

ORIGINAL ARTICLE

Chronic urticaria is associated with a differential helminth–arthropod-related atopy phenotype

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ABSTRACT

The relationship between atopic sensitization and chronic urticaria is still controversial. In this study, we aimed to compare the prevalence of aeroallergen sensitization in chronic urticaria patients with (CU/As+) and without (CU/As–) sensitization against *Anisakis simplex*. Forty-nine CU/As+ and 80 CU/As– patients were studied and skin prick tests (SPT) were performed against aeroallergens. We assessed sensitization in a subgroup of patients with allergic rhinoconjunctivitis and/or bronchial asthma (RCBA) and compared the prevalence with a control group of 522 non-urticaria patients with RCBA. Forty-five percent of CU/As– and 60.4% of CU/As+ patients displayed positive SPT to at least one aeroallergen. CU/As+ patients had a higher prevalence of sensitization against pollen, mould or dander (PMD) (52.2% vs 29.1%, $P < 0.01$), whereas the prevalence of house dust mite (HDM) sensitization was not statistically different (26.3% in CU/As– and 36.7% in CU/As+). However, in chronic urticaria patients with RCBA, 53.8% of CU/As– and 57.9% of CU/As+ patients differed in the prevalence of HDM sensitization compared to the control group (33.5%, $P = 0.03$), whereas no difference could be stated for PMD sensitization. Compared to RCBA patients, both CU/As+ and CU/As– patients have a higher clinically relevant sensitization rate against HDM, thus displaying a differential atopy phenotype.

Key words: *Anisakis simplex*, arthropods, atopy, chronic urticaria, parasite.

INTRODUCTION

Chronic urticaria (CU) is a frequent and disabling illness occurring worldwide in 0.1% of the population.¹ Further, a recent survey in our area estimates the actual prevalence of CU to be approximately 0.6% and the accumulated prevalence of CU to be approximately 2.5–2.9%.² Whereas CU has been classified in physical and idiopathic urticaria, in recent years chronic idiopathic urticaria has been labeled autoimmune in a high percentage of cases.^{1,3} Further, clinical data support the involvement of infectious agents in the pathogenesis of urticaria.⁴ Thus, whereas CU induced by infectious agents has been proposed over

the last 30 years, publications describing these associations are anecdotal.

Acute urticaria, angioedema or anaphylaxis accompanies acute *Anisakis simplex* (*A. simplex*) infection in gastro-allergic anisakiasis.^{5–7} An association of CU with sensitization to *A. simplex* has also been described^{8–10}. In our area, this phenotype of CU patients constitutes up to 50% of patients attending for allergological evaluation and in a relevant subgroup of these patients sensitization against *A. simplex* was explained by a previous parasitism episode of *A. simplex*.¹¹

In a recent study we have shown that in both groups with gastro-allergic anisakiasis (acute

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Received 1 September 2009; accepted 6 December 2009.

urticaria) as well as *A. simplex* sensitization-associated chronic urticaria (CU/As+) patients who also suffer respiratory allergy harbor a different pattern of sensitization against aeroallergens with respect to the general population. In these groups, house dust mite (HDM) sensitization is more frequent and HDM sensitization-associated respiratory symptoms are more prevalent compared to the prevalence in the general population living in the same region.¹² Within the most common groups of sensitizing aeroallergens in our region (e.g. HDM, pollen, mould or animal dander), only HDM belong to the group of arthropods. These have been associated with a T-helper cell (Th)2-biased immunological mechanism such as with *Sarcoptes scabiei*, ticks or other blood-sucking arthropods, which in turn are able to induce urticarial reactions.^{13,14}

Therefore, the hypothesis of this study was that not only CU patients with, but also without sensitization to *A. simplex* display a differential sensitization profile against aeroallergens. HDM would be distinctly associated with CU compared to the other common non-arthropod allergens. In the present study, we therefore sought to first analyze and compare the atopy status as well as respiratory symptoms of CU patients with (CU/As+) and without (CU/As-) sensitization against *A. simplex*. Further we compared the sensitization pattern with a control group of patients with respiratory allergy but without urticaria.

METHODS

We analyzed retrospectively 49 CU/As+ and 80 CU/As- patients attended during 2007 and 2008. The control group was composed of 522 consecutive age-matched non-urticaria patients with allergic rhinoconjunctivitis and/or bronchial asthma (RCBA) of suspected allergic origin attending our allergy Service during 2008.

All patients were studied by means of the skin prick test (SPT) for sensitization against common aeroallergens.

