Arch Gynecol Obstet
DOI 10.1007/s00404-016-4081-2

GENERAL GYNECOLOGY

Inhalant allergy compounding the chronic vaginitis syndrome: characterization of sensitization patterns, comorbidities and responses to sublingual immunotherapy

Demetrios S. Theodoropoulos[1] · Colleen K. Stockdale[2] · Daniel R. Duquette[3] · Mary S. Morris[1]

Received: 18 January 2016 / Accepted: 17 March 2016

Abstract
Objective To characterize sensitization patterns, diagnoses and comorbidities, and to assess the response of lower genital tract symptoms to sublingual immunotherapy for airborne allergens in a select population of patients with chronic vaginitis.
Methods Fifty-two patients referred for allergy evaluation over a 44 month period were studied. Charts were retrospectively reviewed to establish: (1) gynecological diagnoses, (2) allergic-immunological diagnoses, and (3) IgE-mediated sensitivity to airborne allergens on presentation. Patients were contacted at 9–50 months of treatment to assess response to sublingual immunotherapy based on a questionnaire addressing frequency and severity of symptoms and use of medication to control symptoms.
Results Recurrent vulvovaginal candidiasis was identified in 34 (65 %); vulvar vestibulitis syndrome in 12 (23 %); and contact dermatitis in 10 (19 %) patients. Comorbidities included: non-reflux gastrointestinal complaints in 11 (21 %), gastroesophageal reflux in 5 (9 %), migraines in 9 (17 %), chronic non-migrainous headaches in 8 (17 %), and chronic sinusitis in 6 patients (11 %). Asthma was diagnosed in 8 patients (15 %). Oral allergy syndrome was present in 6 (11 %). Most frequent sensitivities were to: ragweed in 33 (63 %), molds in 26 (50 %), dust mites in 23 (44 %), and grass in 12 (23 %) patients. Mono-sensitization was demonstrated for ragweed in 7 (13 %), and for molds, dust mites and grass for 3 (5 %) patients each. Candida sensitization was identified in 15 patients with chronic vaginitis (28 %). Eleven patients with recurrent vulvovaginal diagnosis (32 %) showed Candida sensitization. Response to immunotherapy was generally favorable with pruritus/irritation being more responsive than visceral pain.
Conclusions In a Midwestern referral population, chronic vaginitis compounded by inhalant allergy showed: (1) high incidence rate of recurrent vulvo-vaginal candidiasis, (2) Candida IgE-mediated sensitization in less than one-third of patients with recurrent vulvovaginal candidiasis, (3) comorbid conditions not dissimilar to those of other allergic patients, and (4) allergen sensitization pattern typical for the Midwest.

Keywords Vulvodynia · Chronic vaginitis · Allergic rhinitis · Migraines · Candidiasis · Sublingual immunotherapy · Neurogenic inflammation

Introduction

Chronic vaginal complaints, without infection or trauma, are common in the general population and are one of the most frequent reasons for visits to gynecologists. While many vulvar complaints are under-reported and under-diagnosed, it is estimated that at one point in their life 16 % of all women will have chronic vaginal and/or vulvar pain for at least 3–6 months [1]. For chronic pruritus/irritation, paresthesias or other types of discomfort there are no valid data. The term chronic vaginitis syndrome (ChVS) is used

✉ Demetrios S. Theodoropoulos
dtheodoropoulos@allergy-solutions.com

[1] Allergy Associates of La Crosse, 2727 Midwest Drive, Onalaska, WI 54650, USA

[2] Department of Obstetrics and Gynecology, University of Iowa Hospitals and Clinics, Iowa, IA, USA

[3] Department of Health Education and Health Promotion, College of Science and Health, University of Wisconsin-La Crosse, La Crosse, WI, USA

Published online: 04 April 2016

to characterize this type of chronic or recurrent vaginal complaint. ChVS therefore represents a multifactorial or heterogeneous condition. It includes at least eight different conditions [2, 3].

As far as allergic inflammation is concerned, and depending on specific diagnoses, an estimated 25–54 % of women with ChVS also carry a current diagnosis or a past history of at least one clinically manifested allergic disease [2]. The prevalence of atopic diathesis in the general population, that is, the ability to mount an IgE response and exhibit an immediate type prick and/or puncture hypersensitivity response to allergens is assessed as 50 % but allergic diseases in the general population are present in significantly lower percentages than those reported in the ChVS segment of the population. Expected rates for allergic disease in the general population are 10–20 % for allergic rhinitis, 5–7 % for asthma, and 20 % for a one time incidence of urticaria [4]. These rates indicate that, as compared to the general population, in women with ChVS the prevalence of a pre-existing atopic disposition to mount an IgE response to inhaled allergens, which would normally only represent a potential for the development of an allergic disease, is practically equalized with the actual presence of clinical allergy. There is no clear explanation for this occurrence.

