

Increased Allergic Sensitization to Mugwort in Chronic Urticaria

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Key Words

Chronic urticaria • Mugwort • Atopy • Aeroallergen testing

Abstract

Background: Mugwort pollen is known to cross-react with a variety of spices and vegetables that are typically part of elimination diets used in the treatment of chronic urticaria (CU). **Objective:** We sought to investigate the association between CU and allergic sensitization to mugwort pollen. **Methods:** We conducted 2 case-control studies comparing aeroallergen skin prick test results between patients with and without CU and with or without allergic rhinitis (total n = 202). **Results:** CU patients with coexisting allergic rhinitis were more than twice as likely to be sensitized to mugwort as subjects not suffering from CU (67 vs. 30%; p = 0.004). Ragweed, cat, rat and mite sensitization were also significantly associated with CU. Overall, patients with CU had more positive aeroallergen skin tests than patients without CU (p < 0.005). **Conclusion:** Mugwort sensitization was associated with CU, possibly contributing to beneficial effect of elimination diets.

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Introduction

Chronic spontaneous urticaria (CU) is characterized by recurrent wheals with associated pruritus without an apparent trigger for longer than 6 weeks. Even though accurate data on the prevalence of CU are not available, it is thought to affect about 3–5% of the population at some time in their life [1]. Though autoimmunity against IgE receptors [2] and infections [3] may play a pathogenic role in a subgroup of patients, the cause still remains unclear in the majority of CU cases. Unlike acute urticaria, it is not generally thought that type I allergic reactions are responsible for CU [4–9]. Hence, allergy testing is not generally recommended as part of the diagnostic work-up of CU [10]. Nevertheless, certain food components have been implicated as the cause of ‘pseudoallergic’ reactions resulting in CU [11]. Pseudoallergic reactions are generally thought to be IgE-independent, imitating allergic reactions without sensitization to a specific substance. Despite negative food allergy testing by skin prick and serum allergen-specific IgE, many authors report an improvement in CU in a subset of patients on low pseudoallergenic diets [5, 7, 12–16]. However, sensitization to specific aeroallergens that may cross-react with food ingredients has not been well studied in patients with CU.

A. Tavdy is a college student who worked with us as a volunteer; she holds no academic degree.

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Mugwort (*Artemisia vulgaris*) is a perennial weed common in North America, Europe, Asia and Africa. It cross-reacts with aromatic plants of different botanical families, such as celery, pepper, paprika, parsley, garlic, onion, caraway, mustard, coriander, curry, fennel and mace [17, 18], some of which are contained in commonly used seasoning and spice mixes. A number of proteins have been identified to be potentially responsible for clinical cross-reactivity between mugwort and other plants, including profilins, lipid transfer proteins, cross-reactive carbohydrate determinants, germin- and osmotin-like proteins and high-molecular weight allergens [17, 19].

Because of its potential cross-reactivity with spices (that can act as 'hidden' food ingredients) mugwort may be particularly involved in the etiology of CU. Ingestion of mugwort-cross-reactive food antigens in foods such as seasoning or tomato may induce urticarial symptoms in mugwort-sensitized CU patients. 'Pseudoallergen elimination diets', which appear to benefit a subset of CU patients, typically prohibit ingesting seasoning, spices and tomato, which may all cross-react with mugwort pollen. Nonprotein and protein fractions of these foods may be responsible for triggering symptoms after food challenge in patients who previously experienced marked improvements on a pseudoallergen elimination diet [11]. We have anecdotally observed that mugwort-sensitized patients with CU respond rapidly to a strict pseudoallergen elimination regimen, suggesting that elimination of cross-reacting allergens may be one of the factors explaining the effect of these diets. It should be noted that skin and in vitro testing for the presence of spice-specific IgE is generally difficult and unreliable for directly establishing the diagnosis of pollen-cross-reactive food allergy [11, 20].

To our knowledge, there are no published data on mugwort sensitivity in CU patients. The aim of our study was to determine the association between mugwort pollen sensitization and CU that could potentially trigger symptoms in CU through cross-reactivity with food ingredients.

