



Assessment of circulating FCεRIα in Chronic Spontaneous Urticaria patients and its correlation with clinical and immunological variables

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ABSTRACT

Chronic spontaneous urticaria (CSU) is a chronic type characterized by episodes of wheals with or without angioedema. Autoantibody against the alpha subunit of Fc epsilon receptor (FcεRIα) was detected in CSU patients' sera. The study aims to evaluate the clinical utility of skin tests in CSU patients. In addition, it assesses the presence of circulating FcεRIα in CSU patients and their correlation with other clinical and immunological variables. The study includes 40 healthy controls and 40 CSU patients who had urticaria symptoms for at least 8 weeks. All subjects underwent the following tests: autologous serum skin test (ASST), autologous plasma skin test (APST), immunoglobulin E (IgE), antinuclear antibodies (ANA), antithyroid antibodies (ATA). An in-house enzyme-linked immunosorbent assay was used for FcεRIα detection. The prevalence of ANA and ATA in CSU was 7.5% and 20% respectively. Total IgE was significantly higher in CSU than in controls ($p < 0.0001$). The study detected circulating antibody to FcεRIα in 2.5% of controls and 52.5% of CSU patients ($p < 0.0001$). The prevalence of antibody to FcεRIα was 27.3% and 83.3% of ASST negative and positive patients respectively ($p = 0.0004$). But the prevalence was 17.6% and 78.3% of APST negative and positive patients respectively ($p = 0.0002$). In conclusion, Circulating antibody to FcεRIα has a role in the pathogenic mechanisms of CSU.

1. Introduction

Chronic spontaneous urticaria (CSU) is a chronic type characterized by episodes of wheals with or without angioedema. CSU has a recurrent course which lasts more than 6 weeks (Lima et al., 2017). CSU may have an autoimmune pathogenesis (Sabroe et al., 1999).

Immunoglobulin E (IgE) binds to the Fc epsilon receptor (FcεR) to mediate its action. The high-affinity FcεRI is expressed on the cell surface (eosinophils, mast cells, basophils, and Langerhans cells) (Kraft and Kinet, 2007). Allergic reactions to allergens are mediated by histamine release when allergen binds to surface-bound IgE on mast cells (Hayes et al., 2014). Immunoglobulin G (IgG) binds the alpha subunit of Fc receptor (FcεRIα) was firstly detected in CSU patients' sera by Hide et al. (1993). Circulating antibodies against either IgE or its receptor can release basophil and mast cell mediators. The role of such antibodies in CSU was previously assessed by several studies (Fiebiger et al., 1995; Kikuchi and Kaplan, 2001; Ulambayar et al., 2017).

The autologous serum skin test (ASST) is used to detect urticaria patients. This test was first performed by Grattan et al., (1986). It is an

autoreactivity detection test in which intradermal injection of autologous serum acts directly on the skin vessels or acts indirectly by the release of skin mast cell mediators. Autoreactivity does not denote autoimmune mechanism, but it may be an indicator of mast cell activating autoantibodies (Sajedi et al., 2011). ASST specificity was doubtful as false-positive results appeared due to bradykinin and protease cleaved C5, which released during blood clotting to separate the serum. So, autologous plasma skin test (APST) was used instead of ASST in order to increase the specificity (Asero et al., 2006). Heparin inhibits the cells degranulation process (Asero et al., 2001), so sodium citrate is used for plasma separation (Asero et al., 2006).

This study is designed to evaluate the clinical utility of ASST and APST as reflections of the autoreactivity in CSU patients. In addition, the study assessed the presence of circulating FcεRIα in CSU patients and their correlation with other clinical and immunological variables.

Abbreviations: ANA, antinuclear antibodies; APST, autologous plasma skin test; ASST, autologous serum skin test; ATA, antithyroid antibodies; CSU, chronic spontaneous urticaria; FcεRIα, alpha subunit of Fc receptor Epsilon; IgE, Immunoglobulin E; IgG, Immunoglobulin G; USA, urticaria activity score

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2. Material and methods

This study is a case-control study, carried out in the Allergy Unit of the Microbiology and Immunology Department and clinical pathology department, Faculty of Medicine, Zagazig University.

From July 2017 to November 2017, the study included 40 healthy controls and 40 CSU patients who had urticaria symptoms for at least 8 weeks. CSU disease activity was assessed using the urticaria activity score (UAS) UAS7, which scores wheals number and pruritus intensity within the last 7 days with a score ranging from 0 to 15.

