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Clinical and Laboratory Characteristics of Patients with Chronic Spontaneous Urticaria in a Vietnamese Population

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Chronic spontaneous urticaria · Basophil Histamine Release Assay · Autologous Serum Skin Test · Urticaria Activity Score · Autoimmune chronic urticaria

Abstract
Introduction: This study aims to investigate the clinical and laboratory characteristics of patients with type IIb autoimmune chronic spontaneous urticaria (CSU) in a Vietnamese population and how this correlates with results of the Basophil Histamine Release Assay (BHRA). ***Methods:*** A cross-sectional, single-center study was conducted with 388 CSU patients aged 16 years or older at the Vietnam National Dermatology and Venereology Hospital, from June 2023 to March 2024. Clinical data were collected, and laboratory tests were performed. Patients also underwent the Autologous Serum Skin Test (ASST) and BHRA. A multivariate logistic regression model was performed to identify factors associated with a positive BHRA. ***Results:*** Of the 388 CSU patients, 60.3% had new onset symptoms, 34.0% had angioedema, and 12.6% had comorbid dermographism. Laboratory results indicated that 11.4%, 5.9%, and 1.8% of patients had elevated CRP levels, low total serum IgE levels, and basopenia, respectively. Additionally, elevated IgG anti-TPO levels, positive ANA, and positive ASST were found in 10.6%, 11.4%, and 57.2% of patients, respectively. There were 9.5% who tested positive for BHRA. Multivariate logistic regression identified UAS7 score (OR = 1.047, $p = 0.017$), low basophil levels (OR = 6.749, $p = 0.027$), and low total serum IgE (OR = 3.391, $p = 0.039$) as significant predictors of BHRA positivity. ***Conclusion:*** Our results identified key clinical and laboratory characteristics associated with type IIb autoimmune CSU in Vietnamese patients. Higher UAS7 scores, basopenia, and low IgE levels were significant predictors of BHRA positivity.

Introduction

Chronic spontaneous urticaria (CSU) is characterized by urticaria persisting for more than 6 weeks and is increasingly understood as an autoimmune condition [1–3]. It affects about 1% of the population, with increasing prevalence and a higher incidence in adult females [4]. Asia and Latin America have some of the

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highest point prevalence estimates of chronic urticaria, at 1.4% [4]. This condition significantly impacts quality of life, reduces productivity, and is associated with psychological comorbidities [5]. This underscores the need for better treatment options.

While the exact mechanism behind the pathogenesis of CSU is not fully understood, substantial evidence points to an autoimmune pathway. There are two primary types of autoimmune hypersensitivity associated with CSU: type I and type IIb [6, 7]. Type I autoimmune CSU (aiCSU), also known as autoallergy, involves the presence of an autoantigen that can form a complex with IgE, leading to the activation of mast cells [7]. To date, over 200 autoallergens have been identified as targets of IgE in CSU patients [8]. In vitro studies have confirmed the functional ability of certain autoantibodies, including IgE against TPO [9, 10], IL-24 [11], and double-stranded DNA [12–14]. In type IIb CSU, often referred to as aiCSU, autoantibodies (typically IgG and occasionally IgM and IgA [14]) target high-affinity IgE receptors (FcεRI) or IgE itself on the surface of mast cells and basophils [1]. Diagnosis of type IIb aiCSU is based on three criteria: (1) a positive bioassay (BHRA or BAT-basophil activation marker expression) to demonstrate functionality in vitro, (2) positive autoreactivity demonstrated by an ASST to show relevance in vivo, and (3) a positive immunoassay for specific IgG autoantibodies against FcεRI and/or anti-IgE (using Western blot or ELISA) [15]. Among these diagnostic methods, basophil tests (BHRA and BAT) are regarded as the most reliable standalone tests, with predictive values of 88% and 69% for type IIb aiCSU, respectively [16–18]. Research indicates that at least 8% of CSU patients have type IIb aiCSU, defined by triple positivity [19]. Furthermore, most patients with aiCSU also exhibit autoallergic urticaria [20].

