

Letter

Prevalence and clinical correlation of serum immunoglobulin E in patients with chronic spontaneous urticaria

Immunoglobulin (Ig) G plays a major role in the pathogenesis of autoantibodies by identifying IgG antibodies against IgE or IgG antibodies directed to the α subunit of the high-affinity IgE receptor. Recent studies have reported that omalizumab (a monoclonal anti-IgE antibody) is very effective in the treatment of refractory chronic spontaneous urticaria (CSU).^{1,2} However, the association between serum IgE level and disease severity of CSU is inconclusive. This retrospective study assessed the prevalence of and correlated serum IgE levels with the clinical course of CSU in Asian patients. This study was approved by the institutional review board of the Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Patients with CSU who attended a skin allergy clinic from 2011 to 2015 were enrolled in the study. Nephelometry using less than 100 IU/mL (BN ProSpec; Dade Behring, Inc, Deerfield, Illinois) was used to investigate IgE levels. Clinical characteristics and laboratory findings were compared in patients with CSU with vs without increased IgE levels. All statistical analyses were performed using PASW Statistics 18.0 (SPSS, Inc, Chicago, Illinois). Of 93 patients (21 men, 72 women), 63 had high serum IgE levels (67.7%, 95% confidence interval [CI] 57.7–76.4), with a median of 145.0 IU/mL (range 9.8–1,600.0 IU/mL). Clinical characteristics, including age, sex, disease duration, concomitant diseases, and family and personal histories of atopy, were not significantly different between patients with and without high IgE levels (eTable 1). Using logistic regression analysis, male sex and allergic rhinitis (AR) were significantly associated with increased IgE levels, with adjusted odds ratios (ORs) of 4.16 (95% CI 1.09–15.84) and 11.22 (95% CI 1.39–90.38), respectively. For disease severity, the Urticaria Activity Score for 7 consecutive days (UAS7)³ and medication scoring system² were used. UAS7 scores of 28 to 42, 16 to 27, 7 to 15, 1 to 6, and 0 were classified as severe, moderate, mild, well controlled, and complete response, respectively.³ UAS7 was recorded within 1 week before or after IgE blood sampling. The medication score was calculated by the sum of treatment scores, including antihistamines, oral glucocorticoids, cyclosporine, hydroxychloroquine, and montelukast, during treatment duration.² Thus, a high medication score can characterize severe CSU in a patient who has a low UAS7 score. Associations between serum IgE and clinical and laboratory variables are presented in Table 1. There were no significant differences in IgE levels among groups with mild, moderate, and severe disease activities (eFigure 1) and between groups with normal and abnormal laboratory findings. Serum IgE levels did not correlate with the medication score ($r = 0.102$, $P = .331$; eFigure 2).

Different methods have been used to investigate serum IgE in healthy controls and patients with CU and CSU. Previous studies have shown that IgE levels of patients with CU and CSU are significantly higher (range 174–196 IU/mL) than those of healthy controls (range 42–65 IU/mL), even when the measurement method was different (eTable 2).^{4–6} Our study showed that patients with CSU had a median IgE level of 145.0 IU/mL and 63% of patients had IgE levels higher than 100 IU/mL. Thus, it might be implied that patients with CSU tend to have higher IgE levels than healthy controls.

Although CSU is more common in women, we found a higher prevalence of elevated IgE level in men (OR 4.16, 95% CI 1.09–15.84). Raby et al⁷ found an association between serum IgE level and variants in male-specific locus on chromosome 20p12 (JAG1) in Costa Rican boys. JAG1 is a principal ligand for the NOTCH1 receptor, which is expressed in mature B cells and is related to IgE production. Our study found that patients with CSU and AR showed a significantly increased association with increased serum IgE level compared with the group without AR (OR 11.22, 95% CI 1.39–90.38). The higher IgE levels in patients with CSU and concomitant AR might be partly attributable to AR.

No correlation between disease activity and serum IgE level was found in this study, a finding similar to that of Baek et al,⁵ Chang et al,⁸ and Toubi et al.⁹ In contrast, Kessel et al⁴ reported a significant association between disease severity and serum IgE. This disparity might be due to our study using different activity scores, different serum IgE measurement methods, and different cutoff levels. Laboratory investigations, including autologous serum skin test (ASST), antinuclear antibodies, antithyroglobulin antibodies, and antithyroid peroxidase antibodies, have been reported as markers for the detection of autoimmune origin in patients with CSU.^{4,9} Patients with CUS and positive ASST reactions have been reported to have greater disease severity than patients with negative ASST reactions.⁹ Our findings identified no correlations between ASST result and serum IgE level in patients with CSU. Plasma D-dimer is a fibrin degradation product that represents the ongoing coagulation cascade. There have been several reports on the association between plasma D-dimer level and disease severity in patients with CU.⁵ Our study showed no correlation between IgE levels and plasma D-dimer levels in patients with CSU.