Atopy was considered positive when at least one or more allergens on the intradermal hypersensitivity skin test were positive with the common inhalant allergens. Refractoriness to antihistamines was defined by persistence of symptoms even with an elevation of antihistamine doses for 4-fold.

Before the autologous serum skin test (ASST), antihistamines withdrawal for minimally 5 days was done. ASST was performed by intradermal injection of 50 µL of each (autologous serum, histamine diphosphate, and sterile physiological saline) into the volar forearm. ASST positivity was considered when the wheal induced after 30 min of intradermal serum injection was at least 1.5 mm larger than that was induced by saline injection (Konstantinou et al., 2009). For the APST, citrated blood was centrifuged at room temperature to separate the plasma. Immediately after separation, 50 µL of each (autologous plasma, histamine diphosphate, and sterile physiological saline) was injected intradermally on the volar forearm (Sajedi et al., 2011). The ASST and the APST positivity was considered when the wheal induced after 30 min of intradermal serum/plasma injection was 1.5 mm larger than that was induced by saline injection.

From all subjects, blood samples were collected and serum was separated within 30–60 min of collection, then stored at –80 °C. Antinuclear antibody (ANA) was detected using HEp-2 cells and the immunofluorescence method (Diasorin, USA). Antithyroid autoantibodies (ATA) were detected by using the Thyroglobulin IgG ELISA [Catalog Number: TG070 T] and Thyroid Peroxidase IgG ELISA [Catalog Number: TP069 G] (Calbiotech, Spring Valley, CA). Enzyme Immunoassay for the Quantitative Determination of Immunoglobulin E (IgE) Concentration in Human Serum was used [REF.: E29-006] (Immunospec, Canoga Park, CA).

Detection of anti-FcεR1a autoantibody was conducted by in-house ELISA. Recombinant Human Fcε R1a [Catalog Number: 6678-FC] (Bio-Techne, USA) was reconstituted at 5 µg/mL concentration in a phosphate buffer saline (PBS). The microtitre plate was coated with the antigen and incubated overnight at 4 °C. After that, the plate was washed 3 times with PBS, and then blocked with 1% bovine serum albumin for 2 h at room temperature. After washing, the serum samples were added at a 1:100 dilution with PBS to each well, then incubated for 2 h at room temperature. After washing, peroxidase-conjugated rabbit anti-human IgG [Catalog Number: BA1070-0.5] (Boster, CA, USA) was diluted (to reach 0.1 µg/mL with 0.01 M PBS) and added to each well, then incubated for 1 h at room temperature. The reaction was visualized using 3,3',5,5'-tetramethylbenzidine [Catalog Number: 3652-F10] (Mabtech, Sweden) as a substrate for 10 min. The reaction was stopped by 1 mol/L H₂SO₄. Optical density (OD) was read at 405 nm; and 630 nm was used as a reference filter by BioTek ELx800 Absorbance Microplate Readers (Bio-Tek Instruments, USA). The OD cutoff point was set as the mean of OD for negative controls plus 3 standard deviations. The positivity was considered when the OD exceeded the cutoff value.

3. Statistical analysis

The comparisons between quantitative variables were done using a Student-T test or Manne-Whitney U test. For categorical data, chi-squared (χ²) test was performed. The adjusted odds ratios (OR) and their 95% confidence intervals (95% CI) were determined by Multiple

Table 1

Demographic and clinical characteristics of the studied groups.

Parameter	CSU (No. = 40)	Controls (No. = 40)	p
Age (years) ^a	38.5 ± 10.99	39.3 ± 12.27	0.76
Sex: Male/ Female	14/26 (35/65%)	16/24 (40/60%)	0.64
Duration of illness (months) ^b	22.5 (5–120)	–	
Atopy	24 (60%)	–	
Angioedema	5 (12.5%)	–	
UAS ^a	6.4 ± 4.8	–	
ASST (+ve/-ve)	18/22 (45/55%)	–	
APST (+ve/-ve)	23/17 (57.5/42.5%)	–	
Refractoriness to antihistamines	9 (22.5%)	–	

No.: number of subjects; UAS: urticaria activity score; ASST: Autologous serum skin test; APST: Autologous plasma skin test; +ve: Positive; -ve: Negative.

Data are presented as No. (%) or ^a mean ± SD or ^b median (range).

*Significant.

Logistic Regression Analysis. Statistical analysis was carried out using SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA). p-value < 0.05 was considered significantly different.

4. Results

Demographic and clinical characteristics of CSU patients and controls are shown in Table 1. There were no significant differences between patients and controls for age and gender (p > 0.05).