The two types of CSU can be differentiated by several key clinical and laboratory characteristics, including their responses to various treatments [11, 21, 22]. Recent research indicates that patients with type IIb aiCSU tend to exhibit higher disease activity, longer duration of the condition, and higher rates of concurrent autoimmune diseases [2, 6, 23, 24]. Additionally, these patients often have lower levels of total serum IgE, higher levels of IgG anti-TPO, lower levels of cellular histamine per basophil and may present with basopenia and eosinopenia more frequently [25, 26]. They typically show poor responses to antihistamines and omalizumab but respond well to cyclosporine or Bruton's tyrosine kinase inhibitors [17, 27, 28]. The efficacy of treatments like omalizumab can vary based on the specific endotype of the disease, emphasizing the need to understand the underlying autoimmune mechanisms for accurate diagnosis and effective management of CSU [29].

In recent years, there has been growing interest in understanding the clinical and laboratory characteristics of type IIb aiCSU, especially within different ethnic and geographical populations [1, 3]. The Vietnamese population, with its distinct genetic and environmental backdrop, provides a unique context for studying this condition. However, comprehensive data on the prevalence, clinical presentation, and laboratory markers of type IIb aiCSU in Vietnam are limited. This study aims to investigate the clinical and laboratory characteristics of patients with different subtypes of aiCSU in a national hospital in Vietnam with special emphasis on correlations to BHRA results as BHRA can serve as a marker of type IIb aiCSU. By elucidating the specific features of this autoimmune subtype, we hope to enhance diagnostic accuracy and improve therapeutic strategies tailored to the Vietnamese population. This research is particularly relevant in the context of personalized medicine, where understanding population-specific disease patterns can lead to more effective and targeted treatments.

Methods

Study Settings and Patients

A cross-sectional, single-center study was conducted with 388 patients aged 16 years or older who had CSU. These patients attended the Urticaria Clinic at the Vietnam National Dermatology and Venereology Hospital between June 2023 and March 2024. Inclusion criteria required patients to be diagnosed with CSU according to EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline [30]. They were also required to discontinue antihistamines for at least 3 days, systemic corticosteroids for at least 1 month, and NSAIDs and antibiotics for at least 1 week before undergoing the ASST. All participants provided written informed consent. Patients with pure chronic inducible urticaria (CIndU), those who were pregnant or breastfeeding, and those with acute severe constitutional conditions were excluded from the study. All CSU patients underwent ASST and BHRA. The study received approval from the Institutional Review Board of Hanoi Medical University (number 865/GCN-HDDDDNCYSH-DHYHN). The study adhered to Good Clinical Practice and local regulations.

Data Measurement

The demographic data collection involved documenting the age, gender, and the history of CSU treatment of the 388 CSU patients. Moreover, data collection encompassed the duration since the initial onset of urticaria symptoms, the presence of comorbid CIndU, comorbid angioedema, the severity of itching, the frequency of urticaria episodes per week, the duration of wheals, and the severity of urticaria as measured by the weekly Urticaria Activity Score (UAS7). To ensure accurate evaluation, UAS7 was collected during a period when patients were not taking antihistamines. Patients who were on antihistamines were advised to temporarily discontinue medication before undergoing both the Autologous Serum Skin Test (ASST) and UAS7 assessment.

