

Basophil histamine release activity and disease severity in chronic idiopathic urticaria

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Background: Altered basophil degranulation phenotypes are found in patients with chronic idiopathic urticaria (CIU).

Objective: To evaluate CIU disease severity in relation to basophil histamine release (HR) characteristics.

Methods: Patients with CIU were recruited from allergy and dermatology clinics. Patients with recent use of systemic corticosteroids or immunosuppressants were excluded. Patients completed disease severity surveys and had blood basophils isolated and stimulated for HR using polyclonal goat anti-human IgE and N-formyl-met-leu-phe. The HR was measured using automated fluorometry. Multivariate linear regression analyses were used to investigate relationships between HR data and CIU disease measures.

Results: Fifty patients completed surveys, of which 34 were further categorized into 2 subgroups based on basophil HR response to anti-IgE stimulation: responders ($\geq 10\%$ HR) and nonresponders ($< 10\%$ HR). Responders and nonresponders reported similar use of oral corticosteroids, work absences, and quality-of-life impairment but differed in their patterns of medications used for CIU. Basophil responders had a trend of higher use of the emergency department for CIU management. Multivariate regression revealed that patients with the basophil responder phenotype experienced significantly higher current itch scores ($P = .02$) compared with nonresponders.

Conclusions: Quality-of-life impairment is similar in CIU basophil subsets. Patients with CIU with a basophil responder phenotype report longer disease duration, a higher frequency of emergency department use, and significantly higher itch severity.

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INTRODUCTION

Chronic idiopathic urticaria (CIU) is a skin disorder characterized by recurrent erythematous wheals and intense itching, with or without angioedema, for at least 6 to 8 weeks, and it can persist for years.^{1,2} The pathogenesis of CIU is not completely understood, but mast cell and basophil degranulation of histamine is thought to be of central importance.³ In the past decade, CIU with certain serologic features has been termed *chronic autoimmune urticaria*.⁴ Specifically, up to 30% of patients with CIU have circulating IgG autoantibodies targeting the IgE receptor α -chain (Fc ϵ RI α), whereas approximately 10% have IgG targeting IgE expressed on the surface of basophils and mast cells.⁵ Other studies⁶ have found that 40% of patients with CIU have serum that contains histamine-releasing activity (HRA) as measured by in vitro testing against normal donor basophils. However, these 2 serum factors (HRA and autoantibodies to IgE or Fc ϵ RI α) often do not coexist in the same individual and have led to confusion

as to the serologic classification of autoimmune CIU.⁶ Furthermore, attempts to classify CIU disease severity relative to serologic factor expression have been hampered by the lack of a widely accepted standard assay.^{7,8}

It is well established that basophils of patients with CIU have altered IgE receptor-mediated degranulation.^{9,10} Recently, Vonakis et al¹¹ reported that ex vivo activation of blood basophils in patients with CIU with an optimal dose of cross-linking anti-IgE antibodies is segregated into 2 groups based on the degree of HR: responders and nonresponders. Patients with CIU with nonresponder basophils show depressed ($< 10\%$) HR, whereas basophils of patients with CIU with a responder phenotype show at least 10% HR. Furthermore, altered basophil protein expression of the Fc ϵ RI inhibitory phosphatases SHIP-1 and SHIP-2 correspond to the observed patterns of CIU basophil HR and impact the generation of downstream molecules (phosphoAkt) relevant to degranulation. Evidence also supports that basophil functional phenotypes are stable in patients with CIU and persistent disease symptoms.^{11,12}

Because of the chronic discomfort induced by pruritus, the anxiety induced by the relapsing course, the lack of a specific cause, and the social impairment linked to unpredictable attacks of pruritus and angioedema, it is expected that CIU affects the quality of life (QoL) of patients.^{13,14} In recent studies,¹⁵ Skindex-29 has been used to evaluate urticaria and noted that QoL is markedly reduced in patients with chronic urticaria. In the present study, we explore the relationship of defined CIU basophil functional categories (responder and nonresponder) to CIU disease severity as measured using

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disease survey instruments (Skindex-29 and the urticaria severity score [USS]).

