

The clinical and laboratory characteristics of acute spontaneous urticaria and its progression to chronic spontaneous urticaria

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ABSTRACT

Background: The natural history of the progression from acute spontaneous urticaria (ASU) to chronic spontaneous urticaria (CSU), CSU remains poorly understood.

Objective: To identify clinical and laboratory patient attributes that may be predictive of ASU progression to CSU.

Methods: We prospectively studied consecutive adult patients (age ≥ 18 years) with a diagnosis of urticaria of <6 weeks' duration. Healthy age- and sex-matched subjects served as controls. At study entry, autologous serum skin test (ASST), complete blood cell count, erythrocyte sedimentation rate, thyroid function tests, antinuclear antibodies, antithyroglobulin and antiperoxidase antibodies, and immunoglobulin E level were assessed in all the subjects. ASST and urticaria activity score assessment were performed in all the patients at baseline and then at weeks 7, 12, 24, and 48.

Results: Of 114 patients with acute urticaria and without identifiable causes, 73 patients (64%) were included in the ASU group, 41 patients in the CSU group (36%), and 44 healthy subjects in the control group. At baseline, 26 patients in the CSU group (63.4%) had a positive ASST result, whereas only 17 patients with a positive ASST result (23.3%) were revealed in the ASU group ($p < 0.001$). Patients with baseline ASST positive results were characterized by more profound basopenia (mean [standard deviation], 0.05 ± 0.08 cell/mm³) and more anti-thyroid peroxidase antibodies (18 [41.8%]) than those with the negative baseline ASST result (mean [standard deviation], 0.13 ± 0.09 cell/mm³, $p < 0.001$ more profound basopenia; and 13 (18.1%), $p = 0.009$ more thyroid peroxidase antibodies). We observed the disappearance of ASST positive result in some patients with CSU with baseline positive ASST results, whereas, in some subjects with CSU, baseline negative ASST results came to be positive results throughout the study period. A baseline positive ASST result of patients with ASU was a significant determinant (odds ratio 5.91 [95% confidence interval, 2.57–13.62]; $p < 0.001$) for a CSU diagnosis at week 7.

Conclusion: The patients with ASU who progressed toward CSU were characterized by a positive ASST result, thyroid autoimmunity, and profound basopenia at baseline.

(Allergy Asthma Proc 37:394–399, 2016; doi: 10.2500/aap.2016.37.3971)

Acute urticaria (AU) is differentiated from chronic urticaria based on the duration of illness, and it is estimated that any type of urticaria will affect 20–25% of the population at some point.¹ Chronic spontaneous urticaria (CSU) involves hives that last for >6 weeks and up to 1–5 years.² It is accepted that CSU has no discernable external cause.³ Chronic autoimmune urticaria (CAU) is implicated as a principal cause of CSU and potentially explains 30–50% of previously idiopathic cases.⁴ In CAU, the participation of different pathogenic autoantibodies causes release of histamine after reaction with immunoglobulin E (IgE) epitopes or with the α chain of Fc ϵ RI receptors.^{5,6} These autoim-

mune mechanisms could be detected in patients with CAU by the autologous serum skin test (ASST) and by immunoassay.^{4–9} A positive ASST result correlates with disease exacerbation in patients with CAU.¹⁰

Usually, CSU initially presents as AU. Although several infections, drugs, and foods are the most common triggers of AU, $>50\%$ of AU cases remain idiopathic.^{11–13} These AU cases with unknown origin could be considered acute spontaneous urticaria (ASU). As many as $\sim 25\%$ of cases of ASU in infancy and early childhood may eventually be diagnosed as CSU.¹⁴ Nevertheless, the natural history of the progression from ASU to CSU in the adult population remains poorly understood. The purpose of this study was to identify clinical and laboratory patient attributes that might be predictive of ASU progression to CSU.