Patient selection

All patients were recruited from the Allergy Service of the University Hospital La Princesa in Madrid in the center of the city and from our peripheral Allergy Unit in Coslada, a semirural area.

As this study did not influence diagnostic or therapeutic intervention on the patients, this retrospective study was exempt from institutional review board approval and informed consent.

Chronic urticaria patients were included with at least twice a week spontaneously occurring wheals for at least 6 weeks, independent of other conditions known to be associated with CU. Only patients with suspected food-induced urticaria and urticaria elicited exclusively by physical stimuli were excluded from this analysis.

Criteria to further include patients in the CU/As+ group were a previous history of fish-induced allergic and/or abdominal symptoms, together with a positive SPT against *A. simplex* and detectable specific immunoglobulin (Ig)E against *A. simplex* (>1.5 kU/L).

Chronic urticaria patients with sensitization against *A. simplex* did not have any previous fish-induced allergic and/or abdominal symptoms and did not show any detectable specific IgE by means of SPT nor by serum specific IgE against *A. simplex* (CAP-FEIA; Phadia, Uppsala, Sweden).

The control group was composed of 522 consecutive patients, cross-matched for age, referred to us for allergological evaluation of RCBA of physician-based suspected allergic origin without a history of urticaria. Patients were only included if they displayed a positive SPT to at least one aeroallergen and had no history of urticaria nor a positive SPT against *A. simplex*, which is assessed routinely in all patients attending our Service. As the control group was composed of patients with respiratory symptoms, we could only compare the sensitization profile within the CU/As- and CU/As+ groups, and, further, the sensitization profile of the control group with the subgroups of CU/As- and CU/As+ of patients who also suffered from respiratory allergy.

SPT

Skin prick tests performed were: SPT with *A. simplex* antigen (Lab. IPI, Madrid, Spain); and SPT against aeroallergens (Lab. ALK-Abelló, Madrid, Spain) animal dander (cat, dog), house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Tyrophagus putrescentiae*), five pollen mixtures of grass, tree and weed pollen and mould (*Alternaria alternata*, *Cladosporium herbarum*). SPT was performed by standard technique and was considered

positive with a mean wheal diameter of 3 mm × 3 mm or more. Histamine at 1% concentration and saline solution 0.9% (NaCl) were positive and negative controls, respectively.

Laboratory determinations

Total and specific IgE against *A. simplex* were assessed by CAP-FEIA (Phadia). Specific IgE was considered positive with results of more than 0.35 kU/L, but patients in the CU/As+ group were only included if specific IgE was more than 1.5 kU/L in order to minimize false-positive test results.

Clinical respiratory symptoms

Patients were interviewed about the presence of seasonal or persistent RCBA for at least 2 years, and were included in the control group if physician-based suspicion of allergic RCBA was accompanied by positive SPT to at least one aeroallergen.

Statistics

Statistical analysis was performed using SPSS ver. 15.0 for Windows. Mean ages were calculated in all studied groups and compared by ANOVA.

Prevalences were calculated for sex in all studied groups and compared by χ^2 -test. As pollen is by far the most common sensitizing agent in our region and animal dander as well as mould only rarely sensitize atopic patients without a concomitant pollen sensitization, pollen, mould and animal dander were analyzed together in comparison to HDM sensitization.

Prevalences were calculated for sensitization against: (i) HDM and pollen, mould or dander (PMD) as one sensitization group; (ii) RCBA; and (iii) RCBA-associated aeroallergen sensitization.

χ^2 -Test and Fisher's exact test were used for comparison of sensitized patients and presence of RCBA in the studied and control groups.

RESULTS

General data

Mean age was similar in CU/As- (39.2 ± 13.6 years) and CU/As+ (41.8 ± 11.2 years) patients and not different from the control group after matching for age (39.33 ± 15.5 years). Female patients made up 68.8% in the CU/As-, 81.6% in the CU/As+ and 65.2% in the control groups ($P = 0.06$).