METHODS

Patients

Adults (>18 years of age) diagnosed as having CIU were recruited from Johns Hopkins University allergy and dermatology clinics. The inclusion criterion was a specialist (allergist or dermatologist) diagnosis of active CIU. Patients who had used systemic corticosteroids or other immunosuppressants (cyclosporine or sulfasalazine) in the month before enrollment were excluded due to the known suppression of these drugs on basophil HR.¹⁶ Patients were also excluded if they were diagnosed as having another skin disease, such as urticarial vasculitis, atopic dermatitis, or physical urticaria, or had other etiologies for the urticaria, such as a chronic infection or medication allergy. After providing informed consent, patients completed a written disease severity questionnaire and underwent venipuncture via a protocol approved by the Johns Hopkins Hospital institutional review board.

Basophil Function

Blood basophils of patients were isolated from venous blood by means of dextran sedimentation and were stimulated for HR using polyclonal goat anti-human IgE (0.01–1.00 $\mu\text{g/mL}$) in duplicate using calcium-containing buffers, as described previously.¹¹ Based on an earlier study,¹¹ we found that the 0.1- $\mu\text{g/mL}$ concentration of anti-IgE is optimal to define basophil functional phenotypes. Cells were also stimulated using N-formyl-met-leu-phe (fMLP) (10^{-6}M) as a positive control for basophil degranulation because this pathway is generally preserved in basophils of patients with CIU.^{9,11} Automated fluorometry was used to measure HR.¹⁷ Results for each stimulus are reported as a percentage of the total histamine content found in an aliquot of lysed leukocytes derived from 1 mL of whole blood after subtraction of spontaneous HR from cells in buffer alone. Blood basopenia was noted in certain patients and was defined as total blood leukocyte histamine content of less than 5 ng/mL.

Disease Survey

The written questionnaire was composed of 3 elements: demographics and health care utilization, the USS, and the Skindex-29.¹⁸ The demographic section included age, sex, ethnicity, education, disease duration, family history of urticaria, number of days absent from work or school, number of visits to the emergency department (ED), number of systemic corticosteroid courses, and the type of medications used to treat CIU.

The second element was the USS, a survey used in various forms in many clinical studies and trials in CIU.^{19–22} This survey includes urticarial wheal characterization, itch severity, wheal distribution, systemic symptoms, and wheal duration.²³ The USS was calculated as follows: urticarial activity was estimated according to the number of wheals present at the evaluation time and during a flare of disease. Wheals were scored as follows: 0, no wheals; 1, 1 to 10 small wheals

(<3 cm in diameter); 2, 10 to 50 small wheals or 1 to 10 large wheals; 3, more than 50 small wheals or 10 to 50 large wheals; and 4, almost fully covered with wheals. Current itch score is the patient's rating of itch severity based on a visual analog scale scored from 0 to 10 (none to severe). Itch severity at its worst was scored on a similar visual analog scale. The distribution of the wheals was scored 1 each for involvement of the face, mouth or tongue, scalp, trunk, limbs, palms, and soles (maximum score, 7). Associated symptoms were scored 1 each as follows (maximum score, 6): (1) nausea, diarrhea, abdominal pain, or indigestion; (2) wheeze or breathlessness; (3) palpitations; (4) flushing; (5) joint pain or joint swelling; and (6) headache, malaise, and lassitude.²³ Wheal duration was scored on a 3-point scale as follows: less than 1 hour, 1 to 24 hours, and greater than 24 hours.²³

The third element of the questionnaire was Skindex-29, a validated 29-question dermatology survey assessing the impact of skin disease on QoL in the past 3 months. The scoring of Skindex divides the questions into specific categories: emotions, symptoms, and functioning. The scale score is a mean average in each category.