METHODS

Patients and Setting

We prospectively studied consecutive adult patients (ages ≥ 18 years) who were referred to our outpatient allergy clinic from Ashdod region (Ashdod, Israel) for

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No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article
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a period of 14 months due to a diagnosis of urticaria with <6 weeks' duration. All the subjects who were taking antihistamine (AH) medications at referral discontinued taking the AH at least 4 days before skin testing. The participants had no clinical signs of infection and no clinical signs of food allergy. All the patients with physical and cholinergic urticaria; subjects treated with any medication (except AH); and those with thyroid diseases, systemic lupus erythematosus, and malignancy were excluded. Pregnant or breast-feeding patients were also excluded. To exclude physical types of urticaria, the following tests were performed: test for dermatographism, cold provocation and threshold test by using an ice cube, heat provocation, a threshold test by using warm water, and a pressure test by using pressure of 0.2–1.5 kg/cm² for 10 and 20 minutes. The study protocol was approved by the institutional review board of Barzilai Medical Center, Israel, and all the subjects gave informed consent.

Clinical Evaluation of Urticaria

At study entry, all the patients underwent a physical examination, liver and renal function tests, complete blood cell count, erythrocyte sedimentation rate evaluation, stool analysis for parasite ova, thyroid function tests, antinuclear antibodies, antithyroglobulin and/or antiperoxidase antibodies, and IgE titer. Assessment of urticaria activity was performed according to a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology, the EU-Funded Network of Excellence, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization guidelines.¹⁵ The urticaria activity score (UAS), which is based on the assessment of key urticaria symptoms (wheals and pruritus), was graded from 0 (none) to 3 (severe). This score was used to assess the clinical severity of ASU. The CSU activity was measured by advising patients to document 24-hour self-evaluation scores for 7 days. The mean of the UAS over 7 consecutive days was used.

Fexofenadine hydrochloride, 180 mg once a day (manufacturer's recommended or licensed dose; Tel-fast; Sanofi-Aventis, Netanya, Israel), was used as the drug of choice in the treatment of all the patients with ASU and CSU. The patients were reexamined every 7 days for 6 weeks to assess AH efficacy. Remission was defined as the absence of urticaria symptoms for at least 4 weeks without any medication.

ASST

ASST was performed at baseline and then at weeks 7, 12, 24, and 48. ASST was performed with 50 μ L of the patient's undiluted serum. Serum was collected by allowing the blood to clot at room temperature for 30

minutes and centrifugation at 500 $\times$ g for 10 minutes. This serum was then injected intradermally into the volar aspect of the forearm, along with simultaneously injected controls, including 50 μ L of sterile normal saline solution and freshly prepared histamine (50 μ L of 10 μ g/mL of histamine solution; Histatrol; ALK Abello, Inc., Hørsholm, Denmark). Readings of the autologous serum-induced wheal were taken at 30 minutes as well as the histamine-induced wheal at 10 minutes. The area of wheal was outlined with a thin-tipped marker pen and traced onto an acetate sheet to make a permanent record, which was subsequently used for analysis of areas of the wheal. The mean of the maximum perpendicular diameters of the wheal reactions was used to assess the ASST, the histamine, and normal saline solution control skin tests. The ASST result was considered to be positive if the autologous serum-injected site manifested a wheal with a diameter of ≥ 1.5 mm that of the saline solution site reaction.¹⁶

Statistical Analysis

Continuous variables are expressed as a mean (standard deviation). One-way analysis of variance and Bonferroni *post hoc* examinations were carried out for comparisons among the three groups (ASU, CSU, and control). Categorical variables of ASU and CSU groups were compared by using the Pearson χ^2 test. The Mann-Whitney *U* and Fisher's exact tests were applied for continuous and categorical variables to compare patients with ASST positive and negative results, respectively. Logistic regression was used to examine the effects of demographic, clinical, and laboratory factors on progression of ASU to CSU. For all values, the level of significance of $p < 0.05$ and with Bonferroni adjustment of $p < 0.025$ was considered significant. All statistical analyses were performed by using SPSS for Windows version 19.0 (SPSS Inc., Chicago, IL).

RESULTS

During the study period, 114 consecutive patients with idiopathic AU were referred to our allergy clinic. Of these, 73 patients (64%) had urticaria that resolved during ≤ 6 weeks and were included in the ASU group. The remaining 41 patients (36%) had recurrent wheals and pruritus for > 6 weeks. They were included in the CSU group. Healthy age- and sex-matched subjects ($n = 44$) served as the control group. At baseline, 26 patients in the CSU group (63.4%) had a positive ASST result, whereas only 17 (23.3%) ($p < 0.001$) had a positive ASST result in the ASU group. There were no other differences in demographics and clinical characteristics among the study groups at baseline (Table 1).

