Original Article

Clinicoepidemiologic features of chronic urticaria in patients having positive versus negative autologous serum skin test: A study of 100 Indian patients

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ABSTRACT

Background: Chronic urticaria patients who demonstrate autoantibodies against the high-affinity receptor of IgE (FcεRI) or IgE itself tend to have a high itch and wheal score, and systemic symptoms may have a significant bearing on their management in terms of super pharmacologic doses of antihistamines needed or use of immunomodulators. Most studies have used histamine release assays rather than autologous serum skin tests (ASSTs) for correlating urticaria severity and histamine releasing activity. **Methods:** An ASST was performed in 100 (M:F, 31:69) chronic urticaria patients aged between 14 and 63 (mean, 32.69 ± 13) years with an objective to study the clinicoepidemiologic features like age, sex, age of onset and duration, frequency and distribution of wheals, urticaria severity, angioedema and systemic manifestations in ASST-positive and ASST-negative patients. **Results:** ASST was positive in 46% of the patients and negative in 54% of the patients, respectively. Both groups showed no statistically significant difference for epidemiological details. However, the ASST-positive patients had a higher mean urticaria activity score, frequent involvement of more body sites, particularly palms and soles, presence of throat angioedema and general constitutional, respiratory or gastrointestinal symptoms in comparison with the ASST-negative patients. **Conclusions:** Apparently, ASST-positive patients have more severe clinical manifestations of chronic urticaria. The knowledge will be useful for the treating dermatologists and patients alike in view of its therapeutic implications.

Key words: Urticaria, angioedema, anti-IgE autoantibodies, autologous serum skin test

INTRODUCTION

About 50% of the chronic urticaria patients who demonstrate IgG autoantibodies directed against epitopes expressed on α-chain of the high-affinity receptor of IgE (FcεRI) or IgE itself, often termed as autoimmune urticaria cases, tend to have a high itch and wheal score, systemic symptoms and other associated autoimmune diseases.[1,2] Most studies have used histamine release assays rather than autologous serum skin test (ASST) for correlating urticaria severity and histamine releasing activity. The ASST has a sensitivity of 70% and a specificity of 80% for *in vitro* basophil histamine release when the serum response is at least 1.5 mm greater than the control saline skin test at 30 min.[3,4] Thus, despite health and safety concerns, it can reasonably be employed as a predictive clinical test to diagnose clinically suspected cases of autoimmune urticaria or at least a subgroup of chronic urticaria patients who are more likely to have an endogenous cause for their disease.[5] We performed ASST in chronic urticaria patients with an objective to study the clinicoepidemiologic features in patients with positive or negative ASST. The knowledge will be useful for the dermatologists and patients alike

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as this has a significant bearing on the long-term management of these patients in terms of need to use super pharmacologic doses of antihistamines or immunomodulators, their use may not be justifiable otherwise on the basis of signs and symptoms of urticaria alone.

METHODS

One hundred consecutive patients (excluding pregnant/lactating females and children aged ≤12 years) of chronic urticaria (defined as recurrent urticaria occurring at least twice a week for a minimum of 6 weeks) attending the Outpatient Dermatology Department were enrolled between August 2007 and July 2008 for ASST. Patients having acute urticaria, urticarial vasculitis, physical urticaria (diagnosed on the basis of history/provocation tests) or other systemic diseases known to cause urticaria were also excluded. An ASST was performed after the patients were off antihistamines for 3 days (7 days for long-acting antihistamines and 2 weeks for doxepin), corticosteroids or immunosuppressive agents (for 6 weeks to 3 months) as per the procedure described previously.[3-5] The test was not performed over the areas involved by wheals in the last 24 h. The ASST was considered positive when the average diameter of the autologous serum-induced wheal was >1.5 mm of the saline-induced wheal and the redness of the autologous serum-induced wheal matched that of the histamine-induced wheal [Figure 1]. Age, sex, age of onset, duration, frequency of episodes, number and distribution of individual urticarial wheals or angioedema and systemic manifestations recorded at enrollment were analyzed in relation to the ASST results. Symptoms and signs were graded on the basis of the modified urticaria activity score [Table 1].[6] The Chi Square and Fischer's exact tests were used for categorical variables and the Mann–Whitney non-parametric test was used for the other variables that were not distributed normally. $P < 0.05$, calculated at the 5% level (95% confidence limit), was considered to be statistically significant.

