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 (≥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 (FcεRIα), whereas approximately 10% have IgG targeting IgE expressed on the surface of basophils and mast cells.[5] Other studies[6] 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 FcεRIα) 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 al[11] 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 FcεRI 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 μg/mL) in duplicate using calcium-containing buffers, as described previously.[11] Based on an earlier study,[11] we found that the 0.1-μg/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 μg/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