

Hypersensitivity to aeroallergens in patients with recurrent vulvovaginitis of undetermined etiology

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Abstract

Aim: Recent findings show that the vaginal mucosa can develop an allergic response to environmental allergens and there is a strong association between atopy and some recurrent vulvovaginal infections. In this study, we investigated prospectively the rate of atopy in patients with recurrent vulvovaginitis of undetermined etiology (RVV).

Material and Methods: After being investigated by a gynecologist, 35 patients with RVV who were considered as undetermined etiology formed the study group. The control group consisted of 150 healthy females. Study and control groups were investigated for atopy by means of skin prick test for common aeroallergens. Associated allergic disease and familial atopy history of the subjects were recorded.

Results: The rate of atopy (11/35; 31.4% vs 9/150; 6%) was significantly higher ($P < 0.001$) in the study group than in the controls. Familial history of atopy was significantly more frequent in the study group than in the controls (10/35; 28.6% vs 8/150; 5.3%, $P < 0.05$). RVV in atopics is more associated with seasonal rhinitis than in nonatopics (5/11; 45.4% vs 2/24; 8.3%, $P < 0.05$).

Conclusion: We concluded that a significant number of RVV is associated with atopy. Although the exact mechanism(s) of this relationship remains to be investigated atopy might be a causative and/or contributing factor in the pathogenesis of RVV.

Key words: allergic vaginitis, atopy, recurrent vulvovaginitis, skin prick test.

Introduction

Nasal mucosa, airways and conjunctiva are the tissues most frequently affected by IgE-mediated allergic reactions, and they are well-known and studied as allergic shock organs. However, recent data have shown that the vaginal mucosa is also able to develop allergic response to environmental allergens.¹ As in the nasal mucosa and bronchial epithelium, aeroallergens may cause early and late-phase allergic reactions in the female genitalia, which is clinically presented as chronic and/or RVV.^{1,2}

The relationship between vaginal mucosa and aeroallergens has been described in several reviews and case reports and allergen sensitivity in recurrent

vaginal candidiasis has also been shown.^{1,3–6} However, candida infection is responsible for approximately 30% of RVV cases.⁷

In this prospective study, we aimed to investigate the rate of aeroallergen sensitivity in patients with RVV of undetermined etiology.

Materials and Methods

Study group

This study was conducted at the Department of Allergic Diseases and Department of Gynecology of Gulhane Military Medical Academy (GMMA). GMMA is a teaching hospital that serves as a referral center for

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Turkish Armed Forces and primary care facility in the Ankara Metropolitan area. All patients with RVV were first evaluated by a gynecologist. A detailed medical history, gynecologic examination and a series of laboratory investigations including stained smear preparations, serological studies and cultures for common vulvovaginal pathogens (*Candida albicans*, *Gardnerella vaginalis*, *Mycoplasma* sp., anaerobic *Lactobacilli* sp., *Chlamydia* sp., Herpes simplex virus tip II, Human papilloma virus, Human immunodeficiency virus) were performed in order to exclude infectious, dermatological and other causes of RVV including psoriasis, lichen, pemphigus, lupus, Behcet's disease, sexual abuse and poor hygiene, etc. In addition, empiric treatment trials with oral (metranidasole 1500 mg/day, itraconazole 200 mg/day) and topical preparations (cycloprololamin 1% vaginal cream) were given to the patients who were negative for all tests. After these detailed investigations and treatment trials, the patients in whom a definite etiologic factor for RVV could not be identified were referred to the Department of Allergic Diseases to be investigated for allergy and atopy.

To exclude contact allergens (Type IV hypersensitivity), a patch test with Standardized European Panel was initially performed to all referred patients. Patients who were sensitive to any contact sensitizer were excluded. Consequently, the remaining 35 RVV patients with unknown etiology were served as the study group and further studied for inhalant allergen sensitivity.

Control group

Because the aim of the study was to establish a rate of the aeroallergen sensitivity in patients with RVV of unknown etiology and the endpoint of the study is the rate of the aeroallergen sensitivity, a large control group consisting of 150 healthy female patients without history of atopy, allergic rhinitis, asthma and RVV was established. This group served to determine the frequency of asymptomatic skin prick test (SPT)

positivity to aeroallergens in a normal female population.

Investigations for aeroallergen sensitivity

Individual and familial history of atopy, duration of the RVV symptoms and relationship between symptoms and seasons were interviewed in detail.

All participants underwent SPT with 56 common aeroallergens (ALK SPT, 100 BU/mL, ALK-Abello, Horsholm, Denmark). To exclude false negative and false positive reactions, histamine (10 mg/mL, Stallergens SA, Antony, France) as positive control, and standardized diluent (0.9% sodium chloride and 0.4% phenol, Center Laboratories, Port Washington, USA) as negative control were used. SPT was performed using disposable lancets and the reactions were recorded 15 min after the test. Reactions with a wheal diameter greater than 3 mm with surrounding erythema were considered as positive, if the positive control was positive and negative control was negative.