Because a ASST positive result was the main discriminant between ASU and CSU at baseline, we further performed comparisons of clinical characteristics of all

Table 1 Clinical and laboratory characteristics of the patients and healthy controls

	ASU (n = 73)	CSU (n = 41)	Controls (n = 44)	p Value	
				ASU vs CSU	ASU vs CSU
Age, mean (SD), y	34.7 ± 11.4	33.9 ± 12.2	38.5 ± 14.1	0.734	0.172
Women, no. (%)	40 (54.8)	28 (68.3)	28 (63.6)	0.161	0.629
Baseline UAS, mean (SD)	9.7 ± 3.5	10.2 ± 4.7	0	0.523	<0.001
Baseline ASST positive result, no. (%)	17 (23.3)	26 (63.4)	12 (27.1)	<0.001	0.023
No. basophils, mean (SD), cell/mm ³	0.08 ± 0.11	0.06 ± 0.08	0.19 ± 0.14	0.275	<0.001
Serum total IgE level, mean (SD), U/mL	153.9 ± 262.5	159.3 ± 271.8	112.6 ± 54.9	0.928	0.371
ESR, mean (SD), mm/hr	16.8 ± 10.3	17.3 ± 11.9	15.9 ± 13.4	0.821	0.889
C-reactive protein level, mean (SD), mg/L	5.7 ± 10.1	5.9 ± 9.4	2.75 ± 1.58	0.913	0.132
ANA (Positive > 1/80), no. (%)	2 (2.7)	5 (12.2)	2 (4.5)	0.099	0.578
Thyroglobulin Ab, no. (%)	3 (4.1)	7 (17.2)	1 (2.3)	0.034	0.037
TPO Ab, no. (%)	7 (9.6)	13 (31.7)	3 (6.8)	0.004	0.007
TSH level (0.35–4.94 mIU/l), mean (SD)	2.1 ± 1.4	2.3 ± 1.6	2.4 ± 0.7	0.478	0.455
25-hydroxyvitamin D level, mean (SD), nmol/L	22.5 ± 11.3	23.2 ± 11.9	24.5 ± 12.6	0.759	0.676

ASU = Acute spontaneous urticaria; CSU = chronic spontaneous urticaria; SD = standard deviation; UAS = urticaria activity score; ASST = autologous serum skin test; IgE = immunoglobulin E; ESR = erythrocyte sedimentation rate; ANA = antinuclear antibodies; TPO Ab = thyroid peroxidase antibodies; TSH = thyroid-stimulating hormone. Anti-TPO antibodies > 75 IU/mL and/or antithyroglobulin antibodies > 150 IU/mL.

the patients according to the baseline ASST positive results. Of the 114 patients, baseline ASST results were positive in 43 (37.7%). The patients with baseline ASST positive results were characterized by more profound basopenia (mean [standard deviation], 0.05 ± 0.08 cell/mm³) and more anti-TPO antibodies (18 [41.8%]) than those with the negative baseline ASST (mean [standard deviation], 0.13 ± 0.09 cell/mm³, $p < 0.001$ more profound basopenia; and 13 [18.1%], $p = 0.009$ more anti-TPO antibodies). There were no other differences in clinical and laboratory characteristics among the patients according to the baseline ASST positive results (Table 2).

Similar improvements in the mean UAS over 7 consecutive days were observed throughout the study period (at weeks 7, 12, 24, and 48) in patients with CSU with both a positive and a negative baseline ASST result (Table 3). Interestingly, we noted the disappearance of positive ASST results in some patients with CSU and with baseline positive ASST results, whereas, in some subjects with CSU, the baseline negative ASST result became positive during the study. At week 48, there was no difference in ASST positive results between patients with CSU and with baseline positive ASST results (12 [46.2%]) and baseline negative ASST results (6 [40%]) ($p = 0.747$) (Table 3). After 48 weeks of

prospective observations, no statistically significant differences in CSU duration between the patients with positive and negative ASST results were observed (Table 3). Multivariate analysis after the adjustment for age, sex, and baseline UAS demonstrated that a baseline positive ASST result of patients with AU was a significant determinant (odds ratio 5.91 [95% confidence interval, 2.57–13.62]; $p < 0.001$) for a CSU diagnosis at week 7.