Differences in laboratory findings between the CSU patients and control subjects are shown in Table 2. The prevalence of ANA in CSU patients and controls was 7.5% and 2.5%, respectively (p = 0.31). The prevalence of ATA in CSU patients was 20% and statistically significant when compared with that of controls (p = 0.003).

The prevalence of IgG to FcεR1a was 52.5% in CSU patients, whereas only 2.5% of the controls had positive results (P < 0.0001). According to ASST results, the prevalence of IgG to FcεR1a in CSU patients was 27.3% and 83.3% for ASST (negative and positive respectively) (p = 0.0004) (Fig. 1). As for APST results, the prevalence of IgG to FcεR1a in CSU patients was 17.6% and 78.3% for APST (negative and positive respectively) (p = 0.0002) (Fig. 2).

Association of IgG to FcεR1a with other clinical parameters in CSU patients is illustrated in Table 3. Percentage of females was higher in patients with positive IgG to FcεR1a (81%) in comparison with IgG to FcεR1a-negative patients (47.4%) (p = 0.03). The percentage of positive ASST was higher in patients with positive IgG to FcεR1a when compared to IgG to FcεR1a-negative patients (71.4% and 15.8%, respectively) (p < 0.0001). The percentage of positive APST was higher in patients with positive IgG to FcεR1a in comparison with IgG to FcεR1a-negative patients (85.7% and 26.3% respectively) (p < 0.0001).

There were no significant differences in the age, urticaria duration, UAS, the presence of atopy and of angioedema (between IgG positive and negative groups). The presence of refractoriness to antihistamines

Table 2

Laboratory findings in the studied groups.

	CSU (No. = 40)	Controls (No. = 40)	p
ANA (+ve)	3(7.5%)	1 (2.5%)	0.31
ATA (+ve)	8(20%)	0 (0%)	0.003*
Total IgE (IU/mL)	114.4 (21.4–1782.9)	27.7 (2.1–73.3)	< 0.0001*
IgG to FcεR1a (+ve)	21 (52.5%)	1 (2.5%)	< 0.0001*

No.: number of subjects; ANA: antinuclear antibody; ATA: anti-thyroid antibody; +ve: Positive.

Data are presented as No. (%) or median (range).

*Significant.

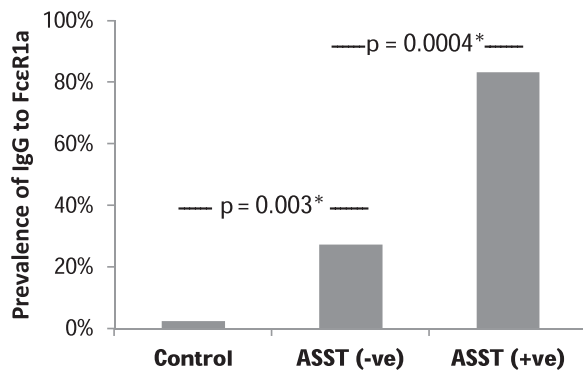


Fig. 1. The prevalence of IgG to FcεR1a in controls and CSU patients (according to their ASST results).

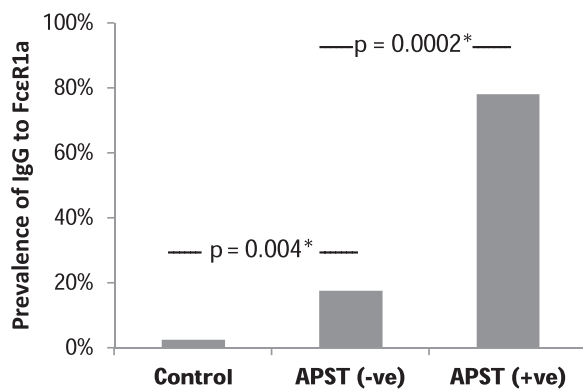


Fig. 2. The prevalence of IgG to FcεR1a in controls and CSU patients (according to their APST results).

Table 3

The association of clinical and laboratory parameters in CSU with the presence of IgG to FcεR1a.