Methods

Study Design and Subjects

Two case-control studies were performed. The cohort for the first study consisted of patients with or without CU who all also had physician-diagnosed allergic rhinitis. The second cohort consisted of patients with or without CU but no rhinitis or other allergic respiratory diseases. The reasoning for studying these 2 co-

horts separately was that allergic respiratory diseases are highly associated with aeroallergen sensitization. Hence, a nonstratified analysis would strongly confound the quantitative comparison of positive allergy skin tests. For the first cohort (subjects with allergic rhinitis), all available medical records of cases with CU and chronic rhinitis (n = 18) and control subjects with the diagnosis of allergic rhinitis but no CU (n = 127) between January 2006 and February 2008 in the Adult Allergy Clinic of the Jacobi Medical Center and North Central Bronx Hospital were reviewed. Cases with physical urticaria were excluded. Aeroallergen skin testing had been routinely performed in all these patients. For the second cohort (subjects without allergic rhinitis or other allergic respiratory disease), all charts of all CU patients without rhinitis or asthma (n = 19) were reviewed during the same time period. Aeroallergen skin testing had also been routinely performed in these patients. Since we could not derive a control group for this group of cases from our Allergy Clinic population (because all other patients had either respiratory allergic disease or other allergic diseases that are strongly associated with allergen sensitization which hence would have confounded our analysis), we derived a control group for these cases (frequency matched by age and gender) from our primary care clinic consisting of 19 patients who were seen for routine follow-up. These patients were screened for the presence or history of allergic diseases, and if there was no indication of allergic disease or CU, aeroallergen skin testing was performed after written informed consent was obtained. The study was approved by the Institute Review Board of the Albert Einstein College of Medicine.

Allergy Testing

Skin prick testing to a standard panel of 22 environmental allergens, a negative glycerin-containing control and a positive histamine control was performed using the Multi-Test device II (Lincoln Diagnostics, Ill., USA) on the flexor sides of both forearms. The allergy test panel included a tree pollen mix (beech, ash, birch, elm, cottonwood, maple, hickory, oak, sycamore, sweet gum), a northern grass pollen mix (kentucky blue/june, orchard, redbud, timothy, sweet vernal), mugwort pollen (*A. vulgaris*), ragweed pollen (giant and short), English plantain pollen, a weed pollen mix (including cocklebur, lambs quarters, red-root/rough amaranth) dust mite, cockroach (American/German), cat hair, dog epithelium, mouse epithelium, rat epithelium, feathers, *Aspergillus fumigatus*, mold spore extract mix I (*Fusarium*, *Mucor*, *Rhizopus*, *Drechslera*, *Aureodasidium*) and mold spore extract mix II (*Alternaria*, *Aspergillus niger*, *Cladosporium sphaerospermum*, *Penicillium notatum*; Greer Laboratories, Lenoir, N.C., USA). A skin test was considered to be positive if the wheal diameter was 3 mm larger in diameter than the glycerin control.

Statistical Analyses

A t test was used for comparison of age (normally distributed, equal variances). Bivariate analysis was performed for all categorical outcomes using Fisher's exact test or Pearson's χ^2 . Medians and interquartile ranges are reported for the total number of aeroallergen sensitizations, and statistical significance was calculated using the Wilcoxon rank sum test due to nonparametric distribution. Multivariate logistic regression models were applied adjusting for sex, age and ethnicity (Hispanic vs. others). We used Stata 11.1 software for all analyses.

Table 1. Subject characteristics

	Allergic rhinitis (n = 145)			No rhinitis (n = 38)		
	CU– (n = 127)	CU+ (n = 18)	p value	CU– (n = 19)	CU+ (n = 19)	p value
Male	25 (20)	10 (56)	0.002	4 (21)	5 (26)	1.000
Age, years	43.9 (13.2)	40.1 (14.8)	0.263	49.2 (11.3)	44.3 (12.6)	0.211
Ethnicity			0.993			0.503
Hispanic	52 (41)	7 (39)		8 (42)	7 (37)	
Caucasian	13 (10)	2 (11)		1 (5)	5 (26)	
Black	31 (24)	5 (28)		5 (26)	4 (21)	
Asian	11 (9)	1 (6)		1 (5)	1 (5)	
Other	20 (16)	3 (17)		4 (21)	2 (10)	
Asthma	49 (39)	5 (28)	0.441	0	0	n.a.

Figures in parentheses represent percentages, except for age, where it represents SD. n.a. = Not applicable.

Results

Subject Characteristics

Table 1 summarizes the patient characteristics of the two study cohorts, i.e. those with and those without allergic rhinitis. Among the study cohort with allergic rhinitis, CU patients differed demographically in terms of the gender distribution; 10 patients (56%) with CU were male compared to 25 patients (20%) without CU. There was no difference in age, gender or ethnicity among the study cohort without allergic rhinitis (table 1).