A clinically significant association between ChVS and allergic responses to inhalants has already been established and specific mechanisms to explain this association have been proposed [5]. A systematic characterization of the gynecological diagnoses in this population and the inhalant allergen sensitizations which account for the exacerbations of vaginitis is needed. Furthermore, the establishment of the inhalant allergy-chronic vaginitis association implies that treatment of allergy, by means of immune modification, could lead to improvement of chronic vaginitis. For this reason, the effect of inhalant allergen-specific immunotherapy on chronic vaginal symptoms needs to be assessed.

A similar clinical association of inhalant allergy with mucosal inflammation of the upper gastrointestinal mucosa via neuro-immune interactions and precipitation of visceral pain responses has been long established [6–8]. Comparable but more complex interactions may also operate in the central nervous system as evidenced by the favorable response of migraines in allergic patients following treatment with allergen-specific immunotherapy [9]. The present study addresses the impact of immune-mediated inflammation on the chronic pain responses of the ChVS and seeks to establish the concept of an underlying continuum of neuronal and mucosal responses to allergens and to allergy-associated mediators of inflammation [10, 11].

Materials and methods

A total of 52 patients with ChVS were identified from the records of the Allergy Associates of La Crosse for the studied period. There were no additional selection criteria, and all patients were included in the study. Patients had been referred over a 44 month period, from January 1, 2011 through August 31, 2014. All patients had originally been assessed and treated for ChVS by a Board certified Obstetrician-Gynecologist. Forty-nine (94 %) were referred for allergy evaluation after their initial management at the tertiary care center Vulvar and Vaginal Diseases Clinic of the University of Iowa Hospitals and Clinics (C.K.S.). Selection of patients with ChVS for referral for allergy evaluation and treatment was based on the Obstetrician-Gynecologist's clinical assessment of a history of any two or more of the following: (1) seasonal allergic symptoms, (2) asthma, (3) chronic sinusitis, (4) immediate type, suspected or established, food-allergic, upper or lower gastrointestinal symptoms, (5) migraines. All patients of the study were evaluated and treated for allergies at the Allergy Associates of La Crosse over the aforementioned time of 44 months. Allergen-specific immunotherapy per standard sublingual immunotherapy protocol was administered to all patients [11]. Informed consent was obtained and Human Research guidelines were followed according to the standard National Institutes of Health Office of Extramural Research recommendations. Institutional Review was by the University of Wisconsin-La Crosse. Records were reviewed for characterization of clinically relevant features. A questionnaire of vulvo-vaginal symptoms and their changes over time was administered at 9–50 months of treatment with sublingual immunotherapy for airborne allergens and (when applicable) Candida and other yeast. Food sensitivities, if assessed, were not treated by any means other than avoidance, and no food immunotherapy was administered.

Gynecological assessment was typified in eight working diagnoses following a previously published analysis of diagnoses in ChVS [2]. Six of them were: recurrent vulvovaginal candidiasis (RVVC), vulvar vestibulitis syndrome (VVS), lichen simplex or sclerosus (LSi/LScl), atrophic vaginitis (AV), desquamative inflammatory vaginitis (DIV) and Physiologic Leucorrhea; and were all considered mutually exclusive in this study population as previously presented [2]. The other two vulvovaginal diagnoses were contact dermatitis (CD) and bacterial vaginosis (BV), which, because of their nature and frequency, were not considered exclusive of other diagnoses and, indeed, in all of the studied patients, invariably co-existed with, had preceded, or complicated one of the former six diagnoses.

Presentation of allergic diagnoses was enlarged to include allergic IgE-mediated disease of the atopic spectrum as well as comorbid mucosal, vascular and skin diseases whose association with allergy has been established in literature. Other diagnoses and relevant surgical procedures were also recorded.

Sensitivity to airborne allergens and Candida was assessed by intradermal skin testing. In a selected ChVS population with an a priori prevalence of atopic disease ranging from 25–54 %, which has been further selected for history of allergic rhinitis and co-morbid conditions, both frequent and high-level skin reactivity had been expected for most airborne allergens [2]. It was for this reason that skin reactivity results were filtered for presentation; skin reactive positives were distributed to size of wheal formed (mm) and only positives representing the three largest wheal sizes were reported. Furthermore, to assess the prevalence of mono-sensitization, the one most prominent positive reaction was presented separately provided its size was >3 standard deviations from the mean of all skin reactivity by wheal size.

