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Females have stronger neurogenic response than males after non-specific nasal challenge in patients with seasonal allergic rhinitis

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ABSTRACT

Epidemiological studies show female predominance in the prevalence of non- allergic rhinitis (NAR) and local allergic rhinitis (LAR). Experimental studies show female patients with allergic rhinitis (AR) demonstrate higher levels of sensitivity to irritants and airway hyperresponsiveness than males. Bronchial asthma shows female predominance in post-puberty patients, and gender interaction with severe asthma endotypes. Fibromyalgia, chronic fatigue syndrome, migraine and chronic cough, syndromes, which are commonly related to neurokinin substance P (SP) in the literature, also show strong female predominance. Studies have demonstrated that sex hormones, primarily oestrogens, affect mast cell activation. Mast cell proteases can amplify neurogenic inflammatory responses including the release of SP.

Based on human epidemiological data and animal experimental data we hypothesized that female patients have different interaction between mast cell activation and neurogenic inflammation, i.e. substance P release, resulting in a different nasal symptom profile.

To test the hypothesis we performed allergen and non-specific nasal challenges in patients with seasonal allergic rhinitis (SAR) out of season and looked for gender differences in subjective and objective responses. The interaction between subjective and objective reactivity was evaluated through the comparison of subjective symptom scores, concentrations of neurokinin substance P (SP) and cellular markers in nasal lavages after low doses of nasal allergen challenges.

Female allergic subjects tended to have higher substance P (SP) concentrations both before and after non-specific challenges. The difference between post-allergen and post – hypertonic saline (HTS) challenge was highly significant in female patients ($p = 0.001$), while insignificant in male subjects ($p = 0.14$). Female patients had significantly stronger burning sensation after HTS challenge than male. These data indicate difference in the interaction between inflammatory cells and the neurogenic response, which is gender- related, and which may affect symptom profiles after challenges.

Different regulation of neurogenic inflammation in females may have impact on symptoms and endotyping in respiratory disorders, not only in allergic rhinitis, but also asthma, chronic rhinosinusitis and irritant -induced cough.

Introduction

Nasal hyperreactivity is an increased sensitivity of the nasal mucosa characterized by symptomatic response to otherwise harmless physical and chemical stimuli: changes in temperature, humidity and exposure to strong odors or irritants. It is a common feature of allergic (AR) and non-allergic rhinitis (NAR) [1]. Patients with allergic rhinitis who have a significant burden of reactivity to environmental triggers are usually diagnosed as mixed rhinitis [2]. Patients with perennial nasal symptoms or symptoms triggered by irritants who have no evidence of sensitization to common aeroallergens, are usually diagnosed as non-allergic rhinitis (NAR), although some of them may suffer from local allergic rhinitis (LAR) [3].

The non-specific hyperreactive response in AR is often considered to be related to the severity of IgE mediated inflammatory response after allergen exposure. However, it may be present also in the absence of

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Table 1
Demographics of the patients in the study.

	Male	Female	All
No SAR patients	12	14	26
Age	38.41 ± 12.4	35.64 ± 9.49	36.92 ± 10.8
Ragweed allergic	5	11	16
Grass allergic	7	3	10
Mean ± S.D. ragweed specific IgE (I.U.)	22 ± 30.2	7.92 ± 9.54	12.57 ± 18.69
Mean ± S.D. grass specific IgE (I.U)	4.5 ± 8.6	2.47 ± 1.96	3.93 ± 7.16

Demographics of the patients in the study. Distribution of the data related to sensitization and specific IgE with the gender distribution is presented in the table. S.D. – standard deviation.

allergen, as in patients with seasonal allergic rhinitis (SAR) out of season, where it is possibly a result of minimal persistent inflammation [4]. A marked late phase response and nasal eosinophilia were often blamed in the literature for enhancing nasal hyperreactivity [5]. However, in the early phase reaction, minutes after contact with allergen, and following degranulation of the mast cells, stimulation of sensory nerves occurs, resulting in the release of neuropeptides and neurokinins. They initiate neural responses characterized by cholinergic reflexes (lacrimation, sneezing, cough) and transitional receptor potential (TRP) channel activation, followed by substance P (SP) release (itch, burning sensation). It was demonstrated that patients with non-allergic rhinitis have transitional receptor potential vanilloid 1 (TRPV1) /SP pathway up-regulation, and have a good response to topical capsaicin treatment [6]. Such a phenomenon was not demonstrated in patients with mixed rhinitis, and no benefits of topical capsaicin were demonstrated in a randomized placebo controlled trial [7], suggesting that the mechanism is different.