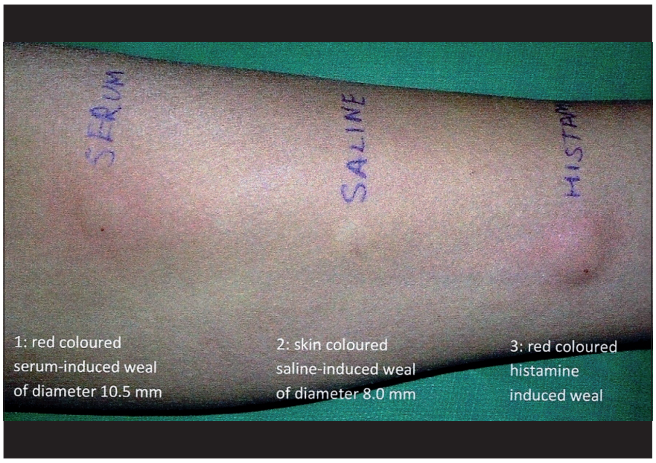

Figure 1: A positive autologous serum skin test. The serum-induced wheal has a diameter ≥1.5 mm of the saline-induced wheal and the redness score =2 (compared with the histamine-induced redness) at 30 min

RESULTS

There were 31 males and 69 females aged between 14 and 63 (mean, 32.69 ± 13) years. The overall duration of disease was 2–240 (mean, 40 ± 40.93) months and the age at onset of symptoms/signs was 2–63 (mean, 30.07 ± 13) years. ASST was positive in 46 (46%) and negative in the other 54 (54%) patients. These two groups did not show any significant difference when compared statistically for age, sex, age of onset and ASST results. The mean duration of urticaria was 43.37 ± 41.13 months and 37.52 ± 37.57 months in the ASST-positive and the ASST-negative patients, respectively, but was statistically insignificant. The mean number (5.0 ± 1.37) of body sites involved by wheals was statistically significant (P-value = 0.03) in the ASST-positive patients as compared with that (4.07 ± 1.32) in the ASST-negative patients, but both the groups did not differ in involvement of various body sites except for more frequent and significant involvement of palms in 29 (63%) and soles in 25 (54%) patients respectively in the ASST-positive patients. A urticaria activity score (UAS) of ≥5 was observed in 44 (96%) ASST-positive and in 19 (35%) ASST-negative patients, while it was <5 in two (4%) ASST-positive and 35 (65%) ASST-negative patients, respectively. The mean urticaria activity score (6.13 ± 1.6) was also significantly ($P < 0.001$) higher in

Table 1: Urticaria activity score

Pruritus severity score
Absent = 0
Present but not disturbing = 1
Disturbing but not hampering daytime activity or sleep = 2
Hampering day time activity or sleep = 3
Wheal score (average no. of wheals in 24 h)
Less than 10 wheals = 1
10–50 wheals = 2
>50 wheals = 3
Involving almost the whole body = 4

A numerical value is assigned to sign/symptom (ignoring the wheal size); Urticaria activity score = pruritus severity score + wheal score

the ASST-positive patients than that (5.13 ± 1.6) in the ASST-negative patients. Angioedema was present in 27 (59%) and 28 (52%) ASST-positive and ASST-negative patients, respectively, but both groups were comparable in the number of episodes (total 1 to >50) and the sites involved (lips, eyelids, buccal mucosa or tongue, hands and feet). In the ASST-positive patients, involvement of the throat was significantly higher ($P < 0.04$) compared with that in the ASST-negative patients. Multiple symptoms were associated in 24 (52%) ASST-positive and 20 (37%) ASST-negative patients, respectively. The gastrointestinal symptoms like abdominal pain, diarrhea, indigestion (13 patients), general malaise, headache, loss of concentration, lassitude, feverish feel and feeling of hot or cold (45 patients), breathlessness/wheezing, palpitations (12 patients) and joint pains (two patients) were more frequent in the ASST-positive cases while symptoms like nausea/vomiting (three patients), flushing (seven patients), joint swelling (one patient) and syncope (three patients) were seen more often in those with negative ASST. However, the difference was not statistically significant ($P = 0.18$).