The ChVS symptoms questionnaire was structured to: (1) characterize the type of discomfort, (2) grade the main symptom on a scale from 1–5, (3) record its change over a period of treatment with sublingual immunotherapy ranging from 9 to 50 months, (4) record changes in the use of relevant medications, which included chronic pain controllers, anti-inflammatories, immune-suppressants, antibiotics, antifungals, topical treatments and antihistamines. The nature of discomfort was studied along two major lines of symptoms: (1) pelvic deep visceral pain, poorly localized, felt as pressure or "deep squeezing," resulting from a combination of soft tissue edema, ischemia, muscle spasm, and (2) surface somatic pain, irritation, tenderness, abrasion, "pins and needles," prickling or pruritus; more or less circumscribed and localized to mucosal or skin surfaces. The two types of discomfort were not considered mutually exclusive. A definite differentiation of either of these patterns from chronic neuropathic pain was not always possible. Patients reporting potentially ambivalent symptoms, such as burning, heat, "ground glass sensation" or soreness, were further questioned until the symptoms could be recorded under one of the two headings of "deep visceral pain" versus "mucosal irritation." The sensation of visceral pain also included all of the following: pelvic pain, cramps, bladder pressure in the absence of known urinary tract infection, "fullness," "weight" and "unpleasantness." Itching was strictly defined as an "immediate and pressing need to scratch followed by some sense of relief upon scratching."

Grading of visceral pain/pressure was as follows:

Level 0 No pain.

Level 1 Subject is sometimes aware of a painful sensation but no action is needed.

Level 2 Pain is absent or ignored for most of the time. Occasional dyspareunia. Use of pain killers is 2 days a week or less.

Level 3 Pain is present most days of the week during day time but does not affect sleep. With the exception of sexual intercourse, pain does not affect regular activities. Systemic medication is needed frequently, that is, 3 days a week or more.

Level 4 Pain interferes with most daily activities. Regular pain control is needed with either single non-steroidal anti-inflammatory drug, trazodone, cyclobenzaprine, anticholinergics, or/and an opioid on a daily basis.

Level 5 Incapacitating pain. Missing days at work and family events because of ChVS. Significant day time spent in bed. Multiple pain controllers are needed or have been recently used, including any of the regimens mentioned above and added prednisone, gabapentin, tricyclic antidepressants, serotonin-specific re-uptake inhibitors, aminoketones, clonidine or anticonvulsants.

Grading of surface somatic pain/irritation/pruritus was as follows:

Level 0 No itching, "pins and needles," or any "pricking" sensation. (These symptoms are hereafter to be collectively referred to as "irritation").

Level 1 Subject is sometimes aware of some irritation but no action is needed.

Level 2 Irritation is absent or ignored during day time most of the days. Antihistamines are taken 2 days a week or less.

Level 3 Irritation is present most of the days but does not affect sleep. Irritation is not noticeable during regular daily activities. Antihistamines are needed frequently, that is, 3 days a week or more.

Level 4 Irritation is persistent and difficult to contain. It affects ability to fall asleep. Conventional oral antihistamines are taken daily. Systemic immune modifiers such as steroids, H2-receptor blockers, blood–brain-barrier-crossing H1-receptor blockers (doxepin) and mast cell stabilizers, or benzodiazepines are used intermittently for control of symptoms.

Level 5 Irritation is constant and interferes significantly with both daily activities and ability to stay asleep. Daily routine treatment is necessary with multiple combinations of those mentioned above in Level 4. Methotrexate, cyclosporine, dapsone, antimalarials, chlorpromazine and pimozide are used or being considered.

Data analysis was performed with the SPSS 13.0 statistical software package (SPSS Inc., Chicago, IL, USA). Categorical data were analyzed with χ^2 test. For continuous data one-way analysis of variance was used.

Results

Gynecological diagnoses included: RVVC, VVS, CD, BV and a single case of Lichen Sclerosus. Some diagnoses previously reported in similar series were not found in our patients and those include atrophic vaginitis, desquamative inflammatory vaginitis and physiologic leucorrhea [2]. This may be attributable to the special characteristics of the studied population; mostly age, socio-economic status and willingness to travel, or the referral population and pattern. The distribution of diagnoses in our patients is clearly skewed and includes a larger than expected number of RVVC, which is 34 patients (65 %) versus 20 % previously reported from a Vaginitis Referral Center [2]. All our patients with CD and BV have more than one gynecological diagnosis for their chronic vaginitis (Table 1).

The diagnosis of allergic rhinitis by the referring gynecologist was confirmed in all patients by skin testing and subsequent clinical response to treatment. Allergy-related comorbidities were consistent with those known to be prevalent in patients with allergies as shown on Table 2 [4]. Ragweed, followed by molds, dust mites and grass, were the most common airborne allergic sensitizers in patients with multiple allergies as well as among patients who were found to have a mono-sensitizing pattern. The contribution of trees and animal dander was relatively low with the single exception of birch allergy which was present in 6 patients (11 %), as shown in Tables 3 and 4.