Laboratory data included complete blood count (eosinopenia defined as <50 cells/mL and basopenia defined as <10 cells/mL), white blood cell count (normal range 4,000–10,000 cells/mL), C-reactive protein (CRP, with high levels defined as >5 UI/mL), serum glutamic-oxaloacetic transaminase (SGOT, normal range < 40 UI/L), serum glutamic-pyruvic transaminase (SGPT, normal range < 40 UI/L), free T3 (abnormal if outside normal range 3.1–6.8 pmol/L), free T4 (abnormal if outside normal range 12–22 pmol/L), thyroid-stimulating hormone (TSH, abnormal if outside normal range 0.27–4.2 mUI/L), IgG anti-thyroid peroxidase (IgG anti-TPO, normal range < 5.61 UI/mL), antinuclear antibodies (ANA), and total serum IgE level (below 40UUI/mL was defined as low IgE level). ASST was conducted following the protocol established by a previous EAACI taskforce [15]. These tests were conducted as routine examinations for patients with CSU at the clinic, not for research purposes. ASST and BHRA were performed free of charge for patients after they consented to participate in the study.

Basophil Histamine Release Assay

The BHRA was conducted by RefLab ApS in Hvidovre, Denmark, as described previously [16, 31]. In brief, blood bank buffy coats were stored overnight with IL-3 before surface IgE was partially removed from the basophils, which were then incubated for an hour with 10% and 20% patient serum. Histamine release was measured by fluorometric detection and total histamine content was determined by lysing the basophils with perchloric acid. The histamine release was expressed as a percentage of the total histamine content. A response greater than 16.5% was considered positive.

Statistical Analysis

Data were analyzed using Stata 17.0. A listwise deletion approach was used to handle missing data. Clinical and laboratory data of patients were compared using the Mann-Whitney U test for continuous variables and chi-square test (or Fisher's exact test) for categorical variables. Results were reported as significant when p values were <0.05. Multivariate logistic regression model was performed to identify factors associated with a positive BHRA. A stepwise backward selection strategy was used to build the reduced model.

Results

Demographic and clinical characteristics of Vietnamese patients with CSU are presented in Table 1, comparing those with negative and positive BHRA. The majority of patients were aged between 25 and 59 years, with a higher prevalence in females (61.9%). All patients had a history of CSU treatment, with a significant portion using second-generation H1 antihistamines (91.7%). Notably, 22.9% of patients had a history of allergy, and 8.5% had a history of autoimmune disease. Additionally, 74.7% had no history of urticaria, while 12.9% experienced chronic urticaria. Family history showed that 13.1% had urticaria, 5.4% had an allergic constitution, and 1.3% had autoimmune disease. There were 9.5% of CSU patients with positive BHRA. No statistically significant difference was found between the BHRA+ and BHRA− groups regarding age, gender, history of CSU treatment, or history of allergy, autoimmune disease, or urticaria. However, the rate of patients with family members with autoimmune disease was significantly higher in the BHRA+ group compared to the BHRA− group ($p < 0.05$).

Table 2 presents the clinical characteristics of CSU patients, comparing those with negative and positive BHRA results. Among BHRA− patients, 61.2% had disease duration of less than 1 year, compared with 51.4% in BHRA+, while a longer disease duration of more than 5 years was more frequent in BHRA+ patients (32.4% vs. 14.5%). Dermographism was present in 12.6% of patients, while 34.0% had angioedema, with 57.6% experiencing it surrounding the eyes, 84.1% around the lips, and 12.9% in the limbs. Most patients (55.4%) experienced daily wheals lasting 1–6 h. The mean duration of CSU from the first onset was 3.0 years, the mean duration of the current episode was 33.6 ± 59.6 weeks, and the mean UAS7 score was 25.7. The duration from the first onset of urticaria showed significant differences,

