

ORIGINAL ARTICLE

Clinical utility of testing for autoimmunity in chronic idiopathic urticaria

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Background: Positive autoimmune testing in patients with chronic idiopathic urticaria (CIU) has previously been associated with more severe disease.

Objective: We sought to determine whether patients with CIU and a positive autoimmune urticaria test finding were more difficult to treat clinically.

Methods: In this retrospective study, 428 patients seen by physicians of the Department of Dermatology, University of Pittsburgh between January 2007 and March 2010 were identified by *International Classification of Diseases, Ninth Revision* code 708.9 for urticaria. Included individuals met clinical criteria for CIU and had an autoimmune urticaria test (chronic urticaria index or CD203 expression test) result in their medical record.

Results: Twenty patients met the study criteria set forth and positive autoimmune urticaria test results occurred in 8 of the 20 patients. In all, 75% of patients in each group (positive and negative autoimmune test findings) were more than 75% clear of disease ($P = 1$) by the last visit. Mean number of distinct medications prescribed for urticaria management in the positive and negative autoimmune groups was 6.9 and 8.4, respectively ($P = .4$). No significant difference was detected between the various medications that led to more than 75% disease clearance in either group. The mean number of patient clinic visits over the study period was 3.1 and 4.8, respectively, for positive and negative groups ($P = .5$).

Limitations: This was a retrospective study with a small sample size.

Conclusion: A positive autoimmune urticaria test finding in the setting of CIU is not indicative of a more complicated clinical course. (J Am Acad Dermatol 10.1016/j.jaad.2010.11.030.)

Key words: autoimmune urticaria test; autoimmunity; CD203 expression test; chronic idiopathic urticaria; chronic urticaria index; IgE antibodies.

Urticaria is a common dermatologic condition, characterized by erythematous wheals caused by mast cell degranulation and histamine release. Approximately 15% to 25% of the population is affected at some point in their lifetime causing a significant disturbance in quality of life.^{1,2} Chronic urticaria (CU) refers to continuous or

Abbreviations used:

ANA: antinuclear antibody
CBC: complete blood cell count
CIU: chronic idiopathic urticaria
CU: chronic urticaria
FcεRI: High Affinity IgE Receptor
HRA: histamine release activity

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intermittent wheals existing for 6 or more weeks that may be caused by physical stimuli, allergy, systemic illness, drugs, or infection.¹ However, in the majority of cases (80%-90%), no eliciting cause is identified.¹ Recently, leading authorities Kaplan and Greaves³ advocate there is no evidence of an exogenous allergen as the cause of CU. In addition, after physical urticaria and urticarial vasculitis are eliminated from consideration CU may be divided into chronic autoimmune urticaria (45%) and chronic

idiopathic urticaria (CIU) (55%).³ A thorough workup for patients with CU includes a history and physical, with attention to temporal associations and symptoms of coexisting autoimmune disease (specifically autoimmune thyroid disease). Laboratory workup may include a complete blood cell count (CBC) with differential, thyroid autoantibodies, and thyroid function testing, in addition to testing for circulating antibodies to the α -chain of the high affinity IgE receptor (Fc ϵ RI) for IgE on mast cells and basophils. As many as 30% to 50% of patients with CIU are thought to have an autoimmune cause of histamine release leading to recurrent hives.^{1,4} The identification of autoimmune pathology in some patients with CIU gives them an explanation for symptoms and may provide the rationale for clinicians to select more aggressive immunosuppressive therapy.

Commercial laboratory testing to detect autoimmune causes of CIU has been available to clinicians for approximately 3 years. The gold standard for determining an autoimmune cause of CU is the histamine release activity (HRA) assay.⁵⁻⁸ The HRA assay, which is equivalent to the CU index developed by IBT Laboratories (Lenexa, KS), detects “functional” autoantibodies and release factors by measuring histamine release when healthy basophils from a non-CIU population are incubated with the patient’s serum. A positive CU index is 10% or higher. The index value correlates with amount of histamine that was released.⁹ Developed by the National Jewish Laboratories (Denver, CO), the CD203 expression test is an alternative commercial test available. It uses flow cytometry to detect CD203 expression on basophils and mast cells. The CD203 expression correlates with HRA by unregulated cross-linking of the Fc ϵ RI receptor and a result greater than 5% is considered positive.¹⁰

The purpose of this study was to evaluate if the application of commercially available autoimmune urticaria testing in clinical practice has usefulness in predicting patient response to treatment and the nature of the treatment course.