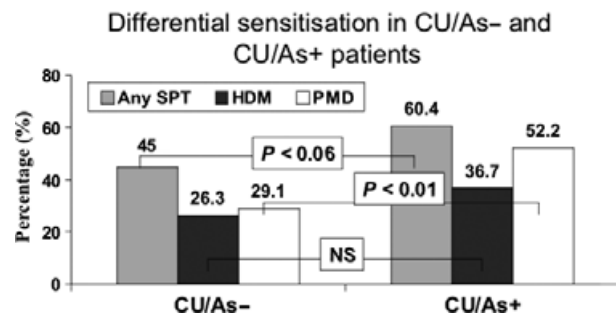


Figure 1. Differential sensitization in chronic urticaria patients with (CU/As+) and without (CU/As-) sensitization against *Anisakis simplex*. Sensitization against at least one aeroallergen (any skin prick test [SPT]), against house dust mites (HDM) or pollen, mould and dander (PMD) in CU/As+ and CU/As- patients. In this analysis, patients of both groups are studied regardless of suffering from rhinoconjunctivitis and/or bronchial asthma.

Sensitization pattern and respiratory symptoms in CU/As- and CU/As±

Forty-five percent of CU/As- and 60.4% of CU/As+ patients displayed positive SPT to at least one aeroallergen ($P = 0.06$).

If we analyzed for a differential sensitization pattern, the prevalence of SPT against HDM was not statistically different with 26.3% in CU/As- and 36.7% in CU/As+ patients, but the difference reached statistical significance if sensitization was analyzed against PMD (29.1% in CU/As- and 52.2% in CU/As+; $P = 0.009$; Fig. 1).

Only 21.3% of CU/As- patients, but 42.2% of CU/As+ suffered from allergic and non-allergic RCBA ($P = 0.013$).

Sensitization pattern in patients with allergic RCBA:

In this analysis, we were able to compare with our control group. In patients with allergic RCBA, seven of 13 (53.8%) CU/As- patients and 11 of 19 (57.9%) CU/As+ patients had higher sensitization rates against HDM than the control group (175/522: 33.5%, $P = 0.03$). There was no difference between the CU/As- and CU/As+ groups.

However, there was no difference of PMD sensitization in any of the three groups: 83.3% in CU/As-, 94.1% in CU/As+ and 95.8% in the control group (Fig. 2).

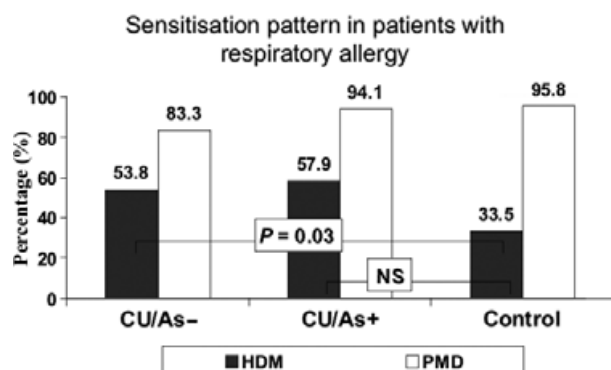


Figure 2. Sensitization pattern in patients with respiratory allergy. Sensitization against house dust mites (HDM) or pollen, mould and dander (PMD) in chronic urticaria patients with (CU/As+) and without (CU/As-) sensitization against *Anisakis simplex*. In this analysis, patients were included who had rhinoconjunctivitis and/or bronchial asthma of physician-based suspected allergic origin plus positivity to at least one aeroallergen. Here, we could properly compare with the control group of patients without urticaria, but with rhinoconjunctivitis and/or bronchial asthma and positive skin prick tests for at least one of the tested common aeroallergens.

DISCUSSION

We have recently shown, that the prevalence of allergic respiratory symptoms in gastro-allergic anisakiasis, but also in *A. simplex* sensitization-associated CU (CU/As+), showed a more frequent HDM sensitization-associated RCBA. On the other hand, these patients had a lower prevalence of PMD-associated allergic disease, compared to the prevalence in the general population. This led to the proposal of a differential definition of atopy, which has been claimed to be especially useful for studies aiming to explain the relationship between allergy and parasites.¹²

As climatic and geographic conditions in the studied region confer low levels of HDM allergen exposure with a subsequent low prevalence of sensitization in the general population, the observed differences in both groups with nematode *A. simplex*-associated acute and CU, gained significance with respect to previous studies on the relationship between helminths and HDM sensitization in mainly tropical regions, where geohelminth burden parallel mite allergen exposure.^{15–17}

We were thus able to differentiate two atopy subphenotypes, which forced us to evaluate in the present study if other forms of CU were also associated with a differential SPT reactivity or respiratory allergy.

Skin reactivity as a risk factor for asthma in industrialized countries has mainly been reported for HDM.¹⁸ But allergic rhinoconjunctivitis in industrialized countries is much more frequent than asthma. Therefore, in spite of the less objective measurement of physician-based evaluation of rhinoconjunctivitis, we were able to have at our disposal an ample sample size in our studied groups if we investigated not only asthma symptoms.