Table 1. Demographic and medical history of patients

Characteristics	BHRA– (*n* = 351)		BHRA+ (*n* = 37)		Total (*N* = 388)		*p* value
	N	%	*N*	%	*N*	%	
Total	351	90.5	37	9.5	388	100.0	
Age-group							
16–24 years	82	23.4	7	18.9	89	22.9	0.512
25–39 years	119	33.9	14	37.8	133	34.3	
40–59 years	124	35.3	11	29.7	135	34.8	
≥60 years	26	7.4	5	13.5	31	8.0	
Gender							
Female	214	61.0	26	70.3	240	61.9	0.268
Male	137	39.0	11	29.7	148	38.1	
History of CSU treatment	351	100.0	37	100.0	388	100.0	
No	24	6.8	2	5.4	26	6.7	0.689
Unknown	74	21.1	10	27.0	84	21.6	
Yes	253	72.1	25	67.6	278	71.7	
Type of treatment (n = 278)							
First-generation H1 antihistamines	16	6.3	0	0.0	16	5.8	0.195
Second-generation H1 antihistamines	230	90.9	25	100.0	255	91.7	0.115
Systemic corticosteroid	44	17.4	3	12.0	47	16.9	0.493
Montelukast	18	7.1	3	12.0	21	7.5	0.378
Traditional medicine	7	2.8	3	12.0	10	3.6	0.018
Others	17	6.7	1	4.2	18	6.5	0.631
History of allergy	78	22.2	11	29.7	89	22.9	0.302
History of autoimmune disease	29	8.3	4	10.8	33	8.5	0.597
History of urticaria							
No	267	76.1	23	62.2	290	74.7	0.08
Acute	43	12.2	5	13.5	48	12.4	
Chronic	41	11.7	9	24.3	50	12.9	
Family history							
Urticaria	46	13.1	5	13.5	51	13.1	0.944
Allergic constitution	18	5.1	3	8.1	21	5.4	0.446
Autoimmune disease	3	0.8	2	5.4	5	1.3	0.020

Percentages in the "Total" column represent the proportion of total patients (N = 388), while percentages in the BHRA– and BHRA+ columns represent the proportion within each subgroup. BHRA, Basophil Histamine Release Assay; CSU, chronic spontaneous urticaria.

with a higher proportion of new cases in the BHRA– group (61.2% vs. 51.4%) and a higher rate of symptoms lasting more than 5 years in the BHRA+ group (14.5% vs. 32.4%). Angioedema in the limbs was more common in the BHRA+ group (50.0% vs. 8.5%, $p < 0.001$). The UAS7 score was significantly higher in the BHRA+ group (30.3 vs. 25.2, $p = 0.003$).

Table 2. Clinical characteristics of CSU patients

Characteristics	BHRA– (*n* = 351)		BHRA+ (*n* = 37)		Total (*N* = 388)		*p* value
	N	%	*N*	%	*N*	%	
Duration from the first onset of urticaria							
<1 year	215	61.2	19	51.4	234	60.3	0.021
1 year	19	5.4	3	8.1	22	5.7	
2–5 years	66	18.8	3	8.1	69	17.8	
> 5 years	51	14.5	12	32.4	63	16.2	
Presence of comorbid CIndU							
None	298	84.9	36	97.3	334	86.1	0.116
Dermographism	48	13.7	1	2.7	49	12.6	
Others	5	1.4	0	0.0	5	1.3	
Present of angioedema	118	33.6	14	37.8	132	34.0	0.606
Eye	66	55.9	10	71.4	76	57.6	0.267
Lip	98	83.0	13	92.9	111	84.1	0.343
Limbs	10	8.5	7	50.0	17	12.9	<0.001
Throat	7	5.9	2	14.3	9	6.8	0.241
Itching severity							
Mild	71	20.2	6	16.2	77	19.9	0.088
Moderate	196	55.8	16	43.2	212	54.6	
Severe	84	23.9	15	40.5	99	25.5	
Number of days with urticaria/week							
< 7 days	67	19.1	8	21.6	75	19.3	0.71
7 days	284	80.9	29	78.4	313	80.7	
Duration of wheal							
< 1 h	47	13.4	3	8.1	50	12.9	0.111
1–6 h	198	56.4	17	46.0	215	55.4	
6–12 h	65	18.5	13	35.1	78	20.1	
12- < 24 h	41	11.7	4	10.8	45	11.6	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Duration from the first onset, years	2.6	5.8	6.5	10.9	3.0	10.9	0.052
Duration of current episode, weeks	34.0	60.9	30.2	46.0	33.6	59.6	0.778
UAS7	25.2	9.3	30.3	10.7	25.7	9.6	0.003

BHRA, Basophil Histamine Release Assay; UAS7, Urticaria Activity Score; ASST, Autologous Serum Skin Test; CIndU, chronic inducible urticaria.