CU patients had more positive skin tests to aeroallergens than patients without CU (fig. 1). In the cohort of patients with allergic rhinitis, patients without CU had a median of 3 positive skin tests (interquartile range 1–6), compared to a median of 6 (interquartile range 4–8) in patients with CU ($p = 0.003$). While aeroallergen sensitization was lower in the cohort without allergic rhinitis, those with CU (but no rhinitis) were still more likely to have positive skin tests (median 1, interquartile range 1–4) compared to those without CU (and no rhinitis; median 0, interquartile range 0–2; $p = 0.036$).

Association between Mugwort Sensitization and CU

In the study cohort with allergic rhinitis, sensitization to mugwort was more than twice as frequent in patients with CU than in patients without CU (67 vs. 31%; $p = 0.007$; fig. 2). In contrast, there was no difference in mugwort sensitization in patients without allergic rhinitis; 5 patients (24%) with CU were sensitized to mugwort compared to 2 patients (13%) without CU (data not shown).

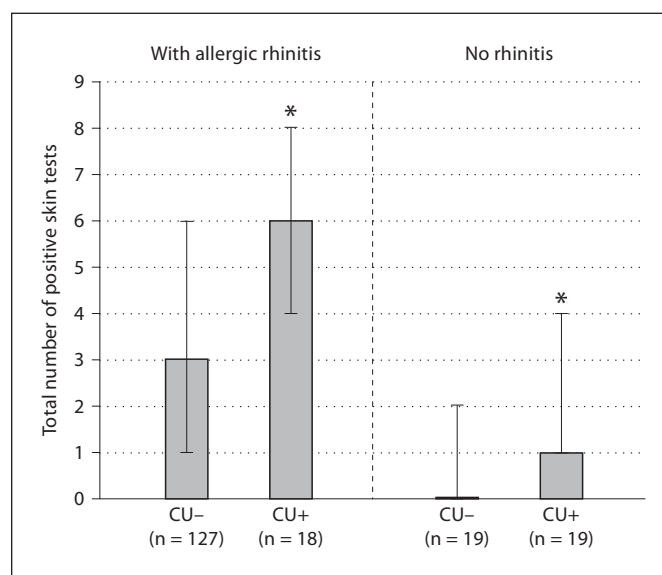


Fig. 1. Total number of positive skin tests in patients with CU (CU+) and without CU (CU–) and with and without coexisting allergic rhinitis. Bars indicate medians and error bars indicate interquartile ranges. * $p < 0.05$.

Association between Other Aeroallergen Sensitizations and CU

We also analyzed if sensitization to allergens other than mugwort was associated with the presence of CU. In the cohort with allergic rhinitis, in addition to mugwort, ragweed, cat and rat sensitization was significantly associated with CU (fig. 3a). In contrast, in the cohort without rhinitis, pollen sensitization was not associated with CU

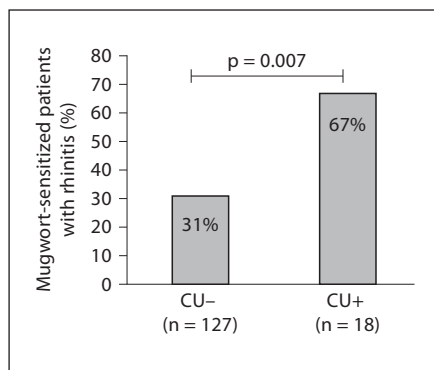


Fig. 2. Proportion of allergic rhinitis subjects with CU (CU+) or without CU (CU-) who had positive skin tests to mugwort.

(fig. 3b). However, in this cohort, dust mite sensitization was strongly associated with CU (8 patients in the group with CU had a positive skin test to dust mite versus 0 patients in the control group; $p < 0.001$), and rat sensitization had borderline statistically significant associations with CU ($p = 0.046$).

After adjusting for age, sex and ethnicity in the allergic rhinitis subgroup, a logistic regression analysis confirmed the strong associations between CU and sensitization to mugwort [odds ratio (OR) 4.0, 95% confidence interval (CI) 1.3–12.3; $p = 0.014$], ragweed (OR 4.7, 95% CI 1.5–15.1; $p = 0.008$), cat (OR 5.8, 95% CI 1.8–19.1; $p = 0.004$) and rat (OR 4.0, 95% CI 1.3–12.1; $p = 0.015$). Similar to the bivariate analysis, the association between other aeroallergen sensitizations and CU was not statistically significant in this logistic regression model. Due to the small number of patients in the non-rhinitis group, with only few sensitizations in the control group, logistic regression was either not possible or did not yield meaningful results in this group (data not shown).

