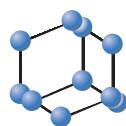


RESEARCH ARTICLE

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Factors Associated with Self-Reported Drug Allergies in a Large Chronic Spontaneous Urticaria Cohort

Christine Rauscher¹, Andrej A. Petrov¹ and Merritt L. Fajt^{1,*}¹Division of Pulmonary, Allergy, and Critical Care Medicine; Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh Pennsylvania USA

Abstract: Introduction: Chronic spontaneous urticaria (CSU) is characterized by recurrent hives without a known trigger. While certain drugs are associated with urticaria exacerbations, the overall drug allergy incidence in CSU is unknown. We hypothesized that the incidence of drug allergy in CSU would be greater than the general population and that there would be distinguishing clinical features of drug-allergic CSU patients.

Methods: 362 adult CSU patients seen over a 10-year period at a University Allergy/Asthma clinic were identified. Patients reported no drug allergies or any drug allergy. Multiple drug allergies were defined as allergies to ≥ 2 chemically unrelated drugs. Using Chi-square or Wilcoxon analysis, we compared demographic features of CSU with and without drug allergy and with multiple vs. single drug allergy.

Results and Discussion: Overall, 202 CSU patients (56%) reported drug allergy. Drug allergic CSU patients were older, with a greater proportion of whites and higher BMI vs. CSU without drug allergy ($p=0.002$, $p=0.047$, $p=0.004$, respectively). Penicillin was the most common drug allergy, with urticaria the most frequently reported reaction. Female sex, white race, older age at the visit, and co-existing asthma were more common in multiple drug allergy ($n=115$) vs. single drug allergy ($p=0.002$, $p=0.02$, $p=0.03$, $p=0.0002$, respectively).

Conclusion: In CSU, the prevalence of self-reported drug allergies was higher than the general population. Drug allergy is associated with older age, white race and higher BMI, while multiple drug allergy was also associated with asthma. These CSU sub-populations should be studied to avoid the potential for morbidity associated with less efficacious and more costly drugs.

Keywords: Chronic spontaneous urticaria, chronic idiopathic urticaria, hives, wheals, angioedema, drug allergy, penicillin allergy, antihistamines.

1. INTRODUCTION

Chronic spontaneous urticaria (CSU) is defined as pruritic wheals (hives) with or without angioedema lasting > 6 weeks without a known trigger [1]. CSU prevalence is estimated at 0.5-5% in the general population and adversely impacts the quality of life [1]. The mean delay from symptom onset to diagnosis is 24 months and can lead to unnecessary avoidance of suspected triggers, including drugs [2]. Although specific drugs that exacerbate urticaria have been identified, including nonsteroidal anti-inflammatory drugs (NSAIDs), there is a relative paucity of literature examining the co-existence of patient-reported drug allergies in CSU [1].

The estimated prevalence of drug allergies in the general population is 15-25%, while the prevalence in CSU is un-

known [3]. Verification of drug allergies in this population is difficult because antihistamine cessation, which is required for performing skin and drug provocation testing, may not be tolerated in CSU. Additionally, urticaria occurring during skin or drug provocation testing may be due to underlying CSU and may not reflect an underlying immunologic drug reaction.

The primary objective of this “real-world” study was to characterize self-reported drug allergies in a large cohort of CSU patients. We hypothesized that there would be a higher prevalence of drug allergies in CSU vs. the general population. Furthermore, we hypothesized that patients with CSU and drug allergies would have distinguishing clinical features compared to those with CSU who did not report drug allergies.

2. MATERIALS AND METHODS

We conducted a retrospective chart review of adult CSU patients seen in a university allergy/asthma clinic over a 10-year period (January 2007- January 2017). Self-reported

*Address correspondence to this author at the Division of Pulmonary, Allergy, and Critical Care Medicine; Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh PA; Tel: 412-864-2148; Fax: 412-648-6869; E-mail: fajtm1@upmc.edu

Table 1. Demographic features of CSU patients.

-	Overall Population (n=362)	Non Drug-Allergic (n=160)	Drug-allergic (n=202)	P-value (Non-drug Allergic vs. Drug-allergic)
Age at CSU onset, yrs [†]	36 (26-50)	32 (24-46)	39 (28-54)	0.002
Age at clinic visit, yrs [†]	39 (29-54)	35 (25-49)	44 (31-57)	0.0003
Sex, F/M	255/107	109/51	146/56	0.39
Race, White/Black/other	272/60/24	111/27/16	161/33/8	0.047
BMI [†]	28 (24-34)	27 (23-32)	29 (25-34)	0.004
Presence of co-existing angioedema, n (%)	223 (62%)	98 (61%)	125 (62%)	0.90
Presence of co-existing asthma diagnosis, n (%)	94 (26%)	36 (23%)	58 (29%)	0.18
Presence of co-existing allergic rhinoconjunctivitis diagnosis, n (%)	160 (44%)	63 (39%)	97 (48%)	0.10

[†]Data presented as median, 25th, 75th interquartile range; *P value determined by Pearson χ^2 and Kruskal-Wallis test
 BMI= body mass index, CSU= chronic spontaneous urticaria, F= female, M= male

Table 2. Demographic and comorbid conditions of CSU patients with single vs. multiple drug allergies.