IgE-mediated sensitization to Candida was detected in 15 of all ChVS patients (28 %) and in only 11 of the RVVC patients (32 %) indicating that IgE-dependent responses are not a necessary prerequisite in all of the RVVC patients.

Table 2 Allergic and allergy-related diagnoses in 52 patients with chronic vaginitis syndrome

Allergic rhinitis	52 (100 %)
Chronic sinusitis	6 (11 %)
Migraines	9 (17 %)
Chronic headaches non-migrainous, not sinus related	8 (15 %)
Oral allergy syndrome	6 (11 %)
Atopic dermatitis	5 (9 %)
Dermatophytosis	4 (7 %)
Contact dermatitis (on allergist's evaluation)	12 (23 %)
Asthma (mild intermittent)	8 (15 %)
Past history of reactive airway in childhood	1 (2 %)
Gastroesophageal reflux	5 (9 %)
Abdominal complaints other than reflux-related	11 (21 %)
Latex allergy with systemic manifestations	2 (3 %)

Following evaluation, the subjects of the study were treated with sublingual immunotherapy for airborne allergens for 9–50 months (median = 26 months, 1 SD = 11 months).

Changes in severity and frequency of deep visceral pain following sublingual immunotherapy for airborne allergens are presented in Fig. 1, where the distribution of subjects to grades of decreasing sense of visceral pain is shown. Twenty-two subjects were identified in whom a visceral type of pain was the leading complaint and who reported no irritating-type surface somatic symptoms. They all reported deep visceral pain as the main reason they sought specialist management and were definite about the absence of other types of discomfort especially pruritus. Eighteen of them were on immunotherapy at the time of the study and available to participate in the questionnaire and phone

Table 1 Diagnoses in 52 patients with chronic vaginitis syndrome

Gynecological diagnoses	
Recurrent vulvovaginal candidiasis (RVVC)	34 (65 %)
Vulvar vestibulitis syndrome (VVS)	12 (23 %)
Contact dermatitis (CD)	10 (19 %)
Bacterial vaginosis (BV)	5 (9 %)
Lichen sclerosus	1 (2 %)
Other gynecological diagnoses in 10 patients with contact dermatitis (CD)	
Recurrent vulvovaginal candidiasis (RVVC)	5 (50 %)
Vulvar vestibulitis syndrome (VVS)	5 (50 %)
Vulvar vestibulitis syndrome (VVS) and bacterial vaginosis (BV)	1 (10 %)
Other gynecological diagnoses in 5 patients with bacterial vaginosis (BV)	
Recurrent vulvovaginal candidiasis (RVVC)	4 (80 %)
Vulvar vestibulitis syndrome (VVS) and contact dermatitis (CD)	1 (20 %)

Recurrent vulvovaginal candidiasis (RVVC) and vulvar vestibulitis syndrome (VVS) are presented as mutually exclusive; all other diagnoses are allowed concurrences

Table 3 Prevalence of immediate type (IgE-mediated) skin reactivities in 52 patients with chronic vaginitis syndrome

	RVVC (%)		VVS	CD	BV
Ragweed	33 (63)	22 (64)	8 (66 %)	7 (70 %)	4 (80 %)
All molds	26 (50)	19 (55)	6 (50 %)	5 (50 %)	3 (60 %)
Alternaria	13 (25)	7 (20)	3 (25 %)	3 (30 %)	3 (60 %)
Cladosporium	10 (19)	4 (11)	4 (33 %)	1 (10 %)	2 (40 %)
Aspergillus	11 (21)	6 (17)	4 (33 %)	1 (10 %)	1 (20 %)
Penicillium	5 (9)	3 (8)	2 (16 %)	1 (10 %)	–
Other molds	5 (9)	3 (8)	1 (8 %)	2 (20 %)	1 (20 %)
Dust mites	23 (44)	18 (52)	3 (25 %)	3 (30 %)	1 (20 %)
Candida	15 (28)	11 (32)	1 (8 %)	3 (30 %)	2 (40 %)
Grass mix	12 (23)	11 (32)	1 (8 %)	2 (20 %)	1 (20 %)
Birch	6 (11)	5 (14)	1 (16 %)	–	–
Oak	3 (5)	3 (8)	–	–	–
Other trees	5 (9)	4 (11)	1 (8 %)	1 (10 %)	–
Cat dander	2 (3)	1 (3)	1 (8 %)	–	–
Dog dander	1 (2)	1 (3)	–	–	–