Statistical Analyses

All the statistical analyses were performed using Stata version 8.0 (StataCorp, College Station, Texas). Multivariate linear regression was used to investigate the relationship between basophil functional data and symptom severity measures while controlling for potential confounders. We considered 3 primary outcome variables: current itch severity, itch severity during a flare, and Skindex-29 score. Comparisons among basopenic patients, nonresponders, and responders were performed using an unpaired *t* test, with *P* < .05 considered statistically significant.

RESULTS

Basophil Functional Characteristics

Of the 50 patients who enrolled in the study, 46 provided a usable blood sample for basophil analysis (Table 1). Patients with CIU were divided into 2 groups based on the basophil degranulation achieved with optimal stimulation with anti-IgE (0.1 $\mu\text{g/mL}$): CIU nonresponders (CIU-NRs) (<10% release of total leukocyte histamine content) and responders (CIU-Rs) (>10% release of total leukocyte histamine content).¹¹ Thirty-four patients had measurable basophil function that could be categorized into CIU-NR (*n* = 15) or CIU-R (*n* = 19) (Table 1). Of the remaining 12 patients who submitted a blood sample, blood basophils could not be classified due to significant basopenia (*n* = 8) (see the "Methods" section) or other technical reasons (*n* = 4), such as the detection limits of the assay system. Significant basopenia has long been recognized in this disease^{9,10,24} and was reflected in this study as reductions in the histamine concentration present in a lysed aliquot of leukocytes representative of 1 mL of whole blood (Table 1). The pattern of fMLP responses seen in study patients with CIU was similar to that previously observed.^{9,11} It is

Table 1. Basophil Functional Characteristics of 50 Patients With CIU

Patient No.	Histamine concentration, ng/1 mL blood leukocytes	Anti-IgE (0.1 µg/mL), % histamine release	CIU category	fMLP (10 ⁻⁶ M), % histamine release
1	<0.5	ND1	NA	ND1
2	Survey only	NA	NA	NA
3	37.3	40	R	2
4	13.25	4	NR	8
5	6.4	8	NR	0
6	23.25	8	NR	10
7	38.05	31	R	67
8	41.15	3	NR	31
9	26.85	52	R	48
10	1.2	ND1	NA	ND1
11	30.5	65	R	47
12	1.7	ND2	NA	ND2
13	3.55	0	NR	10
14	Survey only	NA	NA	NA
15	16.8	17	R	20
16	13.5	13	R	7
17	<0.5	ND1	NA	ND1
18	12.7	18	R	1
19	Survey only	NA	NA	NA
20	34.05	1	NR	0
21	37	12	R	75
22	5.5	ND2	NA	ND2
23	1.1	ND2	NA	ND2
24	1.2	ND2	NA	ND2
25	17.2	0	NR	0
26	2.3	ND1	NA	ND1
27	0.7	ND1	NA	ND1
28	19.45	1	NR	20
29	13.25	61	R	68
30	<0.5	ND1	NA	ND1
31	Survey only	NA	NA	NA
32	18.25	24	R	35
33	12.05	0	NR	15
34	28.15	0	NR	47
35	62.45	1	NR	56
36	13.34	58	R	22
37	19.05	10	R	45
38	39.95	1	NR	32
39	26.7	27	R	59
40	0.5	ND1	NA	ND1
41	25.6	44	R	61
42	37.9	28	R	17
43	49.85	0	NR	43
44	20.5	3	NR	32
45	76.75	59	R	23
46	30.25	55	R	48
47	14.1	24	R	10
48	2.5	ND1	NA	ND1
49	24.7	0	NR	20
50	7.85	64	R	55

Abbreviations: CIU, chronic idiopathic urticaria; fMLP, N-formyl-met-leu-phe; NA, not applicable; ND1, not detectable by assay measurement; ND2, not detectable because of technical instrument error; NR, nonresponder; R, responder.

known that fMLP is an independent biological response and does not necessarily match the release generated by anti-IgE. For example, patient 3 (a CIU-R) has an fMLP-induced response of 2%, with an anti-IgE response of 40%. Vonakis et al¹¹ reported that the fMLP response from CIU-NR basophils is significantly reduced relative to CIU-R basophils.