DISCUSSION

The mean age at onset of urticaria in our ASST-positive patients was 29.65 ± 12 years, while it was 30.43 ± 12 years in the ASST-negative patients. The females outnumbered the males (M:F, 1:2.07) among the ASST-positive patients as compared with those (M:F, 1:1.25) among the ASST-negative patients. The ASST positivity of 46% in our patients appears comparable with the 27–60% positivity reported previously.[7,8-15] The higher ASST positivity in females (76%) than in males (35%) observed by us has been noted previously too.[16] However, the overall age and sex profile of our patients in both the groups was statistically similar and comparable to that reported by most workers.[10-12,14,17] Sabroe *et al.*,[6,7] in two separate studies, did not observe statistically significant variations in other epidemiologic features; the median duration of urticaria was 10 months (2 months to 32 years) in their patients, who released 5% or more histamine from basophils, less than the median duration of 22 months (2 months to 32 years) among patients who did not have histamine releasing activity. Mamatha *et al.*[11] also noted a median duration of 12 months in the ASST-positive patients as compared with 15 months in the ASST-negative patients. However, Toubi *et al.*[8] demonstrated a positive correlation between the chronicity of urticaria and positive ASST in a 5-year follow-up study. Although not statistically significant, the median duration of urticaria was a little longer in our ASST-positive patients, which corroborates with similar observations by Staubach *et al.*[18] The mean number (5.0 ± 1.37) of body sites involved in our ASST-positive patients was significantly higher than that (4.07 ± 1.32) in the ASST-negative patients. Similar observations were also made by Sabroe *et al.*[6,7] in patients with autoantibodies/histamine releasing activity. However, the difference in wheal distribution/body sites involved was not statistically significant in two previous studies.[11,12] The involvement of palms (63%) and soles (54%) was found to be significantly higher in our ASST-positive patients than (35% and 28%) that in the ASST-negative patients; the finding, to the best of our knowledge, has not been reported earlier. Statistically significant higher mean UAS of ≥5 in our 96% ASST-positive patients as compared with that in 33% ASST-negative patients corroborates with other studies.[6-9] Toubi *et al.*[8] demonstrated a trend toward a significant association between the severity of chronic urticaria and ASST positivity and documented a positive ASST in 32% of the patients with moderate to severe chronic urticaria. In two separate studies by Sabroe *et al.*,[6,7] the mean wheal and the itch scores (2.3 and 9.5) at its worst were significantly higher in patients with histamine releasing activity than (1.5 and 8.2) that seen among patients without histamine release. However, not all studies have shown a significant difference in UAS between the ASST-positive and the ASST-egative groups,[12,19] signifying variable UAS presentation among these patients. Although Swerdt *et al.*[17] observed angioedema in 86% of the ASST-positive and 67% of the ASST-negative patients, respectively, he found no statistical significance. However, the observations of Nettis *et al.*,[12] that the prevalence (69%) of angioedema is significantly higher in the ASST-positive cases as compared with that (43%) in the ASST-negative patients, are at variance. All our patients, in both the ASST-positive and the ASST-negative groups, had associated angioedema and were comparable statistically for the number of episodes and sites involved. The involvement of the throat was unusual and significantly higher in our ASST-positive patients. According to Sabroe *et al.*,[6,7] the patients with autoantibodies/histamine releasing activity had a significantly higher number of associated symptoms than in patients without autoantibodies. Gastrointestinal symptoms, flushing and feeling of

hot or cold in particular were significantly high in their patients with autoantibodies/histamine releasing activity. The associated symptoms were present in our 52% ASST-positive and in 37% ASST-negative patients, respectively. Although the difference was not statistically significant, symptoms like nausea/vomiting, abdominal pain, diarrhea, indigestion, breathlessness/wheeze, palpitations, headache, lassitude, joint pains and feeling of hot and cold were more frequent in the ASST-positive patients while flushing, joint swelling and syncope were frequent in the ASST-negative group. The symptoms of malaise, loss of concentration and fever were equivocal in both the groups. Apparently, ASST-positive patients have more severe clinical manifestations of chronic urticaria and may need prolonged and more aggressive therapeutic measures.

Limitations

The study has not determined how many patients in particular groups showed symptoms associated with the hypersensitivity to pseudoallergens that might be the case in a few of these patients. We also did not determine the concurrent presence of Hashimoto's disease or anti-thyroid antibodies, which may contribute to intensification of the symptoms in some ASST-positive cases. Although prolonged symptoms were highly disturbing, assessment for their psychosocial impact or therapeutic outcome in both the groups was not in the scope this work. Last but not the least, ASST itself has its own limitations.

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