the risk of any adverse events. Guidelines [1, 2] suggest that the risk associated with the nasal allergen challenge is low and reduced in well trained staff. The risk of evoking symptoms from the lower respiratory tract is minimized when allergen challenge is preceded by deep inspiration and the dose of allergen is released when the breath is on hold.

Possible limitation of our study includes small cohort of patients and a single center design. Also relatively small number of adverse events reported may limit the value of statistical analysis of association with potential risk factors. There were no severe adverse events reported, thus no risk factors for the most severe or life threatening reactions could be studied. However, this is an observational, real life study and the reported data confirm that allergen challenges are safe, and reflect the situation we can face in our clinical practice in Poland.

In conclusion, we have found that in real life nasal allergen challenges are performed mainly with house dust mites, *Alternaria* and mugwort followed by pollens. Clinical symptoms after the challenge mimic the symptoms reported after the natural exposure to the particular allergen. Visual analog scale represents a simple and sensitive tool in reporting symptoms after the challenge. The nasal allergen challenge was safe as no severe side effects were reported in 109 patients in whom 136 challenges were performed. The number of side effects reported did not increased in patients with diagnosis of asthma and in procedures including 2 challenges per day. Nasal allergen challenge represent a valuable tool in our practice in those cases where other tests, including skin prick test or sIgE determination, do not correlate clearly with the clinical picture, especially in selection of allergens for the specific allergen immunotherapy and in studies of effectiveness of new therapeutical interventions in allergic rhinitis.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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