Patient Demographics

A total of 50 adults were enrolled and provided complete surveys for analysis. Patient characteristics are given for all enrolled patients based on their defined basophil functional category or based on basopenia (Table 2). Most of the patients (74%) were female, with a mean age of 44 years. It was noted that 20% of all patients have a family history of hives. Among the basophil functional categories and basopenic patients, CIU-Rs were significantly less likely to be white and were more likely to have a CIU disease duration greater than 4 years compared with CIU-NRs.

Measures of Disease Burden

Among the notable measures of disease burden in study patients with CIU was the frequent use of rescue systemic corticosteroids (Table 2). Nearly half of the patients reported using at least 1 corticosteroid course in the previous year, and nearly three-quarters reported corticosteroid use during the

lifetime of their CIU disease. All the basopenic patients reported corticosteroid use during their CIU condition. The frequency of ED visits for CIU treatment trended higher in CIU-Rs compared with CIU-NRs in the past year (33% vs 14%; $P = .16$) and during the lifetime of CIU disease (72% vs 43%; $P = .08$). Patients with basopenia also had a higher frequency of ED visits than CIU-NRs. More than half of the patients reported a work or school absence related to CIU, and this occurred at similar frequencies among basophil functional categories and was highest in basopenic patients. Regarding medication use, all the patients have taken antihistamines to control symptoms. Past medication use in the subgroups was different. The CIU-Rs predominantly used oral corticosteroids with antihistamines, whereas the CIU-NRs predominantly used antihistamines, oral corticosteroids, tricyclic antidepressants, and antileukotrienes, in descending order. In the CIU-NR and basopenic groups, there was a higher reported use of leukotriene antagonists and tricyclic antidepressants, such as doxepin, for CIU symptoms compared with in the CIU-R group.

QoL Measures

The impairment of QoL was examined using Skindex-29 measures. The degree of impairment in the 3 categories of emotional, functional, and symptoms was similar between the 2 groups based on basophil functional category (data not shown).

Table 2. Characteristics of Patients With CIU

Characteristics	Total (N = 50)	Basopenic patients (B) (n = 8)	Nonresponders (NR) (n = 15)	Responders (R) (n = 19)	P value NR:R; B:NR; B:R
Age, mean $\pm$ SD, y	44 $\pm$ 16	39.3 $\pm$ 15.6	43.3 $\pm$ 18.4	42.0 $\pm$ 14.9	.41; .35; .29
Female sex, %	74	87.5	87	63	.06; .054; .08
White, %	68	75	87	47	.01; .41; .01
Family history of urticaria, %	20	12.5	7	17	.19; .34; .40
CIU disease duration >4 y, %	52	37.5	47	74	.10; .20; .053
>1 Corticosteroid taper in the past 1 y, %	53	87.5	46	44	.11; .09; .007
>1 Corticosteroid taper in CIU lifetime, %	76	100	71	77	.32; .046; .007
>1 Visit to the ED for CIU in the past 1 y, %	28	50	14	33	.16; .055; .11
>1 Visit to the ED in CIU lifetime, %	60	75	43	72	.08; .02; .09
>1 d of work or school absence in the past 1 y, %	59	87.5	64	53	.16; .15; .04
>1 d of work or school absence in CIU lifetime, %	70	100	71	71	.44; .006; .009
Oral corticosteroids used for CIU, %	70	100	64	72	.21; .004; .01
Antihistamines used for CIU, %	100	100	100	100	
Antileukotrienes used for CIU, %	22	50	36	11	.07; .24; .04
Antidepressants used for CIU, %	44	75	57	11	.001; .35; .004
Current wheal size/number score, mean $\pm$ SD	1.13 $\pm$ 1.20	2.13 $\pm$ 1.36	0.86 $\pm$ 0.95	1.08 $\pm$ 1.27	.29; .02; .04
Wheal size/number score during an urticarial flare, mean $\pm$ SD	2.34 $\pm$ 1.15	2.875 $\pm$ 1.46	2.50 $\pm$ 1.02	2.00 $\pm$ 1.12	.10; .27; .08
Itch during an urticarial flare, mean $\pm$ SD	8.71 $\pm$ 2.20	9.71 $\pm$ 0.76	8.93 $\pm$ 2.67	8.11 $\pm$ 2.31	.18; .16; .007
Wheal locations during an urticarial flare, mean $\pm$ SD, No.	4.53 $\pm$ 1.72	4.88 $\pm$ 1.64	4.64 $\pm$ 1.74	4.68 $\pm$ 1.77	.47; .38; .40
Systemic symptoms during an urticarial flare, mean $\pm$ SD, No.	1.43 $\pm$ 1.53	2.5 $\pm$ 1.60	1.21 $\pm$ 0.97	1.47 $\pm$ 1.87	.30; .03; .08
Wheal duration, mean $\pm$ SD	2.25 $\pm$ 0.60	2.38 $\pm$ 0.52	2.29 $\pm$ 0.73	2.17 $\pm$ 0.62	.31; .37; .19