Only the three largest reactions and all reactions equal to the third largest are presented

Table 4 A distinct mono-sensitization pattern reactivity was observed in 18 of 52 patients with chronic vaginitis syndrome

	RVVC (%)		VVS	CD	BV
Ragweed	7 (13)	4 (11)	3 (33 %)	2 (20 %)	1 (20 %)
All molds	3 (5)	3 (8)	–	–	–
Alternaria	1 (2)	1 (2)	–	–	–
Aspergillus	1 (2)	1 (2)	–	–	–
Penicillium	1 (2)	1 (2)	–	–	–
Dust mites	3 (5)	3 (8)	–	–	–
Grass mix	3 (5)	3 (8)	–	1 (10 %)	–
Candida	1 (2)	1 (2)	–	1 (10 %)	–
Cat dander	1 (2)	1 (2)	–	–	–

interview. There was a shift towards lower levels of pain after immunotherapy for 9–50 months. No patient was entirely free of pain after 9–50 months of immunotherapy. The number of patients with pre-treatment pain Level 5 (incapacitating pain) decreased by more than 50 % (p value = 0.052).

Somatic pain, often referred to by patients as "irritation," was the leading complaint in 46 subjects. Pruritus of various degrees, sometimes undistinguished from said irritation, was invariably present. The population of patients complaining of such irritating-type symptoms comprised 41 patients compliant with immunotherapy and 38 willing to participate in the questionnaire-interview process. Nine of these patients also reported deep visceral pain as an infrequent concurrent symptom but not as their first reason for seeking specialist help. Somatic pain/pruritus as the leading symptom of ChVS, appeared to be more susceptible to immunotherapy than visceral pain. Nine patients (23 %) achieved a symptom-free status. The number of patients with constant, incapacitating, sleep-disrupting irritation declined from 14 to 5 (64 % decline). Significant p values were obtained for distribution of subjects allocated to the two ends of the somatic pain/pruritus severity spectrum (Fig. 2).

Discussion

Historically, the search for a treatable allergic condition contributing to RVVC was mostly directed towards Candida sensitization. The association of RVVC with IgE-mediated inflammatory responses to Candida has been demonstrated and Candida immunotherapy has been proven successful in controlling symptoms and decreasing the need for antifungal regimens [12, 13]. These studies contributed to greater awareness of the contribution of Candida IgE mediated responses to the pathogenesis and course of ChVS. It is obvious, however, that while it is only a small number of ChVS patients who exhibit IgE sensitization to Candida, the prevalence of allergic rhinitis among women with RVVC may be as high as 71 % [14]. For women with sensitivities to airborne allergens a causative relation had to be sought beyond Candida. It has been repeatedly postulated that treatment of airborne allergen sensitivity may result in improved management of ChVS but proof of such a cause-and-effect response is scarce and prospective, placebo-controlled, multicenter studies have not been carried out [15].

The mechanisms which allow for the vaginal mucosa to be repeatedly exposed and sensitized to airborne allergens are not fully delineated. The existence of a countercurrent blood flow in the female genital tract, which allows inhaled and ingested compounds to selectively accumulate in the vaginal wall has provided an anatomic and physiologic basis for the airborne allergy-chronic vaginitis association but, obviously, further studying is needed [16, 17].

In our series, all patients had multiple courses of antifungal medications over the years preceding the study, and almost all reported some favorable response to general measures meant to decrease vaginal Candida exposure; however, IgE-mediated sensitivity to Candida was present in only 28 % of all ChVS patients and, as a matter of fact, this percentage was not significantly higher among patients with an established RVVC diagnosis. This observation makes it quite likely that, at least for the largest number of patients, recurrent vulvo-vaginal Candida infection was more likely to have been a secondary event that further complicated the original offense rather than a causative allergy-producing factor. This is consistent with data