Parameter	Positive IgG to FcεR1a (No. = 21)	Negative IgG to FcεR1a (No. = 19)	p
Age (years) ^a	38.6 ± 12.1	38.4 ± 10.2	0.97
Sex : Male/ Female	4/17 (19/81%)	10/9(52.6/47.4%)	0.03*
Duration of illness (months) ^b	20 (6–60)	24 (5–120)	0.39
Atopy	11 (52.4%)	13 (68.4%)	0.30
Angioedema	3 (14.3%)	2 (10.5%)	0.72
UAS ^b	8 (0–15)	3 (0–13)	0.12
ASST (+ve)	15 (71.4%)	3 (15.8%)	< 0.0001*
APST (+ve)	18 (85.7%)	5 (26.3%)	< 0.0001*
Refractoriness to antihistamines	6 (28.6%)	3 (15.8%)	0.33
ANA (+ve)	2 (9.5%)	1 (5.3%)	0.61
ATA (+ve)	7 (33.3%)	1 (5.3%)	0.03*
Total IgE (IU/mL) ^b	87.8 (21.4–1782.9)	124.2 (40.2–1207.1)	0.12

No.: number of subjects; UAS: urticaria activity score; ASST: Autologous serum skin test; APST: Autologous plasma skin test; ANA: antinuclear antibody; ATA: anti-thyroid antibody; +ve: Positive.

Data are presented as No. (%) or ^a mean ± SD or ^b median (range).

*Significant.

(28.6% vs. 15.8%) showed a higher trend in patients with IgG to FcεR1a compared to those without IgG to FcεR1a although no statistical significance difference was found ($p = 0.33$). There were no statistically significant differences in ANA and total IgE between IgG to FcεR1a positive and negative patients. The percentage of positive ATA was higher in patients with positive IgG to FcεR1a compared to IgG to

FcεR1a-negative patients (33.3% and. 5.3% respectively) ($p = 0.03$) (Table 3).

Multiple Logistic Regression Analysis of IgG to FcεR1a of CSU patients revealed a significantly higher risk of positive ASST (adjusted OR = 14.7, 95% CI = 1.8–111.1, $p = 0.01$) and of positive APST (adjusted OR = 10.3, 95% CI = 1.15–90.9, $p = 0.03$). Regarding the type of gender, females were statistically insignificant in patients with IgG to FcεR1a (adjusted OR = 2.4, 95% CI = 0.3–20.4, $p = 0.39$). Positive ATA was statistically borderline in anti FcεR1a positive patients (adjusted OR = 11.6, 95% CI = 0.9–142.8, $p = 0.05$).

5. Discussion

The prevalence of ANA in CSU patients and controls was 7.5% and 2.5% respectively. The prevalence of ATA in CSU patients was 20% and significantly higher when compared with that of controls. Ulambayar et al. (2017) reported that the prevalence of ANA and ATA in CSU patients was 20.8% and 24.8% respectively. Also, Altrichter et al. (2011) stated that CSU patients have been repeatedly reported to show a high incidence of autoimmune thyroiditis. Up to 33% of patients reportedly expressed an increase of ATA in comparison with only 5% of healthy individuals. Ye et al. (2012) found that 33.3% of Korean chronic urticaria patients exhibited a positive result for ATA and ANA. The frequency of antibodies to thyroglobulin, thyroperoxidase or both is estimated at 12–29% in urticaria patients. The results are really similar regarding ATA and the percentage positives for normals is correct at 3–6%. (Verneuil et al., 2004; Najib et al., 2009; Abd El-Azim and Abd El-Azim, 2011; Mohamed et al., 2016). The present results revealed a borderline risk of ATA and anti FcεR1. Such an association of ATA and anti FcεR1 has been proved by Kikuch et al. (2003).

This study found that the frequency of ASST positivity in CSU patients is 45%. This goes in agreement with Abd El-Azim and Abd El-Azim (2011), who stated that 39.6% of their chronic autoimmune urticaria had a positive ASST result, and the prevalence of positive ASST results in CU patients was reported to vary from 34% to 70% in various studies (Nettis et al., 2002; Bakos and Hillander, 2003; Caproni et al., 2004; George and Balachandran, 2008; Vikramkumar et al., 2014; Beevi et al., 2017). ASST may generate false-positive results due to the high amount of bradykinin generated during the serum preparation (Ward et al., 1970; Fusari et al., 2005; Asero et al., 2011).

The present study detected a nonsignificant female predominance among CSU cases (65%). Although Caproni et al. (2004) and Abd El-Azim and Abd El-Azim (2011) stated that their studies found a female predominance in CAU patients. The total IgE level is significantly higher in CSU patients when compared to control subjects with a threefold increase in CSU. This result agrees with those of Altrichter et al. (2011) who found that nearly 50% of CSU patients exhibit a significantly fourfold increase in the level of total serum IgE.