Abbreviations: CIU, chronic idiopathic urticaria; ED, emergency department.

Current Disease Activity and Basophil Characteristics

Regarding disease activity as measured using the USS, a similar number of wheals at the time of assessment was noted between basophil functional categories and was greatest in basopenic patients (Table 2). Likewise, the characterization of an urticarial flare in terms of number of wheals, itch, number of wheal locations, systemic symptoms, and average individual wheal duration was similar among the basophil functional categories. Urticarial flares in basopenic patients were characterized as having greater itch and systemic symptoms. However, in response to a measure of instantaneous disease activity, current itch, we noted a significant difference between the basophil CIU-R and CIU-NR groups (score, 3.36 and 0.92, respectively; $P = .02$), with a difference of 2.44 (Fig 1). The higher itch score reported by CIU-Rs occurred despite a similar number of reported current wheals. Basopenic patients also had significantly higher current itch than CIU-NRs, despite a similar reported pattern of medication use.

DISCUSSION

The findings of this disease survey of patients with CIU support that these patients have a significant disease burden based on the number of ED visits, health care utilization, work absences, and use of systemic corticosteroids. We noted that a subset of patients with CIU with a basophil responder phenotype experienced heightened itch and increased use of the ED compared with patients with a nonresponder basophil phenotype.

Previous studies have shown that patients with CIU with antibodies against IgE or IgE receptor have more severe disease²³; however, the assays used to establish autoimmunity are not standardized to allow for widespread use of such biomarkers. We simultaneously evaluated a patient's CIU disease severity

with measures of basophil HR. To our knowledge, this is the first attempt to relate CIU disease severity to the function of a cell implicated in the disease pathogenesis. Given the prominence of pruritus as a symptom of CIU, we compared current itch report at the time of the questionnaire with categories of basophil degranulation. In recent investigations^{11,12} of CIU basophils, basophil functional categories were stable across time in individuals with active disease. We have also seen that CIU-R basophils have reduced SHIP-1 protein levels, an inhibitor in the FcεRI histamine degranulation pathway, compared with healthy donor basophils and CIU-NR basophils. This finding may contribute to higher HR and itch scores in CIU-Rs compared with CIU-NRs despite a similar number of wheals and medication use at survey evaluation.¹¹ In contrast to CIU-R and healthy basophil donors, CIU-NR basophils have higher protein levels of SHIP-1 and SHIP-2, leading to reduced histamine degranulation via the IgE receptor.¹¹ This basophil signaling abnormality in CIU-NR may contribute to a lower itch score. There was similar use of antidepressants and leukotriene antagonists by CIU-NRs and basopenic patients, yet CIU-NRs had much lower current itch scores.