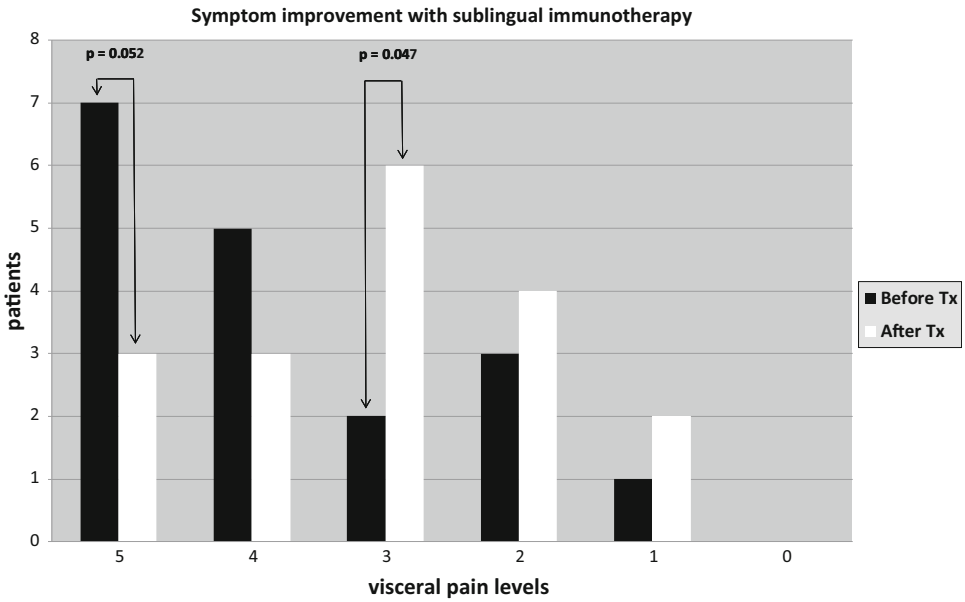

Fig. 1 Distribution to pain perception levels of 22 ChVS patients complaining of visceral pain: at onset of immunotherapy and at 9–50 months of treatment. *p* values *greater than* 0.065 are not shown. Six of these patients reported no surface somatic pain (irritation) or pruritus as concurrent symptoms

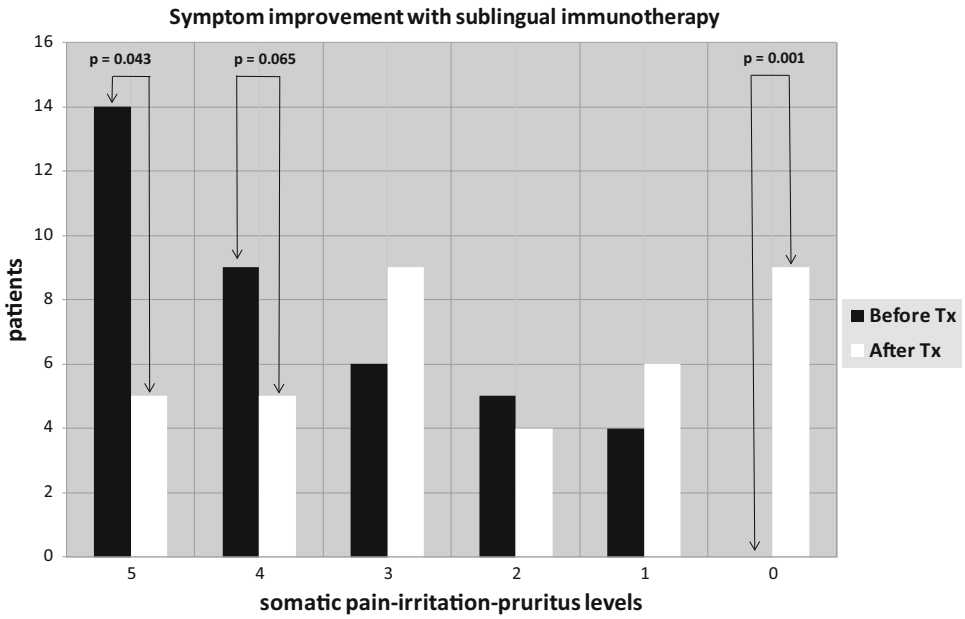

Fig. 2 Distribution of 38 ChVS patients to six levels of surface somatic pain-irritation-pruritus perception: at onset of immunotherapy and at 9–50 months of treatment. *p* values *greater than* 0.065 are not shown. Although localized irritation with or without pruritus was the chief complaint, nine patients also reported visceral pain

previously published which postulate a well-defined sequence of pathophysiological events in patients with ChVS. These start with histamine release from allergen-sensitized mast cells which, in addition to late-phase prostaglandin release from degranulating mast cells, also causes macrophages to locally produce inordinate amounts of prostaglandin E_2(PGE_2). According to this model, PGE_2 suppresses the cellular immune responses necessary to contain Candidiasis and/or other fungal proliferation [18, 19]. In short, by causing an increase in local (or distantly produced) PGE_2 levels, localized allergic sensitization and subsequent responses may induce an immunosuppressed state in the vaginal milieu [20]. Our study supports this theory as it indicates that IgE-mediated allergic responses to Candida, which were demonstrated in only 32 % of our patients with RVVC, are not a necessary prerequisite for the induction of such a state of immunosuppression, and that sensitization and regularly occurring mast cell activation-degranulation due to a variety of other (i.e. non-Candida) allergens, such as airborne ones, can be consistent with the production of RVVC just as well as of other forms of the ChVS [20].