DISCUSSION

In this prospective observational study, we identified clinical and laboratory attributes of patients that were predictive of ASU progression to CSU. We also noted factors related to the natural history of CSU over 48 weeks. The UAS was an important parameter for predicting the severity of CSU in previous studies.^{2,17,18} Nevertheless, we found that baseline UAS had no impact on ASU progression toward CSU. The baseline ASST positive result was the only clinical parameter that discriminated ASU from CSU during the first 6 weeks (ASU) after the beginning of urticaria and angioedema attacks. During the first 6 weeks (ASU), patients with a positive baseline ASST result were further characterized by more-severe basopenia and more anti-TPO antibodies.

Table 2 Clinical and laboratory characteristics of the patients with acute urticaria according to the baseline ASST positivity

	Baseline ASST Positive Result (<i>n</i> = 43)	Baseline ASST Negative Result (<i>n</i> = 71)	<i>p</i>
Age, mean (SD), y	35.7 ± 11.4	33.8 ± 12.1	0.408
Men, no. (%)	19 (44.2)	27 (38)	0.558
Atopy, no. (%)*	14 (32.6)	31 (43.7)	0.323
Angioedema, no. (%)	11 (25.6)	23 (32.4)	0.528
Diagnosis of CSU at wk 7, no. (%)	26 (60.5)	15 (21.1)	<0.001
UAS, mean (SD)	10.3 ± 3.9	9.1 ± 4.2	0.131
No. basophils, mean (SD), cell/mm ³	0.05 ± 0.08	0.13 ± 0.09	<0.001
IgE level, mean (SD), U/mL	162.7 ± 259.1	145.3 ± 277.5	0.740
Thyroglobulin Ab, no. (%)	13 (30.2)	8 (11.2)	0.023
TPO Ab, no. (%)	18 (41.8)	13 (18.1)	0.009
TSH level (0.35–4.94 mIU/L), mean (SD)	2.0 ± 1.6	2.4 ± 1.5	0.181
25-hydroxyvitamin D level, mean (SD), nmol/L	21.8 ± 12.1	23.5 ± 11.7	0.459
ESR, mean (SD), mm/hr	16.1 ± 9.5	17.3 ± 12.4	0.587
C-reactive protein, mean (SD), mg/L	5.3 ± 10.9	6.1 ± 9.7	0.684
ANA positive, no. (%)	3 (7.3)	4 (5.6)	0.705

ASST = autologous serum skin test; SD = standard deviation; CSU = chronic spontaneous urticaria; UAS = urticaria activity score; IgE = immunoglobulin E; TPO Ab = thyroid peroxidase antibodies; TSH = thyroid-stimulating hormone; ESR = erythrocyte sedimentation rate; ANA = antinuclear antibodies.

Anti-TPO antibodies > 75 IU/mL and/or antithyroglobulin antibodies > 150 IU/mL.

*Defined as a positive skin test to at least 1 common inhalant allergen, including house-dust mites, animal dander, mold, and pollens.

Table 3 Comparisons of clinical characteristics of patients with CSU according to baseline ASST positivity

	Baseline ASST Positive Result (<i>n</i> = 26)	Baseline ASST Negative Result (<i>n</i> = 15)	<i>p</i>
ASST positive result at wk 7, no. (%)	26 (100)	0	<0.001
UAS7 at wk 7, mean (SD)	24.3 ± 4.9	21.8 ± 5.4	0.137
CSU resolved at wk 12, no. (%)	1 (3.8)	0	1
ASST positive result at wk 12, no. (%)	24 (92.3)	3 (20)	<0.001
UAS7 at wk 12, mean (SD)	16.8 ± 3.1	15.1 ± 5.2	0.195
CSU resolved at wk 24, no. (%)	9 (34.6)	10 (66.7)	0.059
ASST positive result at wk 24, no. (%)	17 (65.4)	4 (26.7)	0.024
UAS7 at wk 24, mean (SD)	7.1 ± 2.4	5.3 ± 1.9	0.146
CSU resolved at wk 48, no. (%)	15 (57.6)	11 (73.3)	0.502
ASST positive result at wk 48, no. (%)	12 (46.2)	6 (40)	0.747
UAS7 at wk 48, mean (SD)	5.4 ± 2.1	4.6 ± 1.7	0.508

CSU = chronic spontaneous urticaria; ASST = autologous serum skin test; UAS7 = mean of the urticaria activity score over 7 consecutive days; SD = standard deviation.