METHODS

After obtaining approval from the institutional review board, adult patients seen by physicians of

the Department of Dermatology, University of Pittsburgh between January 2007 and March 2010 were identified by *International Classification of Diseases, Ninth Revision* code 708.9 for urticaria. Individuals were included in the study if they met clinical criteria for CIU (characteristic wheals lasting <24-48 hours occurring most days for >6 weeks,

without a physical urticaria or urticarial vasculitis) after a thorough history, physical examination, and laboratory testing for HRA assay documented in their medical record. Patients may also have had a screening CBC with differential, thyroid autoantibodies, thyroid function tests, or biopsy. Data extracted from the medical record included: patient demographics, medical history, medication records, appointment frequency, and response to treatment. Reviewed laboratory evaluation included: CBC with differential, CU index or CD203 expression, thyroid-stimulating

hormone, thyroglobulin antibody, thyroid peroxidase antibody, and antinuclear antibody (ANA). Information was entered into 2007 Microsoft Excel database program (Microsoft Corporation, Seattle, WA).

Patients were separated into two groups, positive and negative autoimmune test result based on a positive result for either CD203 expression or CU index testing. A greater number of distinct medications, a greater proportion of second- or third-line agents used, or a greater number of clinic visits may represent more difficult disease to control or resistance to therapy. For this reason, the mean total distinct medications were calculated for each group and variance was assessed using the Mann-Whitney U test. Medications were separated into first-line therapies such as anti-histamine/leukotriene inhibitors, and second-line agents such as anti-inflammatory/immunomodulators (ie, cyclosporine, mycophenolate mofetil, azathioprine, colchicine, hydroxychloroquine, dapsone, famotidine, nifedipine, atenolol) and the mean medications in each therapy category was calculated per patient group. The level of disease control at last visit was assessed and patients were classified as: (1) “poor” if disease persisted or was less than 75% clear; (2) “good” if disease occurred sporadically or was better than 75% clear; or (3) “clear” if disease resolved. The proportion of patients more than 75% clear in the

CAPSULE SUMMARY

- Chronic idiopathic urticaria with a positive autoimmune urticaria test result has been reported to be associated with more extensive disease.
- Patients with chronic idiopathic urticaria and a positive autoimmune urticaria test result in this study had no statistically significant difference in the complexity of their clinical treatment.
- Obtaining an autoimmune urticaria test in chronic idiopathic urticaria may help identify the root cause of the disease process but is not essential for the clinical management of the urticaria.

Table I. Characteristics of chronic idiopathic urticaria study population

Patient characteristics*	Female	Male	Total
Patients, No. (%)	18 (90)	2 (10)	20
Mean age, y	51.1	46.5	50.7
CD203, ratio +/total tested (%)	2/4 (50)	1/1 (100)	3/5 (60)
CU index, ratio +/total tested (%)	5/14 (36)	0/1 (0)	5/15 (33)
Combined autoimmune test, ratio +/total tested (%)	7/18 (39)	1/2 (50)	8/20 (40)

CU, Chronic urticaria.

*Other comorbidities (No. of patients): hypertension (6), endometriosis (2), hypothyroidism (3), coronary artery disease (1), hyperlipidemia (3), glaucoma (1), macular degeneration (1), peptic ulcer disease (2), asthma (1), diverticulitis (1), blood clots (2), osteoarthritis (1), osteoporosis (1), tinea versicolor (1), and depression (1).

Table II. Mean distinct medications documented in medical record per patient with positive and negative autoimmune urticaria test results

Measured distinct prescription	+ Autoimmune test (n = 8)	– Autoimmune test (n = 12)	P value (<.05 significant)
Mean total distinct medications	6.9	8.4	.4
Antihistamine/leukotriene inhibitor	5	5.9	.4
Anti-inflammatory/immunomodulator	1.0	1.4	1.0

positive and negative autoimmune groups were compared using Fisher exact test. The current medications to which patients responded well and achieved greater than 75% clearance in each group was assessed and compared using Fisher exact test. The total numbers of visits for each patient were recorded and the mean visits per patient group were calculated and compared with the Mann-Whitney U test.