Table 3 shows the laboratory characteristics of CSU patients based on BHRA status. Among BHRA– patients, 53.0% were ASST positive, while almost all BHRA+ patients (97.3%) tested positive. Overall, 57.2% of the total cohort had a positive ASST result, with a statistically significant difference observed between the two groups ($p < 0.001$). The complete blood count revealed that 10.6% had abnormal white blood cell counts, 13.5% had

Table 3. Laboratory characteristics of CSU patients (N = 388)

Characteristics		BHRA− (n = 351)		BHRA+ (n = 37)		Total (N = 388)		p value
		N	%	N	%	N	%	
ASST+		186	53.0	36	97.3	222	57.2	<0.001
White blood cell, cells/mL	Normal	311	89.1	34	91.9	345	89.4	0.602
	Abnormal	38	10.9	3	8.1	41	10.6	
(n = 386)	Mean (SD)	7.7 (2.1)		7.3 (1.8)		7.6 (2.1)		0.301
Eosinophil, cells/mL	Normal	304	87.1	30	81.1	334	86.5	0.307
	Eosinopenia	45	12.9	7	18.9	52	13.5	
(n = 386)	Mean (SD)	154.3 (130.8)		138.5 (110.6)		152.8 (128.9)		0.438
Basophil, cells/mL	Normal	345	98.9	34	91.9	379	98.2	0.003
(n = 386)	Basopenia	4	1.2	3	8.1	7	1.8	
	Mean (SD)	46.5 (36.5)		34.8 (22.0)		45.3 (35.5)		0.004
CRP, UI/mL	Normal	306	89.7	29	78.4	335	88.6	0.039
(n = 378)	Elevated	35	10.3	8	21.6	43	11.4	
	Mean (SD)	2.4 (4.8)		2.9 (3.7)		2.4 (4.7)		0.080
SGOT, UI/L	Normal	320	93.8	34	91.9	354	93.7	0.644
(n = 378)	Abnormal	21	6.2	3	8.1	24	6.3	
	Mean (SD)	24.0 (9.7)		25.1 (11.5)		24.1 (9.8)		0.707
SGPT, UI/L	Normal	298	87.4	32	86.5	330	87.3	0.875
(n = 378)	Abnormal	43	12.6	5	13.5	48	12.7	
	Mean (SD)	24.0 (18.6)		24.5 (16.7)		24.0 (18.4)		0.802
ANA (n = 351)	Negative	281	89.2	30	83.3	311	88.6	0.293
	Positive	34	10.8	6	16.7	40	11.4	
FT3, pmol/L	Normal	322	95.8	34	91.9	356	95.4	0.275
(n = 373)	Abnormal	14	4.2	3	8.1	17	4.6	
	Mean (SD)	4.9 (1.3)		4.8 (1.0)		4.9 (1.2)		0.913
FT4, pmol/L	Normal	314	92.9	36	97.3	350	93.3	0.309
(n = 375)	Abnormal	24	7.1	1	2.7	25	6.7	
	Mean (SD)	17.6 (2.9)		17.3 (2.5)		17.5 (2.8)		0.996
TSH, mUI/L	Normal	318	94.4	35	94.6	353	94.4	0.953
(n = 374)	Abnormal	19	5.6	2	5.4	21	5.6	
	Mean (SD)	1.8 (1.1)		1.5 (0.9)		1.7 (1.1)		0.176
IgG anti-TPO, UI/mL	Normal	313	89.2	34	91.9	347	89.4	0.609
(n = 388)	Abnormal	38	10.8	3	8.1	41	10.6	
	Mean (SD)	26.6 (135.8)		4.7 (14.3)		24.5 (129.4)		0.294
IgE, UI/mL	Non-low total serum	333	94.9	32	86.5	365	94.1	0.040
(n = 388)	Low total serum	18	5.1	5	13.5	23	5.9	
	Mean (SD)	317.7 (394.3)		265.5 (247.5)		312.8 (382.8)		0.714
Ratio of IgG anti-TPO/IgE (n = 388)	Mean (SD)	0.17 (0.97)		9.42 (57.12)		1.05 (17.66)		0.619