Discussion

In agreement with our hypothesis, we found that mugwort sensitivity is more common in patients with CU, as is ragweed sensitization, but this is only seen in individuals with concomitant rhinitis. We also found that patients with CU are more allergic to other aeroallergens (i.e. cat and rat) than those without CU, regardless of the presence or absence of allergic rhinitis. Dust mite sensitization was associated with CU in patients without respiratory allergic disease.

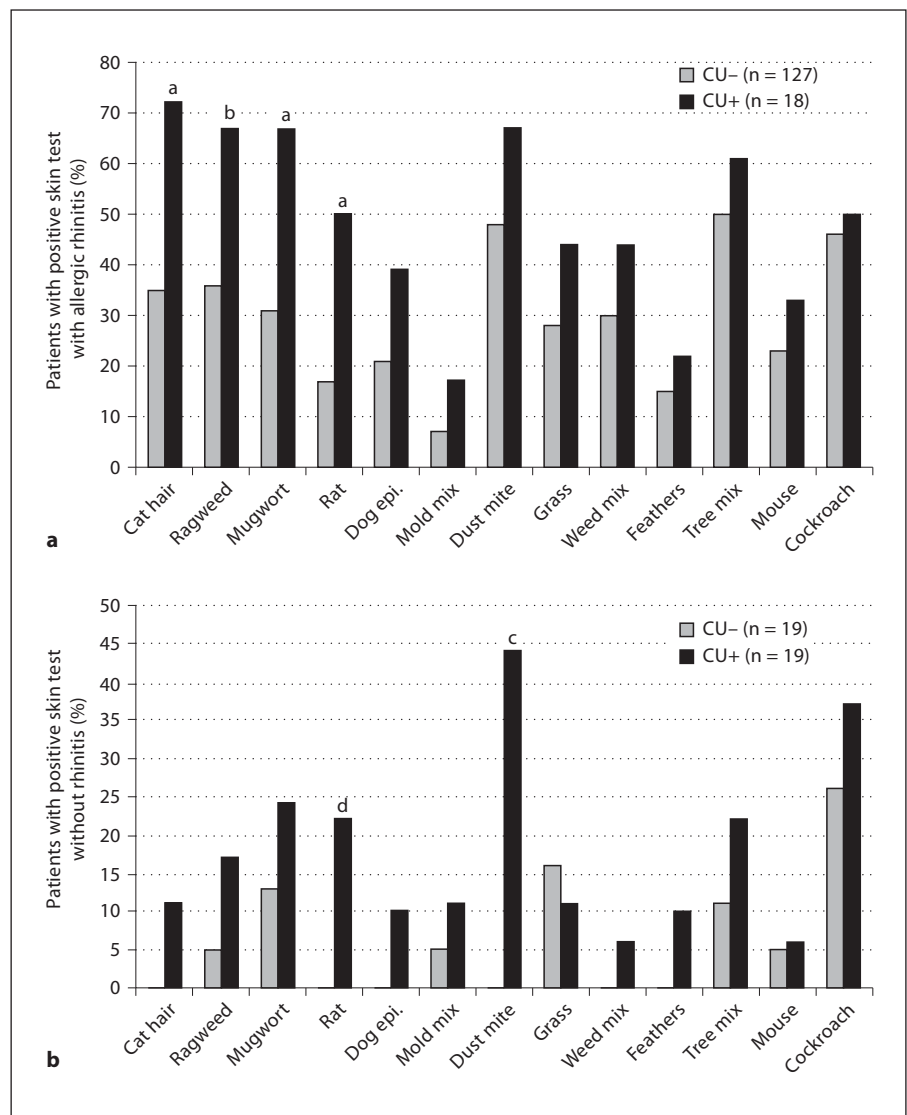
The fact that we found a statistically significant association between mugwort (as well as ragweed) sensitization and CU in the group with allergic rhinitis but not in the group without allergic respiratory diseases is most likely due to the fact that both the number of allergic sensitizations as well as the total sample size was much higher in the allergic rhinitis group compared to the group without allergic respiratory disease. A much larger sample size of patients without allergic respiratory diseases would be needed to detect potential associations between these allergens and CU.