Statistical analyses

SPSS (SPSS for Windows, SPSS, Chicago, IL, USA) statistical package was used for statistical analyses. Univariate analysis was performed using chi-squared test for proportion of atopy, allergens, familial history of atopy and associated allergic disease. Mean values of the groups was compared with Mann-Whitney *U*-test. A *P*-value less than 0.05 was considered statistically significant.

Results

Characteristics and SPT results of the study and control groups are shown in Table 1. More patients with RVV (11/35, 31.4%) had a positive SPT result than healthy subjects (9/150; 6%, *P* < 0.001). House dust mite was the leading allergen in both groups, but was more frequent in RVV patients (17.1%) than in controls (3.3%, *P* < 0.05), while the groups did not differ significantly

Table 1 The comparison of skin test results study and control group

	Study group		Control group		<i>P</i>
Number of patients	35		150		
Presence of atopy	11	31.4%	9	6%	<i>P</i> < 0.001
Familial history of atopy	10	28.6%	8	5.3%	<i>P</i> < 0.001
Allergy to mites	6	17.1%	5	3.3%	<i>P</i> < 0.05
Allergy to pollens	5	14.3%	9	6%	NS

NS, not statistically significant.

Table 2 Differences between atopic and nonatopic patients of the study group

	Atopics (<i>n</i> = 11)	Non-atopics (<i>n</i> = 24)	Significance
Mean age (years)	28.73 ± 7.11	27.63 ± 6.24	NS
Familial history of atopy	6 (54.5%)	4 (16.7%)	<i>P</i> < 0.05
Duration of symptoms (months)	37.64 ± 19.45	35.24 ± 14.14	NS
Associated allergic disease [†]	5 (45.4%)	2 (8.3%)	<i>P</i> < 0.05

[†]All of the associated allergic diseases were seasonal rhinitis, i.e. none of the subjects had asthma. NS, not statistically significant.

with respect to pollen sensitivity. Patients with RVV also differed significantly with respect to familial history of atopy (10/35, 14.3%) when compared to the controls (8/150, 5.3%, *P* < 0.001).

Table 2 demonstrates the differences between atopic and nonatopic patients with RVV. Atopic patients had more coexisting allergic seasonal rhinitis (5/11, 45.4%) compared to nonatopics (4/24, 16.7%, *P* < 0.05). Mean age and duration of symptoms did not differ significantly between atopic and nonatopic subjects with RVV. None of the patients had an associated asthma. RVV symptoms were significant in pollen season in four of five pollen sensitive patients. Similarly, five of six mite sensitive patients complained of perennial VV symptoms.

Discussion

This prospective study has demonstrated that atopy is more frequent in RVV patients with undetermined etiology than in healthy individuals. The leading aeroallergen was the house dust mite. In addition, atopic patients with RVV had more familial history of atopy and associated seasonal allergic rhinitis. These data indicate a possible role of aeroallergen sensitivity in pathogenesis of RVV. Furthermore, another interesting finding was that RVV symptoms manifested more during pollen season for patients sensitive to pollens, while house dust mite sensitive patients had perennial symptoms, showing a close connection between sensitizing allergen and RVV symptoms.

RVV remains a common problem in daily practice of gynecology in terms of challenges both in diagnosis and treatment. A wide variety of factors may be related to inflammation of female genitalia, including infections by specific pathogens (*C. albicans*, *Gardnerella*, *Mycoplasma*, *Chlamydia trachomatis*, anaerobic *Lactobacilli*, Herpes simplex virus, Human papilloma virus), sexually transmitted diseases, systemic or localized dermatologic disease (psoriasis, lichen, pemphigus,

lupus, pellagra, Behcet's disease, Paget's disease), exposure to irritants (soaps, toilet paper, and warm water), poor hygiene and allergy.^{1,8} *Candida* infection is widely considered responsible as an etiologic factor for almost all RVV cases. However, it was shown that many women with RVV (68.9%) are not infected with *Candida*. Recent studies demonstrated that a great variety of allergens including aeroallergens are able to provoke allergic reactions in the female genital tract; however, the exact incidence of the allergic vulvovaginitis is not yet known.¹

Several case reports described previously allergic vulvovaginitis due to various allergens including inhalant ones.⁹⁻¹² Many of the clinical reports proposed that a great variety of allergens including *C. albicans*, seminal fluid components, contraceptive spermicides, latex, medications, inhalants and even food may cause IgE-mediated allergic reactions in the female genitalia.^{1,13-17} Furthermore, some recent review articles defined allergic vulvovaginitis as an important cause of vulvovaginitis.^{1,8} In contrast, it has been previously demonstrated that there is a strong association between atopy and recurrent vaginal candidiasis suggesting that allergic reactions in vaginal mucosa could also facilitate colonization of *C. albicans* as well as causing allergic inflammation.^{3,5} In another study, it was found that the majority of women with recurrent vaginal candidiasis had impaired type-1 T cell response with inability to produce appropriate levels of IFN- γ when stimulated with *C. albicans* antigen *in vitro*.⁴ These data suggest that allergic reactions may play a role in pathogenesis of RVV irrespective of involving *C. albicans* in eliciting the symptoms.