eosinopenia, and 1.8% had basopenia. Elevated CRP levels were present in 11.4% of patients. Abnormalities in SGOT and SGPT were found in 6.3% and 12.7% of patients, respectively. For antibodies, 10.6% of patients had abnormal levels of IgG anti-TPO, and 11.4% tested positive for ANA. Abnormalities in FT3, FT4, and TSH were present in 4.6%, 6.7%, and 5.6% of patients, respectively. Low total serum IgE levels were observed in 5.9% of patients. Comparing BHRA− and BHRA+ groups, notable differences were observed. Elevated CRP levels were significantly more frequent in BHRA+ patients (21.6%) compared to BHRA− patients (10.3%) (p = 0.039). Low total serum IgE levels were more common in BHRA+ patients (13.5%) than in BHRA− patients (5.1%), showing a significant difference (p = 0.040). Additionally, the rate of basopenia was significantly higher in BHRA+ patients (8.1%) compared to BHRA− patients (1.2%) (p = 0.003). A significantly higher proportion of positive BHRA patients had a positive ASST (97.3% vs. 53.0%, $p < 0.001$).

Table 4 shows the results of a stepwise multivariate logistic regression analysis to identify factors associated with BHRA+. The BHRA+ group had significantly higher UAS7 scores (OR = 1.047, p = 0.017, 95% CI = 1.008–1.087), higher rate of basopenia (OR = 6.749, p = 0.027, 95% CI = 1.243–36.660), and higher rate of low total serum IgE levels (OR = 3.391, p = 0.039, 95% CI = 1.065–10.794) than the BHRA− group. These laboratory characteristics increased the likelihood of a positive BHRA.

Discussion

This study investigated the clinical and laboratory characteristics of patients with CSU in a Vietnamese population with special emphasis on type IIb aiCSU and BHRA as a marker hereof. The main findings include a 9.5% rate of BHRA positivity and significant associations between BHRA positivity and higher UAS7 scores, abnormal basophil counts, and low IgE levels. These results underscore the complexity and heterogeneity of CSU and highlight the importance of specific biomarkers in diagnosing and managing this condition.

The rate of BHRA positivity in our study was 9.5%, consistent with previous studies indicating that a subset of CSU patients exhibits type IIb autoimmune characteristics [16, 18, 19]. Our study found an ASST positivity rate of 57.2%, similar to the approximately 50% in a prior study [32]. These tests make up two-thirds of the criteria for an aiCSU diagnosis, and the rate of both tests being positive was 9.3% in our results. The sensitivity and specificity of a positive ASST to identify a patient with positive BHRA were 97% and 47%, respectively. The sensitivity of ASST+ for BHRA+ in our study was higher than that reported in prior research indicating a sensitivity of 87% [33]. This study reaffirms that while ASST alone is not a reliable screening test for BHRA, it has an excellent negative predictive value for BHRA and autoimmunity.