-	SDA (n=87)	MDA (n=115)	P-value
Age of CSU onset, yrs [†]	39 (25-52)	39 (30-55)	0.19
Age at clinic visit, yrs [†]	41 (29-53)	46 (33-59)	0.03
Sex, F/M	53/34	93/22	0.002
Race, White/Black/other	64/16/7	97/17/1	0.02
BMI [†]	29 (26-34)	29 (24-35)	0.70
Presence of co-existing angioedema, n (%)	55 (63%)	70 (61%)	0.73
Presence of co-existing asthma diagnosis, n (%)	13 (15%)	45 (39%)	0.0002
Presence of co-existing allergic rhinoconjunctivitis diagnosis, n (%)	39 (45%)	58 (50%)	0.43
Drug-allergy category (Listed in order of overall frequency)	-	-	-
Penicillin allergy, n (%)	21 (24%)	45 (39%)	0.025
Sulfa allergy, n (%)	11 (13%)	39 (34%)	0.0005
NSAID allergy, n (%)	12 (14%)	36 (31%)	0.004
Opiate allergy, n (%)	8 (9%)	35 (30%)	0.0003
Cephalosporin allergy, n (%)	4 (5%)	19 (17%)	0.008
Quinolone allergy, n (%)	4 (5%)	18 (16%)	0.013
Radiocontrast media, n (%)	2 (2%)	13 (11%)	0.016

[†]Data presented as median, 25th-75th interquartile range; *P value determined by Pearson χ^2 or Kruskal-Wallis test;
 BMI= body mass index, CSU= chronic spontaneous urticaria, F= female, IV= intravenous, M= male, MDA= multiple drug allergies, NSAID= non-steroidal anti-inflammatory drugs, SDA= single drug allergy

drug allergies and associated comorbid and demographic features were assessed using the electronic medical record. Patients were categorized as reporting drug allergies or reporting no drug allergies (NDA). For patients reporting any drug allergies, they were further classified as having single (SDA) drug allergies or multiple drug allergies (MDA), reactions to ≥ 2 chemically unrelated drugs. We compared the clinical features of these groups using Chi-square analysis (categorical variables) or Kruskal-Wallis/ANOVA (continuous variable). A p-value <0.05 was considered statistically significant. Statistical analyses were performed using JMP Pro (SAS Institute Inc., Cary, NC). This study was approved by the Institutional Review Board at our facility.

3. RESULTS

In total, 362 CSU patients were identified, and 62% had concomitant urticaria and angioedema. Drug allergy was re-

ported in 56% (n=202) of CSU patients. Patients with drug allergy had an older age at urticaria onset and at clinic visit for urticaria, had a higher BMI and differed by race (more whites) than those without a drug allergy but were not different by sex or co-existence of angioedema, asthma or allergic rhinoconjunctivitis (Table 1).

Penicillin was the most common drug allergy class reported (n=66, 32% of drug allergic CSU patients, Table 2). The most common self-reported manifestations of penicillin allergy included urticaria (n=24), rash (n=22), isolated angioedema (n=7), anaphylaxis (n=6), gastrointestinal symptoms (n=4), unknown reaction from childhood (n=2) and respiratory symptoms (n=1). Nonsteroidal anti-inflammatory drug allergy was reported in 48 drug-allergic CSU patients. In drug allergic CSU patients, more females reported a cephalosporin allergy than males (14.4% vs. 3.6% respectively, p=0.03). There was otherwise no difference in reported

drug allergy class by sex. There was no difference in reported drug allergy class by race.

We then performed an analysis of CSU sub-populations with single and multiple drug allergies. Of those with drug allergy, 57% (n=115) reported MDA. In our MDA patients, the range of reported drug allergy classes was 2-18. Twenty patients reported drug allergy to 5-10 medications, and three patients had 11 or more drug allergies. Patients with MDA reported a significantly higher rate of penicillin, sulfa, NSAID, opiate, cephalosporin, quinolone, and radiocontrast media allergies compared to SDA (all p-values<0.025, Table 2). Female sex, white race, and older age at the visit were more common in patients with MDA vs. SDA (p=0.002, p=0.02, p=0.03, respectively, Table 2). MDA patients also reported a higher prevalence of self-reported asthma vs. SDA (39% vs. 15%, p=0.0002, Table 2). There was no difference in allergic rhinoconjunctivitis or the presence of concomitant angioedema in SDA vs. MDA CSU sub-populations. Overall, there was no difference in patient-reported latex allergy or contact dermatitis in CSU by drug allergy (drug allergic vs. no drug allergies and MDA vs. SDA).