Only PMD sensitization differed between CU/As+ and CU/As- patients. A higher PMD sensitization rate in CU/As+ could be due to an increased risk of *A. simplex* sensitization in atopic patients. On the other hand, there were no significant differences with respect to HDM sensitization in both groups. This is interesting, because cross-reactivity has been discussed between HDM and *A. simplex*.^{19,20} Therefore, a previous estimation of HDM sensitization rate in the general population in our region of approximately 8% is here by far lower not only in CU/As+, but also in CU/As- patients.¹²

In the present study, when analyzing only patients who also suffered respiratory symptoms, we confirm a nearly twofold higher prevalence of HDM sensitization not only in patients with CU/As+, but also a higher prevalence in those of the CU/As- group, compared to our control group. This difference could not be stated for other aeroallergens, as with the PMD group. Cross-reactivity has been postulated between HDM and *A. simplex*,^{19,20} and glutathione S-transferase, paramyosin or tropomyosin have been found to be shared by helminth parasites and HDM.²¹ Further, cross-reactions are known between *A. simplex* and other helminths or arthropods.^{22,23} These facts could partly explain the observed association of HDM- and *A. simplex*-sensitization in the CU/As+ group. However, the also higher HDM sensitization rate in the CU/As- group with respiratory allergy is interesting, as it implies that the positive association between *A. simplex*- and HDM-sensitization in CU/As+ patients, is not exclusively due to cross-reactivity. Thus, irrespective of the different clinical features of the two studied CU phenotypes, an important number of patients in both CU/As+ and CU/As- groups share a similar atopy phenotype.

Up to now, there is no convincing evidence about a possible relationship between atopy and CU. Only a few studies showed an association of CU with

a predominant HDM skin reactivity.^{24,25} Furthermore, a recent report has shown that the prevalence of positive SPT to both food allergens and aeroallergens in patients with CU was common but had little clinical relevance.²⁶ Paralleling our own experience, it is possible that a positive association can only be detected in regions where HDM, due to geographic and climatic conditions, are not a common source of sensitization like in our studied region. On the other hand, we do not support the idea that HDM are causative in the origin of CU. Due to the possible cross-reactivity between HDM and other arthropods or helminths, a positive SPT could rather reflect a sensitization against any of these agents.^{20,27,28} Together with our previous above summarized results we hypothesize that HDM reactivity is only a genetically-linked indirect marker of a predisposition to recognize arthropod and/or helminth allergens with a further predisposition to cutaneous acute or CU symptoms.

Urticaria is one of the skin manifestations, which are related to helminths or arthropods with a cutaneous phase: *Schistosoma*, *Strongyloides*, *S. scabiei*, as well as ticks and other blood-sucking arthropods have been involved in Th2-based immunological mechanisms.^{13,29} All are arthropods or helminths to which humans could have evolved a general mechanism of defense.³⁰ Respiratory allergies (above all bronchial asthma) against HDM become more prevalent in urbanized and affluent populations.³¹ These are generally exposed to diminished "natural" helminth antigens and elevated "domestic" HDM, cockroach and possibly other arthropod antigens.³² The situation in industrialized countries might be that as parasitic infections are light and sporadic they produce an enhancement of the allergic phenotype.³³ In analogy to the relationship between rising asthma prevalences and diminishing helminth infections, such as with *Ascaris lumbricoides* or *Necator duodenale* with a pulmonary phase, we propose urticaria in HDM-sensitized patients to be equally related to a missing natural helminth or arthropod with a cutaneous phase. This could explain the elevated HDM sensitization rate not only in our *A. simplex*-associated CU patients, but also in our CU group without sensitization to *A. simplex*.

In our present study, we state an interesting dissociation: whereas CU/As+ compared to CU/As- patients have a higher prevalence of PMD

sensitization but not HDM sensitization, it is especially HDM sensitization that accounts for a clinically-relevant association with RCBA in CU/As+ patients. Thus, whereas CU/As+ patients are more frequently sensitized against PMD, the translation to clinically-relevant allergy is associated with HDM sensitivity, even in a region with a low burden of HDM allergens.

Taken together, the results about the relationship between CU and helminths or arthropods encourage further research on the possible underlying mechanisms.

ACKNOWLEDGMENT

This work was supported by a grant from FUNDACION MMT 2009.

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