The length of treatment with sublingual immunotherapy at the time the symptom questionnaire was submitted

varied from 9 to 50 months and, with a median of 26 months and SD 11 months, was considered adequate since clinically evident response to immunotherapy is expected to begin at 6 months and most immunotherapy protocols run a conventional course of 60 months [4]. This retrospective study has its limitations since no placebo control was studied, the recruitment of patients was not multi-centered and no blinding was applied. It does however show a favorable response of ChVS symptoms to manipulation of allergic responses by immunotherapy as compared to symptoms prior to use of immunotherapy.

The nature and overlap of symptoms in ChVS is complex and cannot be simply categorized under the dual heading of visceral pain versus irritation. Neurogenic inflammation, retrograde sensory nerve activation, chronic neuropathic pain but, most importantly, mutual neuro-immune interactions hitherto not studied, probably amplify the original inflammatory response independently of its original pathogenesis. The classifications of pain patterns as presented here is not meant to be final or complete but it underlines the multifactorial and diverse nature of ChVS. The demonstration of at least two major types of presenting symptoms and two types of response to immunotherapy, one characterized by visceral pain and one dominated by somatic pain-pruritus, indicates the existence of multiple underlying pathophysiological abnormalities. It may also be helpful in determining the likelihood of a favorable response to allergen immunotherapy in select patients.

As far as explanation of immune responses are concerned, mast cell activation and degranulation with both immediate and late-phase effects are thought to be instrumental in the production and perpetuation of the ChVS [18, 19]. It is possible that differential distribution of the two major types of mast cells (chymase positive mast cells versus chymase negative ones) to specific anatomic sites may account for the differences observed in response to immunotherapy. There are no data regarding the ways different types of mast cells may respond to exposure to allergens. Furthermore, there are no data regarding the chymase status of mast cells in the vaginal mucosa. There are no data either regarding the chymase status of mast cells at the endings of neurons and how chronic neuropathic pain may be affected by the activation/degranulation of such mast cells. This differentiation is significant because chymase positive mast cells release higher amounts of vasoactive and inflammatory substances, are widely distributed to serosal surfaces, and are also more prevalent in the skin than chymase negative mast cells.

In the present study, somatic pain (mucosal/skin circumscribed irritation) was demonstrated to be amenable to the manipulation of the immune system by sublingual immunotherapy, and, to some extent, the same may turn out to be true for visceral pain too (see Figs. 1, 2). The discrepancy in response to immunotherapy may represent differences in the nerve conduction of the two kinds of symptoms; differences in the nature of neuro-immune interaction; the generally more complex nature of the generation and perception of visceral pain as opposed to surface somatic pain/pruritus; or involvement of different types of effector cells (mast cells). It may also reflect the impact that a smaller size of participants had on the outcome of symptom scores. Furthermore, compliance with immunotherapy, and regular allergy-immunology follow up may be a significant impacting factor as very few patients had sought any kind of treatment for their allergies and their referral to an allergy clinic was prompted by the identification of allergy or allergy comorbidities in the course of their gynecological evaluation.

The emergence of at least two distinct patterns of ChVS symptom response is supported by this study. Patients who presented with visceral pain showed poorer symptom response to treatment as compared to patients with irritant/pruritic type symptoms (with or without associated pain). This is not an unusual finding and is indeed a recognized feature of neurogenic inflammation complicating, precipitating or amplifying allergic inflammatory responses or being caused by them. Such an association of allergic inflammation with various organ-specific painful syndromes has been described and has been shown to invariably include a lowered pain threshold [6–10].

In conclusion, it has been long known that sensitization to airborne allergens can lead to allergic responses in the vaginal mucosa [5, 14, 15]. The present study delineates the allergic and comorbid parameters of this association in a highly selected Midwest population referred for tertiary care level treatment of ChVS. Sensitization patterns do not appear to be different from the general Midwestern population. The present study indicates that chronic vaginitis in selected patients may be susceptible to immunotherapy. Longitudinal, multicenter, placebo-controlled, prospective studies will be needed to establish the degree of efficacy and describe expected outcomes of immunotherapy for ChVS.

These findings add credit to the notion of a cohesive mucosal entity which, while involving non-continuous and functionally unrelated mucosal surfaces, is still subject to an integrated allergic response. Nociceptive mechanisms involving a neuro-immune, probably bi-directional interaction may be different in patients who complain of exclusively visceral pain, and the same could be true for patients with isolated neuropathic pain. Patients who present with surface somatic pain/irritation or pruritus (with or without other types of pain), appear to be more susceptible to immunotherapy.