In our study, several significant clinical and laboratory characteristics of CSU were identified. We found that 34% of CSU patients presented with angioedema, a proportion higher than the 14.4% reported in a large Japanese multicenter study conducted at primary-care facilities [34] but closer to rates described in tertiary settings, where more severe and refractory cases are concentrated, including a Japanese referral-center study reporting approximately 20% [35]. A recent meta-analysis also reported a global prevalence of angioedema at 36.5% and 29.4% in Asia, suggesting that our finding is broadly consistent with data from other Asian populations [36]. CIndU, particularly dermographism, was observed in 12.6% of our patients. This proportion is lower than the 22.7% reported by Saito et al. [34] in Japan, but differences in study design and reporting must be considered as that study did not specify rates of dermographism coexisting with CSU. Geographic variation has also been documented, for example, by Sánchez et al. [37], who reported dermographism rates ranging from 14.4% in Bogotá to 28.5% in Medellín. Moreover, dermographism is often less frequent in patients with angioedema, which may partly explain the lower prevalence observed in our cohort given the relatively high rate of angioedema [34, 38].

With regard to autoimmune comorbidities, Kolkhir et al. [23] reported that 28% of CSU patients had at least one autoimmune disease, most commonly thyroid autoimmunity followed by vitiligo. In our cohort, 8.5% of patients had autoimmune diseases, such as thyroid disorders or rheumatoid arthritis. The incidence of autoimmune thyroid disease in CSU varies widely across studies [39, 40] and has been linked to a more chronic disease course and a higher risk of angioedema. We also evaluated the IgG anti-TPO/IgE ratio, a proposed biomarker for type IIb aiCSU. Although the mean ratio was higher in BHRA+ patients compared with BHRA− (9.42 ± 57.12 vs. 0.17 ± 0.97), the difference did not reach statistical significance (p = 0.619). This lack of significance may be attributed to the relatively small sample size of the BHRA+ group, which limited statistical power. Furthermore, while low IgE levels were more common in BHRA+ patients, the frequency of

Table 4. Stepwise multivariate logistic regression to identify associated factors with BHRA+

Factors	Odds ratio	*p* value	95% CI	
UAS7 score	1.047	0.017	1.008	1.087
Basophil (basopenia vs. normal ref)	6.749	0.027	1.243	36.660
CRP (abnormal vs. normal ref)	2.355	0.072	0.926	5.993
IgE (low total serum vs. non-low total serum ref)	3.391	0.039	1.065	10.794
FT3 (abnormal vs. normal ref)	2.589	0.173	0.658	10.189
Having dermographism (yes vs. no ref)	0.208	0.133	0.027	1.609

ref, reference group.

abnormal IgG anti-TPO did not differ substantially between groups. It is possible that with a larger BHRA+ cohort, the IgG anti-TPO/IgE ratio would demonstrate a statistically significant difference, consistent with previous studies.

Laboratory results in CSU patients revealed elevated CRP levels, low total serum IgE levels, and basopenia, indicating an inflammatory and autoimmune component. The detection of autoantibodies, such as antithyroid antibodies and positive ANA, further underscores the autoimmune nature of CSU. These clinical and laboratory markers are essential for understanding the disease's severity, guiding diagnosis, and developing more effective, personalized treatment strategies [1, 3]. In our study, elevated CRP was more common in the BHRA+ group than in the BHRA− group (21.6% vs. 10.3%, $p = 0.039$). In literature, elevated CRP is a significant predictor of poor or no response to antihistamines, which explains why a higher rate of type IIb aiCSU patients tend to fail antihistamine treatment [41].

Multivariate logistic regression identified higher UAS7 scores, basopenia, and low total serum IgE levels as significant factors associated with BHRA positivity. Our study aligns with previous research demonstrating that BHRA positivity is closely associated with disease activity in CSU patients [19]. Studies have shown that BHRA correlates with more severe urticaria symptoms and disease progression, particularly in patients with moderate to severe activity scores [42]. This association highlights the utility of BHRA in assessing disease severity and treatment responsiveness. Elevated disease activity is also associated with an increased CSU burden, including more frequent angioedema and higher levels of inflammatory markers like CRP and D-dimer [43]. These findings underlines the importance of BHRA as a valuable tool for understanding and managing CSU by correlating test results with clinical manifestations and disease activity, thereby aiding in the development of personalized treatment strategies [5, 44, 45].