Newer assays using CIU serum to induce expression of basophil surface activation markers have been developed to assist in defining "autoimmune" CIU; however, they rely on individual donor basophils and are not currently standardized.²⁵ Given the lack of disease markers in CIU and of a well-established assay for serologic factors, CIU basophil functional profiles are attractive markers for exploring different clinical subsets of CIU. The present data imply that patients with CIU basophil responder phenotype have features consistent with more active disease, such as increased ED visits and longer disease duration. These data also suggest that patients with significant basopenia experience increased disease severity, as noted by the frequent use of oral corticosteroids and work absences. CIU-NRs and basopenic patients also have an increased history of leukotriene antagonist and antidepressant drug use. An analysis of the indirect and direct medical costs in this same population revealed that most costs are related to the large number of medications used to control symptoms.²⁶ We did not directly evaluate the socioeconomic status of these patients and the potential impact it may have on the medication differences noted in basophil groups.

A limitation of this study is the ability to record basophil function. Of 46 blood samples, only 34 could be classified due to the basopenia and other technical issues. Because of the exclusion of patients actively receiving immunosuppressive medicines or systemic corticosteroids, we likely have excluded individuals with high disease severity. A larger sample size is required to attain significance given the large number of variables evaluated by the questionnaire. Although the survey asked about medication use, it did not evaluate the effectiveness of each class of medication. We have now amended the survey to evaluate current medication use and efficacy. The literature review initially revealed a specific CIU questionnaire, the USS, that was included as part of this study. However, the USS addresses the patient's subjective

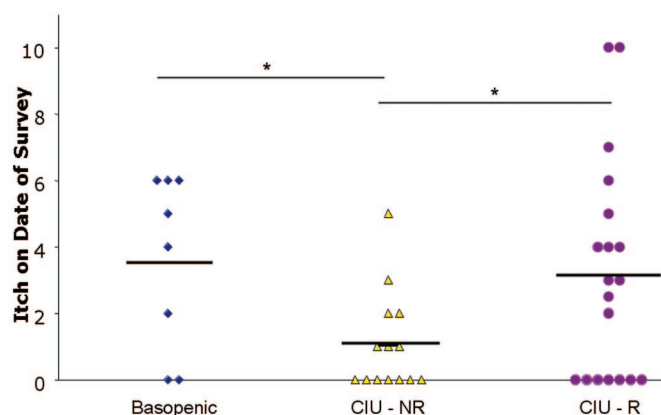


Figure 1. Current itch severity scores. Significant differences in current itch exist between patients with chronic idiopathic urticaria (CIU) based on responder (CIU-R) and nonresponder (CIU-NR) status. Mean itch severity: NR, 0.92 and $r = 3.36$; mean difference, 2.44 ($*P = .03$ after controlling for potential confounders, such as race, sex, disease duration, and family history). Basopenic patients also had higher itch scores (3.92) compared with CIU-NRs ($*P < .03$). Horizontal bars indicate means for each group.

symptom scores. We added several questions to evaluate the number of medications, onset of disease, disease duration, family history, and health care utilization. Skindex-29 has been used to evaluate urticaria in previous studies and noted that QoL is markedly reduced in patients with chronic urticaria. However, Skindex is a skin-specific and not a urticaria-specific QoL instrument and, thus, may not be sensitive enough to detect differences in urticaria populations. Since study initiation, Baiardini et al²⁷ created a health-related QoL (HRQoL) tool specifically designed for chronic urticaria (Chronic Urticaria Quality of Life Questionnaire). Staubach et al¹⁵ noted that social functioning and emotions were the areas of QoL most affected in patients with chronic urticaria. Grob et al²⁸ used a French HRQoL survey and discovered that chronic urticaria severely impairs HRQoL at the same level as psoriasis or atopic dermatitis on certain dimensions. Overall, patients with CIU have a significant disease burden independent of their basophil phenotype. However, the CIU basophil responder group has features consistent with a more severe disease based on ED use and increased current itch scores that may be related to shifts in the FcεRI pathway to histamine degranulation in their basophils. The implications of the existence of CIU subsets are to improve the selection of effective medication classes and patient information regarding the impact of the disease on their QoL.

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