CSU has frequently been associated with autoimmune disease.^{19–21} Published studies reported frequencies of thyroid autoimmunity in patients with CSU that ranged from 23 to 39%.²² Patients with coexisting thyroid autoimmunity and CSU have a more-severe and prolonged course of urticaria than those without thyroid autoimmunity.²³ However, the frequency of thyroid autoimmunity in patients with ASU has not been studied previously. Our study found no statistically

significant difference in the frequency of thyroid autoantibodies between patients with ASU and the healthy controls. However, these autoantibodies were more prevalent in patients with CSU. The antithyroid antibodies likely play a pathophysiologic role in CSU but not in ASU.

Highly cytokinergic IgE antibodies with polyreactivity to TPO in sera were shown to induce mast cell activation.²⁴ Some patients with CSU express IgE anti-

bodies against TPO as a unique pathophysiologic mechanism of CSU.²⁵ In addition, the presence of human IgE antibodies that react to thyroglobulin is also closely associated with the autoimmunity of CSU.²⁶ In addition, patients with CSU and with a highly specific IgE to TPO showed a favorable response to anti-IgE therapy.²⁷ Whether the above-mentioned mechanisms of thyroid autoimmunity have some effects in ASU progression toward CSU must be elucidated in further clinical and experimental studies.

There are limited data on the prognostic role of ASST in ASU and in predicting disease severity and the duration of CSU. Results of our study indicated a potential use of ASST to predict the ASU progression toward CSU. Nevertheless, no significant differences were noted in CSU duration and disease activity among the subjects with both baseline positive and negative ASST results over 48 weeks of prospective observation. Interestingly, throughout the study, we observed a reversion in the baseline positive ASST result into a negative ASST result in some patients with CSU. We noted positive ASST results in other subjects with baseline negative ASST results. Moreover, a similar proportion of CSU remission was achieved, notwithstanding the baseline ASST positive result at 48 weeks. This finding may agree with previous studies, which revealed no association between ASST positive results and a longer duration of disease activity in patients with CSU.²⁸ In general, a systematic review provides significant heterogeneous data on the prognostic role of ASST reactivity in CSU despite the fact that ASST conversion has not been assessed in the previous studies.²⁸

Another important question that arose from our study is whether a positive ASST result represents the same type of autoreactivity and indicates the presence of similar mast cell-activating autoantibodies in patients with ASU and patients with CSU. Generally, the presence of functional autoantibodies must be confirmed by the basophil histamine release assay and their specificity confirmed by the immunoassay.¹⁶ Mast cells were found to be critically involved in serum-mediated vascular leakage in both ASU and CSU through IgE- and IgG-independent mechanisms.²⁹ The hypothesized biologic factors that activate mast cells in ASU may also be related to blood coagulation and the complement system.^{30,31}

Analysis of recent data indicated that coagulation and/or fibrinolysis proteases in serum may act as natural C3 and C5 convertases to generate biologically active anaphylatoxins (C3a and C5a). These then link both cascades *via* multiple direct interactions *via* a complex serine protease system.³² We do not presently know whether the plasma bradykinin-forming cascade and the complement pathways are equally involved in the pathophysiology of ASU and CSU.

CONCLUSION

Angioedema, atopy, higher total serum IgE and C-reactive protein, and lower serum 25-hydroxyvitamin D levels have previously been identified as factors associated with a longer CSU duration and severity.^{2,17,32–36} Still, our study revealed no evidence to support the role of these parameters in predicting an advancement of ASU toward CSU. We note that the main limitation of our study is that we did not compare functional autoantibodies by basophil histamine release and/or immunoassays in patients with ASU and in patients with CSU. Additional research is needed to determine possible pathophysiologic mechanisms that discriminate ASU from CSU.

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