Similarly, BHRA+ was associated with low total serum IgE levels and low basophil counts, which aligns with prior studies [16, 19]. The association between BHRA and low total serum IgE levels highlights the intricate mechanisms governing allergic responses. The proportion of patients with low basophil counts ranges from 7% in non-aiCSU patients to up to 30% (and potentially as high as 45%) in aiCSU patients [18, 46]. The cause of basopenia may be attributed to the migration of basophils from the blood to the skin. Basophils are related to the severity of CSU and treatment response [46], as patients with basopenia tend to have more severe disease, and as the condition improves, basophil counts tend to recover. Although the rate of basopenia in our study was relatively low, there was still a significant difference between the BHRA+ and BHRA− groups. Understanding these relationships is essential for developing targeted therapies to control basophil-mediated histamine release in allergic and autoimmune conditions.

The findings from this study have several important clinical implications. We identified higher UAS7 scores, basopenia, and low IgE levels as significant predictors of BHRA positivity, suggesting that these biomarkers can be effectively used to identify patients with type IIb aiCSU. These patients may benefit from alternative treatments such as cyclosporine or Bruton's tyrosine kinase inhibitors, especially if they fail with H1 antihistamines and omalizumab. The higher prevalence of angioedema in BHRA+ patients, particularly in the limbs, indicates that clinicians should be vigilant for this symptom and manage it appropriately to improve patient outcomes. Additionally, the study highlights the importance of considering family history as a higher rate

of autoimmune diseases among family members of BHRA+ patients suggest a genetic predisposition. Combining diagnostic tests, despite ASST alone not being sufficient, enhances diagnostic accuracy and supports a comprehensive approach to identifying type IIb aiCSU, ultimately leading to more personalized and effective treatment strategies.

This study has several limitations. First, the cross-sectional design limits the ability to infer causality between identified factors and BHRA positivity. Second, the study was conducted at a single center, which may limit the generalization of the findings to other populations. Third, while we included a comprehensive range of clinical and laboratory parameters, other potentially relevant biomarkers or clinical features may not have been captured. Additionally, the reliance on patient self-reporting for some clinical data could introduce recall bias. Therapeutic responses were not assessed in this study; further longitudinal research focusing on treatment outcomes in BHRA+ patients will be essential to determine how these biomarkers can guide clinical decision-making. Finally, our study only implemented two out of the three tests required for aiCSU diagnosis. Including IgG autoantibodies against FcεRI and anti-IgE to meet all three criteria would help better characterize the clinical and laboratory features of this patient population in Vietnam.

Conclusion

In our study, 9.5% of CSU patients tested positive for BHRA− a marker of type IIb aiCSU. Our results identified key clinical and laboratory characteristics associated with type IIb aiCSU in Vietnamese patients. Higher UAS7 scores, basopenia, and low IgE levels were significant predictors of BHRA positivity. These findings can enhance diagnostic accuracy and inform personalized treatment strategies for CSU in the Vietnamese population, contributing to more effective management of this condition.

Statement of Ethics

The study received approval from the Institutional Review Board of Hanoi Medical University (number 865/GCN-HDDDDNCYSH-DHYHN). The study adhered to Good Clinical Practice and local regulations. Written informed consents were obtained from patients. For patients under 18 years old, written informed consents were obtained from parents/guardians.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

My N.T.T.: methodology, writing, investigation, analysis, and project administration; My L.H.: investigation, supervision, and validation; Minh V.N.: investigation and validation; Katrine B.: writing – original draft, software, and analysis; Per S.S.: methodology, writing – review and editing, supervision, and resources; Doanh L.H.: methodology, supervision, resources, and project administration. All authors approved the final version of manuscript.

Data Availability Statement

Data cannot be publicly shared due to the data protection regulation of Hanoi Medical University. Data are available upon reasonable request from the corresponding author.

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