RESULTS

Of the 20 patients who met inclusion criteria, 18 were female (90%) and two were male (10%) (Table I). The mean patient age at the time of chart review was 50.7 years (51.1 years for women, 46.5 years for men). Fifteen patients were tested for CU index and 5 of these patients had positive findings (33%). Five patients underwent CD203 expression testing and 3 of the 5 had positive results (60%). For each patient, an autoimmune urticaria test/IgE antibody test was ordered. Whether a CD203 expression test or CU index was ultimately obtained was a function of the laboratory chosen by the patient. Overall, 8 of the 20 patients had a positive test result (40%), suggesting an autoimmune cause to their disease (Table I).

No patient had evidence of leukocytosis or peripheral eosinophilia. Eighteen of the 20 patients had biopsy specimens demonstrating urticaria. Each of the 3 patients tested for ANA in the positive autoimmune group had an ANA greater than or equal to 1:80 and did not meet criteria for systemic lupus erythematosus. None of the 9 patients in the negative autoimmune group had a positive ANA

($P < .05$). Three patients (15%) had a history of hypothyroidism; however, no additional history of autoimmune disease was discovered on the search of patient medical histories. All of the 3 patients with a history of hypothyroidism had a positive autoimmune urticaria test result ($P < .05$). Thyroid autoantibodies were positive in 2 of 3 patients with hypothyroidism in the positive autoimmune group (none had active thyroiditis) and none of 7 patients in the negative autoimmune group were positive.

The means of the total distinct medications were 6.9 and 8.4 for positive and negative autoimmune groups, respectively ($P = .4$). The means of antihistamines/leukotriene inhibitors per patient were 5 and 5.9, respectively, for positive and negative autoimmune groups ($P = .4$). The mean anti-inflammatory/immunomodulator agents per patient were 1 and 1.4, respectively (Table II) ($P = 1$).

In all, 75% (6 of 8) of patients with a positive autoimmune test result were more than 75% clear at last visit, whereas 9 of 12 patients (75%) with a negative autoimmune test finding were more than 75% clear (Table III) ($P = 1$). Isolating only the patients with disease clearance greater than 75% (Table IV), 50% of patients with positive autoimmune test result achieved disease clearance with antihistamine/leukotriene inhibitor use and 50% with anti-inflammatory/immunomodulator agents. Patients with negative autoimmune test findings improved to better than 75% clearance in 44% of cases with antihistamine/leukotriene inhibitor use and 56% with anti-inflammatory agent/immunomodulator agents. The mean number of patient clinic

Table III. Level of disease control at last examination in patients with positive versus negative autoimmune urticaria test result

Current level of control	+ Autoimmune test (n = 8)	– Autoimmune test (n = 12)
Clear, No. (%)	2 (29)	4 (33)
Good (>75% clear), No. (%)	4 (57)	5 (42)
Poor (<75% clear), No. (%)	1 (12.5)	3 (25)
Lost to follow-up	1 (12.5)	0 (0)

visits over the 3-year study period was 3.1 and 4.8, respectively, for positive and negative autoimmune groups ($P = .5$). Using identical study parameters, no difference between patients with a positive CD203 expression or CU index was found when they were directly compared against each other.

DISCUSSION

The initial indication that CIU pathology of some patients is a result of autoimmune phenomena was the induction of immediate wheal and flare response in patients who received an intradermal injection of autologous serum by Malmros¹¹ in 1946. This process, known as the autologous serum skin test, although not a standardized test, has been used diagnostically for many years in patients with CIU.¹² Further study revealed histamine release inducing IgG autoantibodies to the α -chain of the Fc ϵ RI receptor for IgE on mast cells/basophils. These antibodies have been demonstrated in 30% to 50% of patients with CIU.^{1,13-15} IgG antibodies to the IgE molecule itself have been identified in a small (10%) subset of patients with CIU.¹³ Currently, the known autoantibodies fail to explain the mechanism of action in the remainder of patients suspected of having autoimmune CIU. Further mechanisms are suspected such as basopenia, functional mast cell/-basophil defects, and unidentified serum histamine release factors.^{12,16-18}

Numerous different approaches have been taken to identify patients with an autoimmune cause of urticaria in clinical practice and in study settings. One approach has been to characterize basophil phenotypes based on its *ex vivo* degranulation response to polyclonal anti-IgE substrate. Basophils from patients with CIU have reduced histamine release compared with healthy subjects.¹⁷ Another approach is to use Western blot to detect antibodies to the Fc ϵ RI receptor and IgE molecule itself, however, these antibodies have been identified in other skin diseases and healthy subjects and their role in CIU is not clear.¹⁹ As previously described, the autologous serum skin test has been used since 1946 in various