There were some notable limitations associated with this study. Given the retrospective nature of this review, baseline IgE level was not available because a blood sample was not taken during the first patient visit. In addition, partial treatment of CSU might have influenced serum IgE levels. A prospective study should be undertaken to further investigate possible correlations between serum IgE level and the clinical course of CSU.

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Table 1
Associations between serum IgE levels in patients with chronic spontaneous urticaria and clinical and laboratory variables

	Total, n (%)	Patients with elevated IgE, n (%)	IgE levels (IU/mL), median (min–max)	P value ^a
UAS7 (n = 93)				.436
Mild	39 (41.9)	25 (39.7)	117.0 (10.6–940.0)	
Moderate	41 (44.1)	27 (42.9)	142.0 (9.8–1,600.0)	
Severe	13 (14.0)	11 (17.5)	246.0 (51.6–747.0)	
ASST (n = 31)				.075
Negative	23 (74.2)	18 (78.3)	185.0 (17.7–926.0)	
Positive	8 (25.8)	5 (21.7)	103.0 (17.1–430.0)	
ESR (n = 39)				.404
Normal	31 (79.5)	22 (84.6)	169.0 (9.8–940.0)	
Increased (>20 mm/h)	8 (20.5)	4 (15.4)	101.2 (36.3–774.0)	
ANA (n = 70)				.471
Negative	66 (94.3)	46 (93.9)	159.5 (9.8–926.0)	
Positive	4 (5.7)	3 (6.1)	117.0 (78.1–169.0)	
Antithyroglobulin Ab (n = 73)				.650
Negative	61 (83.6)	43 (82.7)	169.0 (17.2–940.0)	
Positive	12 (16.4)	9 (17.3)	203.0 (10.6–747.0)	
Antithyroid peroxidase Ab (n = 74)				.423
Negative	68 (91.9)	49 (92.5)	180.5 (17.7–940.0)	
Positive	6 (8.1)	4 (7.5)	139.5 (10.6–774.0)	
D-dimer (n = 76)				.457
Normal	47 (61.8)	33 (62.3)	128.0 (9.8–804.0)	
Increased (≥500 ng/mL)	29 (38.2)	20 (37.7)	176.0 (31.2–940.0)	
Disease duration (n = 93)				.118
<12 mo	41 (44.1)	29 (46.0)	169.0 (10.6–1,600.0)	
≥12 mo	52 (55.9)	34 (54.0)	135.5 (9.8–804.0)	

Abbreviations: Ab, antibody; ANA, antinuclear antibodies; ASST, autologous serum skin test; ESR, erythrocyte sedimentation rate; max, maximum; min, minimum; UAS7, Urticaria Activity Score for 7 consecutive days.

^aBy Kruskal-Wallis or Mann-Whitney test.

In summary, more than half the patients with CSU evaluated in this study had high serum IgE levels. Male sex and AR were significantly associated with increased IgE levels, but no significant association between increased serum IgE level and disease severity was found.

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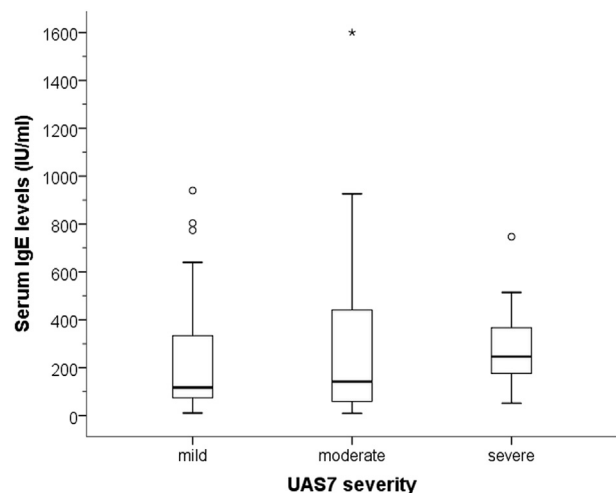
Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.anai.2015.12.007>.