Epidemiological studies have indicated a female predominance in the prevalence of both NAR and LAR [8,3] Experimental studies show female AR subjects demonstrate higher level of airway hyperresponsiveness [9] and sensitivity to irritants than males [10,11]. High nasal responsiveness to a broad range of environmental triggers and irritants may interact with multiple chemical sensitivity (MCS). MCS includes non-immune mediated response to a contact with low concentrations of variable chemical compounds, which may induce a broad range of vague and non-specific symptoms, including those related to the airways. This disorder is more common in females, but also in allergic and asthmatic individuals.

Bronchial asthma shows female predominance in post-puberty patients, and gender interaction with severe asthma endotypes. Fibromyalgia, chronic fatigue syndrome, migraine, depression and chronic cough, syndromes, which are commonly related to stress exposure and neurokinin substance P (SP) in the literature, also show strong female predominance [12]. Studies have demonstrated that sex hormones, primarily oestrogens, affect mast cell activation [13]. Mast cell proteases can amplify neurogenic inflammatory responses, including the release of SP, probably by the activation of protease activated receptors 2 (PAR-2). Tryptase from the activated mast cells interacts with neural PAR-2 in skin, gut and airways which leads to the release of SP and calcitonin gene related peptide (CGRP), promoting neurogenic inflammation. However, tryptase and chymase from the mast cells may also prevent or decrease neurogenic inflammation by degrading excessive neuropeptides, acting as a bio-feedback mechanism [14].

It is not clear whether gender differences in the prevalence and severity of non-specific airway hyperreactivity reflect the difference in neuro-allergic response in challenge tests.

Hypothesis. Based on human epidemiological data and animal experimental data we hypothesized that female patients have different interaction between mast cell activation and neurogenic inflammation, i.e. substance P release, resulting in a different nasal symptom profile. We have attempted to explore these areas in a preliminary study which includes gender comparison of the severity of neurogenic inflammation and inflammatory cell activation after allergen and non-specific challenges in patients with isolated SAR out of season, to avoid priming and perennial allergen exposure.

Subjects and methods

After signing informed consent forms, patients who were referred to the Rhinology diagnostic laboratory in the University Hospital Centre “Sestre milosrdnice”, Zagreb School of Medicine, for the evaluation of their nasal hyperreactivity, were recruited for the study. The study was approved by the Ethics Committee of the University Hospital Centre “Sestre milosrdnice”, Zagreb School of Medicine.

The subjects consisted of 26 grass and/or ragweed pollen allergic volunteers. Demographics of the patients is shown in Table 1. Inclusion criteria were: the history of AR symptoms in at least two past pollen seasons, skin prick test positivity to either grass or ragweed pollen and/or serum specific IgE to the respective allergen. Patients with sensitization to perennial allergens, acute rhinitis, chronic rhinosinusitis, nasal polyps, bronchial asthma, significant septal deformity, and those who were taking topical or systemic medication in the past 4 weeks which may interfere with the response to provocation were excluded. Patients who suffered from non-specific nasal hyperreactivity to environmental stimuli during and out of season, or throughout the year, were not excluded.

Recruited patients filled in a questionnaire on their history during past pollen seasons and visual analog scale (VAS) for nasal and ocular symptoms. They also filled in the a irritant index scale questionnaire.

On Day-1, 500B.U. per nostril in 0.2 ccm of aqueous solution with lyophilized allergen (Croatian Immunological Instute, Zagreb, Croatia), either the specific grass, according to SPT (Phleum pratense, Dactylis glomerata) or ragweed pollen (Ambrosia elatior), respectively, were applied to both inferior turbinates with micropipette. On the next day 80 mcg of histamine was applied per nostril in the same fashion. More than 48 h after histamine challenge, nasal provocation was done with 2 ml of 2% hypertonic saline (HTS). Before allergen, and HTS provocation, visual analog scale (VAS) subjective scores of nasal and ocular symptoms and baseline nasal lavage were done. VAS scores, and nasal lavage were done 15 min after each challenge.

Evaluation of nasal and ocular symptoms was done using a VAS questionnaire. Symptoms evaluated were: nasal obstruction, hypersecretion, nasal itch, burning sensation in the nose, ocular itch and lacrimation.

Nasal lavage and mediator analysis

Nasal lavage was performed 15 min after each challenge with 3 ccs of warmed saline per nostril. The subjects were seated with the head extended 30 degrees from horizontal, abstaining from breathing and swallowing. After 20 s the patients expelled the lavage into the container which was kept on ice until completion of the experiment. The recovery of fluid was 50–80%. The lavages were centrifuged at 1600 × *g*