Vaginal mucosa can also be a site of an allergic reaction similar to the nose, eyes, lungs and skin. In order to understand the pathogenesis of allergic reactions in the vagina, one should explain first how the vagina can be exposed to allergens. The routes of inhalant allergens for vaginal sensitization would be mainly direct contact or systemic accumulation. For example house

dust mite, which is the most frequent and the only significant allergen associated with RVV in our study can be introduced to the vagina via direct contacts with hands and clothes. In addition, it has been suggested an inhaled or digested compound may accumulate in the vagina.¹ This situation may be possible by counter-current blood flow in the female genital tract and may be an explanation of how inhaled or digested antigens may accumulate in the vagina and cause allergic reactions.

Vaginal mucosa itself is capable of causing allergic reactions. The vaginal basal lamina, which underlies the vaginal epithelium, contains macrophages, Langerhan's cells, eosinophils, plasma cells, especially IgG and IgA producing ones, and mast cells.^{1,18} Once the vaginal lumen exposed to an allergen directly or, as abovementioned, an inhaled or digested allergen accumulates in the vagina, the allergen transports through interepithelial channels to the basal lamina and interacts with mast cell-bound specific IgE. This event induces the release of histamine and other inflammatory mediators such as leukotrienes, prostaglandins, and platelet-activating factor, causing symptoms of vulvovaginitis.

Another relation between atopy and recurrent vulvovaginal symptoms is that allergic reactions in the vaginal mucosa could facilitate the colonization or infection with *C. albicans* as a secondary event due to the break of the natural resistance to pathogens.³ An interesting pilot study supporting this suggestion from another point of view has been recently published. White *et al.*¹⁹ showed that symptomatic relief to some degree was achieved in patients with recurrent vulvovaginal candidiasis by zafirlukast, a leukotrien antagonist, and suggested that it might be an alternative treatment to suppressive antifungals for women affected by recurrent vulvovaginal candidiasis. Non-specific vaginal hypersensitivity, which can be triggered by nonallergic factors as in other target organs of the allergy, may be another pathogenetic mechanism of allergic vulvovaginitis.¹ Recurrent bacterial, viral and parasitic infections may be likely to induce atopy and hypersensitivity as suggested previously.²⁰

To our knowledge, this study has demonstrated the association of atopy and RVV with undetermined etiology for the first time in the published literature, as patients with recurrent vaginal candidiasis were mostly included in other studies dealing with the issue.³⁻⁶ Although SPT is a valuable and useful diagnostic tool to document atopy in daily medical practice, we must admit that lack of vaginal provocation test during an

asymptomatic period, determination of total and specific IgE levels and eosinophil count in blood and vaginal smears as limitations of our study. These investigations could have likely supported the diagnosis of allergic vulvovaginitis. Although, we suppose that this limitation can not invalidate our results and SPT might be enough to document aeroallergen sensitivity (i.e. atopy) as we did not aim to make a diagnosis of allergic vulvovaginitis. However, we have planned a study in a larger population in order to investigate the incidence of allergic vulvovaginitis by performing other above-mentioned allergic tests and their alterations with therapy.

It is difficult to prove the role of an inhalant allergen in a vaginal inflammatory reaction, especially in mite sensitive patients whose complaints are sustained during the year. However, proving this may be easier in pollen sensitive patients whose symptoms exacerbate only in pollen seasons. In our study group, RVV complaints mostly related to the kind of allergens that the patients were sensitive to. In such cases, diagnosis can be verified by allergen elimination and/or anti-allergic treatments. Allergen elimination is an important therapeutic measure in the allergic diseases, which may offer significant relief. The environmental control methods which are being recommended to patients with allergic rhinitis and/or asthma may also provide symptomatic relief in VV patients.¹² Anti-allergic drugs such as oral antihistamines, corticosteroids, chromones and leukotrien antagonists may also improve the symptoms.^{1,11,19} Furthermore, successfully treated patients with allergen specific immunotherapy have been described in the medical literature.^{12,21}

As a conclusion, in this study we have shown that atopy is significantly frequent in patients with RVV and this finding suggests that allergy to inhalant allergens may have a role in pathogenesis of RVV with unknown etiology. Clinicians should be aware of this issue in order to alleviate the diagnostic challenges, however, exact relationship between atopy and RVV remains to be investigated by means of epidemiological and immunological studies.

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