4. DISCUSSION

The present study indicates that CSU patients have a significantly higher prevalence of self-reported drug allergies compared to the general population (56% vs. 15-25%). Moreover, a high percentage of CSU patients reported MDA, 57% of drug allergic CSU, with 23 reporting allergy to ≥ 5 medication types. We speculate that many of these patients may be misdiagnosed with drug allergy due to their underlying CSU.

Penicillin was the most common drug allergy reported in our CSU cohort, similar to Silverman *et al.* [4]. We observed a higher prevalence of reported penicillin allergy (18.2%) compared to 10% reported in the general population [5]. Interestingly, urticaria was the most commonly reported reaction in our CSU cohort. In our CSU patients with penicillin allergy, 68% reported additional drug allergies, similar to the 70.9% reported by Silverman *et al.* [5]. NSAID hypersensitivity was reported in approximately 13% of our CSU patients, which is similar to the confirmed rate reported in Sanchez's CSU cohort [6].

In our study, asthma was reported in 29% of our drug allergic CSU patients, with the MDA CSU patients having the highest reported asthma prevalence (39%). This is higher than the reported asthma rates in our region and two other CSU cohorts in different regions (10-14%) [6-8]. This discrepancy could be due to selection bias as patients were evaluated at an allergy/asthma clinic instead of other clinics, such as dermatology or primary care. We also speculate that many of the patients that reported asthma may actually have vocal cord dysfunction (VCD), consistent with our prior report of the misdiagnosis of asthma in 42% of patients with VCD [9]. Additionally, we previously reported a higher prevalence of drug allergy in VCD compared to asthma and control groups [9]. As these patients were seen for urticaria, VCD diagnosis was not assessed in this cohort. Atopy did

not differentiate drug allergy in CSU, similar to the lack of relationship between atopy and drug allergy in the general population [4].

The current study identified several novel clinical features of drug allergy in CSU. While Lokaj-Berisha *et al.* found a higher BMI in urticaria patients vs. controls [10], our study has uniquely identified a higher BMI in drug allergic CSU patients vs. CSU without drug allergies. Additionally, we identified older age in association with drug allergy in CSU (both drug allergic CSU vs. CSU without drug allergy and MDA CSU vs. SDA CSU). As overall medication use may be greater in patients with older age and increased BMI, in these CSU patients, a drug allergy label may create diagnostic dilemmas for clinicians treating these patients.

One significant limitation of a "real-world" study is the use of self-reported drug allergies, known to be over-reported. Silverman *et al.* also used self-reported drug allergies in their urticaria study [5]. Additionally, skin and drug provocation testing were not performed. Furthermore, evaluation for drug allergy in a chronic urticaria patient population is challenging as most patients are unable to discontinue high dose antihistamines for testing. Although we did not investigate patients with isolated angioedema, there were no differences in the presence of comorbid angioedema in drug allergic vs. NDA CSU (62% vs. 62%) nor for those CSU patients with single vs. MDA (63% vs. 61%).

CONCLUSION

In summary, we show a high rate of reported drug allergies and asthma in our CSU cohort. The drug allergy label can lead to less efficacious and more costly alternative therapies. Furthermore, asthma diagnosis may interfere with provocation testing. Physicians who care for these patients need to take detailed drug allergy and asthma histories. Evaluation of these patients is complex because chronic antihistamine therapy, which is a mainstay of chronic urticaria treatment, precludes gold criterion allergy testing. When CSU is in remission, and patients are able to stop antihistamine therapy, the diagnosis of drug allergy should be further investigated with testing to prevent the morbidity associated with the drug allergy classification in chronic urticaria. Ultimately, better ways of evaluating the incidence of true drug allergy in CSU are needed.

LIST OF ABBREVIATIONS

BMI	=	Body Mass Index
CSU	=	Chronic Spontaneous Urticaria
F	=	Female
IV	=	Intravenous
M	=	Male
MDA	=	Multiple Drug Allergies
NDA	=	No Drug Allergies

NSAID = Nonsteroidal Anti-inflammatory Drugs

SDA = Single Drug Allergy

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective study was approved by the Institutional Review Board at the University of Pittsburgh Pennsylvania, USA [PRO14110320].

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The study on humans was conducted in accordance with the ethical rules of the Helsinki Declaration and Good Clinical Practice.

CONSENT FOR PUBLICATION

Written consent were obtained from the patients.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

FUNDING

None

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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Declared none.

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