The prevalence of IgG to FcεR1a was 52.5% of CSU patients whereas only 2.5% of the controls had positive results of IgG to FcεR1a. Fiebiger et al. (1995) demonstrated that 37% of CSU patients had IgG auto-antibody against FcεR1a in their sera. Ferrer et al. (1998) reported that Anti-FcεR1a antibody was found in 64% of CU patients. This IgG to FcεR1a can be detected in 24%–60% of CSU patients (Sabroe et al., 1999, 2002; Grattan, 2004). Kaplan and Joseph (2007) introduced findings that agree with those of the present study and include large numbers of patients. Ulambayar et al. (2017) reported, in their study, that Anti-FcεR1a antibody was found in 24.8% of CSU patients, and it was detected in 3.1% of NCs. On another hand, the percentage was somehow high in the study of Eckman et al. (2008) since it reached 57% positive anti FcεR1a in normal control subjects. Also, Vasager et al., (2006) and Cho et al., (2013) cast doubt on anti FcεR1a specificity in the CSU.

The prevalence of IgG to FcεR1a, according to ASST results, in CSU patients was 13.6% and 83.3% for ASST negative and positive patients, respectively. Also, Ulambayar et al. (2017) reported that positivity rates

for IgG autoantibody to FcεR1α were significantly higher in ASST positive CSU patients than in ASST negative CSU patients (32.8% versus 16.4%).

Regarding association of IgG to FcεR1α with other clinical parameters in CSU patients, the female percentage was higher in patients with positive IgG to FcεR1α (81%) when compared to IgG to FcεR1α negative patients (47.4%). Ulambayar et al. (2017) reported that sex was found to be an important factor associated with positivity for IgG to FcεR1α. This was noted in (6.1%) of male versus (31.5%) of CSU female patients.

The percentage of positive ASST was higher in patients with positive IgG to FcεR1α when compared to IgG to FcεR1α negative patients (71.4% and 15.8%, respectively). This IgG to FcεR1α proved to be relevant in CSU patients with positive ASST (Staubach et al., 2006; Altrichter et al., 2011). Lee et al. (2014) found that the presence of IgG anti-FcεR1α was detected in 70% of CU patients with positive ASST. Using the immunodot technique, Ulambayar et al. (2017) reported that positivity rates for IgG autoantibody to FcεR1α were significantly higher in ASST positive CSU patients than in ASST negative CSU patients (32.8% vs. 16.4%).

Immunoblotting is a poor way to detect such antibodies, and as noted, has a highly false positive rate in normal controls. ELISA gives also false positives, but this may depend on the antibody used (Ferrer et al., 1998). Discrepancies were due to non-functional IgG2 antibodies (Soundararajan et al., 2005) or cross-reactions of alpha chain with IgG autoantibodies directed against other autoantibodies or carbohydrates which interfere with the results of binding assays (Pachlopnik et al., 2004).

The percentage of a positive APST was higher in patients with positive IgG to FcεR1α in comparison with IgG to FcεR1α-negative patients (85.7% and 26.3%, respectively). So, APST can be considered a reflection of the autoimmunity in CSU patients. In contrast, Asero et al. (2006) reported that most patients with chronic urticaria are positive on APST mainly due to the generation of thrombin and partially due to the presence of circulating antibodies. In the skin tests, the use of normal serum or plasma instead of saline as a negative control may help in excluding the autoreactivity.

The present study found that no statistically significant difference between IgG positive and IgG negative patients as regards age, duration of illness, atopy status, angioedema, and UAS. ANA positivity and total serum IgE level show no significant difference between IgG positive and IgG negative patients. This goes in line with Ulambayar et al. (2017) who reported that there were no significant differences in mean values of age, serum total IgE levels, urticaria duration and UAS (between IgG to FcεR1α positive and FcεR1α negative groups).

The present study found that there is no statistically significant difference between positive IgG patients and IgG negative patients as regards refractoriness to antihistamines. This goes in agreement with Ulambayar et al. (2017) who reported that the proportion of antihistamines refractory patients between IgG to FcεR1α positive and negative patients was not different.

The higher prevalence of IgG to FcεR1α in patients with positive ASST needs further prospective studies of a larger sample to evaluate IgG to FcεR1α as a potential biomarker in CSU and to predict therapeutic outcomes of the new immunological treatment protocols.

6. Conclusions

Circulating IgG to FcεR1α was detected in 52.5% of CSU patients, including 83.3% of ASST-positive patients and 78.3% of APST-positive patients. Circulating IgG to FcεR1α involved in the pathogenic mechanisms of CSU.

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Conflict of interest

The authors declare that they have no conflict of interest.

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