Table IV. Medication class associated with more than 75% disease control in patients with positive versus negative autoimmune urticaria test result

Medication class associated with control >75%	+ Autoimmune test (n = 6)	– Autoimmune test (n = 9)
Antihistamine/leukotriene inhibitor, No. (%)	3 (50)	4 (44)
Anti-inflammatory/immunomodulator, No. (%)	3 (50)	5 (56)

settings.^{11,12} The basophil HRA assay is commercially available and is currently considered the gold standard for identifying autoimmune urticaria.^{4-6,9,20} The CD203 expression test is also commercially available and is 77% sensitive and 82% specific. Unfortunately, when each test was applied to the same group of patients none of the above evaluations consistently identify the same patient subset. A number of studies have been conducted to support each method; however, to date, it remains unclear which test most accurately identifies patients with autoimmune urticaria.^{6,7,17,21-23}

According to the literature, an estimated 30% to 50% of all patients with CIU have an underlying autoimmune cause of disease.^{1,4} In studies, autoantibodies via HRA assay to the Fc ϵ RI receptor have been demonstrated in 30% to 40% of patients with CIU.^{4,13-15} In our patient group, 40% exhibited autoantibodies to the Fc ϵ RI receptor, identified with either the CU index or the CD203 expression test.

Although patients with and without positive autoimmune test findings may present similarly and have identical histology,^{23,24} a correlation between HRA assay positivity and worse disease was demonstrated by Sabroe and Greaves.²³ This study involved sera collection and interviews of 78 patients with CIU, 15 patients with dermatographism, 10 patients with cholinergic urticaria, and 39 healthy subjects. The serum of each patient was tested using HRA assay, Western blot, and autologous serum skin test. CIU severity was determined based on the presence or absence of subjective itch, wheal distribution, urticarial activity, and systemic symptoms. Overall, patients with a positive HRA assay had more severe urticaria than patients with a negative test result.^{7,12} Our hypothesis was that patients with a positive autoimmune test finding are more difficult to treat, require a greater number of prescriptions and clinic visits, and should respond more readily to immune suppressants versus patients without a finding of autoimmunity. However, our study failed to demonstrate a statistically significant difference in these parameters between the two patient populations.

A difference in average total distinct prescriptions failed to reach statistical significance. In fact, the negative autoimmune group had a higher number of mean distinct prescriptions per patient of 8.4 versus 6.9 in the positive autoimmune group. The mean distinct medications prescribed per patient in each group were similar. The same fraction of patients in each group—75% of patients with a positive autoimmune test result versus 75% with a negative autoimmune test result—were more than 75% clear of disease as of their last clinic visit. In addition, of the patients doing well (>75% clear), the type of medication that the patients responded favorably to was similar. The expectation was for patients with a positive autoimmune test result to respond well to anti-inflammatory/immunomodulator medications but perhaps not as well to antihistamines. Of the well-controlled patients with a positive test result, 50% responded to antihistamines/leukotriene inhibitor and 50% to second- or third-line anti-inflammatory/immunomodulator agents. Of the patients with a negative autoimmune test result, 44% responded to antihistamine/leukotriene inhibitor agents and 56% responded to anti-inflammatory/immunomodulator agents. In contrast to our initial hypothesis, the number of patient visits during the 3-year period was similar in each group ($P = .5$).

Identification of patients with autoantibodies to the mast cell/basophil FcεRI receptor in the study group did not imply worse disease course, increased difficulty in treatment, or response to specific therapies. Therefore, perhaps the identification of autoantibodies in CIU is not necessary for disease management, but rather may be used as a research tool or as means to provide patients with a sense of reason behind the origin of their urticaria. The average cost for both tests is \$100. Although relatively inexpensive, when translated to the estimated 0.5% to 2% of people worldwide affected by CU at some point in their lifetime, it totals a large cost.^{25,26} In addition, testing for CBC and other autoimmunity seemed insignificant for patient treatment. The current study is limited by its retrospective nature, small sample size, possible bias of being performed at a major academic institution, and current tests do not identify all of the patients in whom an autoimmune phenomenon may exist. In the future, a large prospective cohort study is needed to more accurately guide the clinical use of laboratory testing for autoimmune urticaria.

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