The present study indicates that chronic vaginitis in allergic patients can be complicated by inhalant allergen

sensitization and subsequent inflammation. Since allergic sensitization patterns, clinical features and relevant comorbidities in women with ChVS do not appear to be any different from other allergic patients of the same geographic area, the presented association is considered an inhalant allergy compounding the chronic vaginitis syndrome.

Compliance with ethical standards

Funding No funding was received for this study.

Conflict of interest None of the authors of this study has any conflict of interest to declare.

Animals This article does not contain any studies with animals performed by any of the authors.

Ethical approval All procedures performed were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Human Research guidelines were followed according to the standard National Institutes of Health Office of Extramural Research recommendations. Institutional Review and approval was by the University of Wisconsin-La Crosse. Informed consent was obtained from all individual participants included in the study.

References

1. Harlow BL, Stewart EG (2003) A population-based assessment of chronic unexplained vulvar pain: have we underestimated the prevalence of vulvodynia? J Am Med Womens Assoc 58:82–88
2. Nyirjesy P, Peyton C, Weitz V, Mathew L, Culhane JF (2006) Causes of chronic vaginitis: analysis of a prospective database of affected women. Obstet Gynecol 108:1185–1191
3. Danby CS, Margesson LJ (2010) Approach to the diagnosis and treatment of vulvar pain. Dermatol Ther 23:485–504
4. Wasserman SI (2012) Approach to the patient with allergic or immunologic disease. In: Goldman L, Schafer AI (eds) Cecil medicine, 24th edn. Elsevier, Philadelphia, pp 1612–1615
5. Moraes PSA, Taketomi EA (2000) Allergic vulvovaginitis. Ann Allergy Asthma Immunol 85:253–267
6. Theodoropoulos DS, Lockey RF, Bukantz SC, Boyce HW Jr (1999) Gastroesophageal reflux and asthma: a review of pathogenesis, diagnosis and therapy. Allergy 54:651–661
7. Theodoropoulos DS, Ledford DK, Lockey RF, Pecoraro DL, Rodriguez JA, Johnson MC, Boyce HW Jr (2001) Prevalence of upper respiratory tract symptoms in patients with symptomatic gastroesophageal reflux disease. Am J Resp Critic Care Med 164:72–76
8. Theodoropoulos DS, Ledford DK, Lockey RF, Pecoraro DL, Boyce HW Jr, Bukantz SC (2002) Visceral sensitivity in gastroesophageal reflux. Dig Dis Sci 47:2554–2564
9. Theodoropoulos DS, Katzenberg DR, Jones WM, Morris MS, Her C, Cullen NAM, Morris DL (2011) Allergen-specific sublingual immunotherapy in the treatment of migraines: a prospective study. Europ Rev Med Pharmacol Sci 15:1117–1121
10. Theodoropoulos DS and Cullen NAM (2011) Antigen presentation by dendritic cells and the practice of immunotherapy. Ann Respir Med 2. http://www.slm-respiratory.com
11. Theodoropoulos DS, Morris MS, Morris DL (2009) Emerging concepts of sublingual immunotherapy for allergy. Drugs of Today 45:737–750
12. Rigg D, Miller MM, Metzger WJ (1990) Recurrent allergic vulvovaginitis: treatment with *Candida albicans* allergen immunotherapy. Am J Obstet Gynecol 162:332–336
13. Moraes PSA (2000) *Candida albicans* allergen immunotherapy in recurrent vaginal candidiasis. J Invest Allergol Clin Immunol 10:305–309
14. Moraes PSA (1998) Recurrent vaginal candidiasis and allergic rhinitis: a common association. Ann Allergy Asthma Immunol 81:165–169
15. Berman BA (1964) Seasonal allergic vulvo-vaginitis caused by pollen. Ann Allergy 22:594–597
16. Bendz A, Einer-Jensen N, Lundgren O, Janson PO (1979) Exchange of krypton 85 between the blood vessels of the human uterine adnexa. J Reprod Fertil 57:137–142
17. Sjoberg I, Hakanson S, Holm SE (1990) Accumulation of penicillin in vaginal fluid. Obstet Gynecol 75:18–22
18. Witkin SS, Jeremias J, Ledger WJ (1988) A localized vaginal allergic response in women with recurrent vaginitis. J Allergy Clin Immunol 81:412–416
19. Witkin SS (1993) Immunology of the vagina. Clin Obstetr Gynecol 36:122–127
20. Weissenbacher TM, Witkin SS, Gingelmaier A, Scholz C, Friese K, Mylonas I (2009) Relationship between recurrent vulvovaginal candidosis and immune mediators in vaginal fluid. Eur J Obstetr Gynecol Reprod Biol 144:59–63