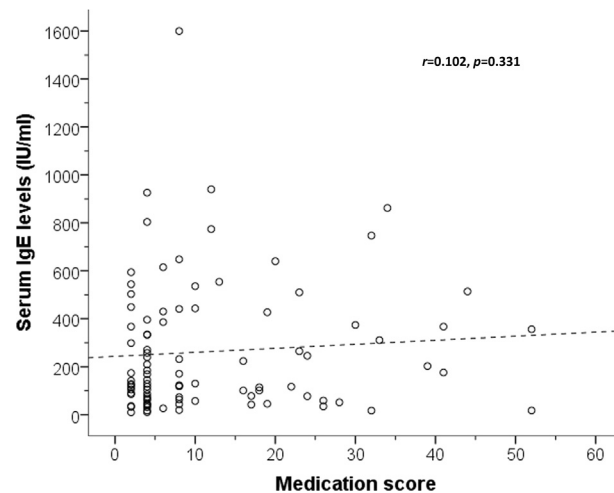
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eFigure 1. Urticaria Activity Score for 7 consecutive days (UAS7) severity relative to serum immunoglobulin E (IgE) levels in patients with chronic spontaneous urticaria.



eFigure 2. Medication score relative to serum immunoglobulin E (IgE) levels in patients with chronic spontaneous urticaria.

eTable 1

Demographic and clinical data of 93 patients with chronic spontaneous urticaria

	Total (N = 93)	Elevated IgE (n = 63)	Normal IgE (n = 30)	P value
Age (y), mean $\pm$ SD	39.8 $\pm$ 13.2	40.0 $\pm$ 14.1	39.4 $\pm$ 11.3	.830
Sex, n (%)				.045 ^b
Women	72 (77.4)	45 (71.4)	27 (90.0)	
Men	21 (22.6)	18 (28.6)	3 (10.0)	
Angioedema, n (%)	28 (30.1)	18 (28.6)	10 (33.3)	.640
Disease duration (mo), median (min–max)	12 (2–146)	12 (2–146)	12 (2–66)	.692
Concomitant diseases, n (%) ^a	44 (47.3)	33 (52.4)	11 (36.7)	.156
Atopy	20 (21.5)	17 (27.0)	3 (10.0)	.062
Dyslipidemia	14 (15.1)	10 (15.9)	4 (13.3)	1.000
Thyroid diseases	8 (8.6)	5 (7.9)	3 (10.0)	.710
Diabetes mellitus	5 (5.4)	3 (4.8)	2 (6.7)	.656
Hypertension	4 (4.3)	3 (4.8)	1 (3.3)	1.000
Infection	4 (4.3)	4 (6.3)	0 (0.0)	.301
Other	4 (4.3)	2 (3.2)	2 (6.7)	.592
History of atopy, n (%) ^a	20 (21.5)	17 (27.0)	3 (10.0)	.062
Allergic rhinitis	17 (18.3)	16 (25.4)	1 (3.3)	.010 ^b
Asthma	5 (5.4)	4 (6.3)	1 (3.3)	1.000
Allergic conjunctivitis	2 (2.2)	1 (1.6)	1 (3.3)	.543
Atopic dermatitis	1 (1.1)	1 (1.6)	0 (0.0)	1.000
Family history of atopy, n (%)	13 (14.0)	11 (17.5)	2 (6.7)	.211
Allergic rhinitis	11 (11.8)	9 (14.3)	2 (6.7)	.493
Asthma	2 (2.2)	2 (3.2)	0 (0.0)	1.000

Abbreviations: IgE, immunoglobulin E; max, maximum; min, minimum.

^aPatients might have been scored for more than 1 of the listed diseases.

^bP < .05 indicates statistical significance.

eTable 2

Comparison between patients with chronic urticaria and healthy controls using serum IgE measurement methods from the present study and previous studies

Study, year	Serum IgE measurement method	Patients		Healthy controls	
		n	Serum IgE level (IU/mL) ^a	n	Serum IgE level (IU/mL) ^a
Present study	nephelometry (BN ProSpec, Dade Behring, Inc, Deerfield, Illinois)	93 (CSU)	145.0 (9.8–1,600.0)	—	—
Kessel et al, ⁴ 2010	Ridascreen, ELISA kit (R-Biopharm, Darmstadt, Germany)	203 (CU)	182 ± 16.12	81	65.36 ± 5.4
Staubach et al, ⁵ 2008	CAP FEIA (Pharmacia Diagnostics, Uppsala, Sweden)	118 (CU)	174 ± 22	38	42 ± 7
Baek et al, ⁵ 2014	immunoradiometric assay (SR300, Stratec Biomedical AG, Birkenfeld, Germany)	48 (CU)	196 (15.0–1,395.0)	—	—

Abbreviations: CSU, chronic spontaneous urticaria; CU, chronic urticaria; ELISA, enzyme-linked immunosorbent assay; FEIA, fluorometric enzyme immunocapture assay; IgE, immunoglobulin E.

^aSerum IgE levels are presented as mean ± SD or median (minimum to maximum).