Our cross-sectional study design confines the interpretation of the results to an association between specific aeroallergen sensitizations and the presence of CU. However, the higher frequency of mugwort sensitization in CU patients may indicate a pathogenetic role. However, in contrast to the celery-mugwort-birch syndrome, in which mugwort-cross-reactive foods trigger immediate type I allergic reactions, CU patients do not usually report symptoms immediately after ingestion of food but develop hives at any time, and often without any obvious trigger. Delayed IgE-mediated reactions to mammalian carbohydrate determinants have recently been described [21], but the role of plant-derived carbohydrate determinants in triggering delayed IgE-mediated reactions has not been well investigated. However, delayed IgE-mediated reactions to cross-reactive carbohydrate components in spices in mugwort-sensitized patients is a compelling theory that could explain delayed food-induced symptoms in the subgroup of mugwort-sensitized CU patients.

We also observed an association between ragweed sensitization and CU that may be explained by cross-reactivity of profilin antigens between mugwort and ragweed pollen [22]. In contrast, their major allergens, mugwort Art v 1 and ragweed Amb a 1, seem to be unrelated proteins [23].

We also found associations of indoor allergen sensitization (i.e. rat, cat and dust mite) with CU. The association between sensitization to dust mite and CU was also found in other studies [9, 24]. The role of these indoor allergen sensitizations is yet to be investigated. However, recent studies indicate that the serum of patients with CU contains intrinsic factors that lead to mast cell degranulation through mechanisms that bypass the IgE receptor [25]. In addition, a recent study showed elevated total (but not mature) tryptase levels in CU patients compared to atopic and nonatopic healthy controls, indicating an activated state of mast cells or increased mast cell number [26]. These findings suggest that patients with CU are intrinsically prone to mast cell degranulation. Hence, if the

Fig. 3. Aeroallergen sensitization of patients with CU (CU+) and without CU (CU-). **a** In patients with coexisting allergic rhinitis. ^a $p < 0.01$; ^b $p = 0.02$. **b** In patients without allergic rhinitis. ^c $p = 0.001$; ^d $p = 0.05$. epi. = Epithelium.



threshold for mast cell degranulation is intrinsically decreased in patients with CU, exposure to small amounts of ubiquitous allergens such as dust mite (environmentally or via cross-reactive food antigens) or low-level exposure to pollen-cross-reactive food antigens may theoretically be sufficient to elicit symptoms in sensitized CU patients [27]. In this sense, not only specific elimination diets but also environmental control measures to reduce exposure to indoor allergens may contribute to symptom improvement in sensitized CU patients.

Our data indicate that for every aeroallergen that we tested, sensitization was more frequent in patients with CU, even after stratification by the presence or absence of allergic rhinitis. This may have several explanations; the

higher degree of atopy in CU may be one of the reasons why these patients developed CU in the first place [27]. Alternatively, an increased number and irritability of skin mast cells in CU patients could lead to higher rates of positive skin tests in CU. Comparing skin test results with serum allergen-specific IgE levels in CU and control patients could help clarify this hypothesis.

Despite the limitation of its cross-sectional design, a strong aspect of our study was that all diagnoses were based on allergists' evaluations, and aeroallergen testing was performed without bias, because all patients were routinely tested for aeroallergen sensitization (with the exception of the prospectively enrolled control group for the non-rhinitis cohort). Hence, all patients with CU who

were seen in the allergy clinic during this time period were tested for aeroallergens, regardless of the presence or absence of respiratory allergic diseases. Therefore, the description of our CU population and rhinitis patients can be considered a representation of the CU referrals seen in our city hospital-based allergy specialty clinics of the North Bronx.

In conclusion, mugwort sensitization was found to be more frequent in patients with CU. Whether a subgroup of patients with CU sensitized to mugwort benefits from diets specifically tailored to avoid mugwort-cross-reactive ingredients rather than more extensive elimination diets, as well as the question of which particular antigens (e.g. profilins, carbohydrate determinants) may be re-

sponsible for this phenomenon, remain to be investigated. Albeit preliminary, our observations suggest that allergic sensitization to particular antigens such as mugwort that have not previously been investigated in the context of CU may play a pathogenetic role. If confirmed in prospective studies, the role of allergy testing may be reconsidered in patients with CU.

Disclosure Statement

None of the authors, their relatives or their institutions have any direct or indirect financial interest in the publication of this paper.

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