Original Article

Chronic Urticaria in Blacks: Is Autoimmunity An Important Etiological Factor?

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Abstract

Background: The etiology and pathophysiology of chronic urticaria is poorly understood with several implicated factors. The role of autoimmunity has been explored by several studies with such studies on chronic urticaria lacking in the black population despite the significant morbidity caused by chronic urticaria. **Aim:** We assessed the possible contribution of autoimmunity in the etiology of chronic urticaria using autologous serum skin testing (ASST). **Materials and Methods:** Sixty consecutive patients with chronic spontaneous urticaria (CSU) with age- and sex-matched controls in a ratio of 2:1 had ASST done for comparison. Student's *t*-test and Chi-square were used to compare means and percentages, respectively. **Results:** The male:female ratio of CSU was 1:2.5 with females presenting more often. The ASST was noted to be significantly positive in patients compared to controls with a positivity rate of 68.3% in the former compared to 16.7% in the latter ($P = 0.0001$). A higher incidence of angioedema was also documented in patients with a positive ASST in association with urticaria (23/28, $P = 0.04$). **Conclusion:** Overall, we conclude from our study that autoimmunity may be a possible cause of chronic urticaria in Nigerians which may also be extrapolated to other black population. Patients with positive ASST may have more severe disease which may be important when educating and counselling the patients about the course of the disease. This study is the first to assess the possible role of autoimmunity in a predominantly black population and will serve as a baseline for future studies.

Keywords: Autoimmunity, autologous serum skin testing, chronic urticaria

Introduction

Chronic spontaneous urticaria (CSU) is defined by the presence of wheals and itching with or without angioedema present for more than six weeks.[1-3] The etiology and pathophysiology is poorly understood and despite comprehensive investigations, the cause of CSU in most patients remain undiagnosed.[1,4-6] In a subset of patients grouped as having *autoimmune urticaria*, circulating autoantibodies against the high affinity immunoglobulin E (IgE) receptor FCεRI or against IgE that functions as mast cell activating signals have been identified.[7,8]

The autologous serum skin testing (ASST) is an *in vivo* clinical test that may be used as a predictive assessment of the presence of functional circulating autoantibodies with a sensitivity of 80% and specificity of 90% as documented by Sabroe *et al*.[9] The aim of this study was to assess the possible role of autoimmunity in chronic urticaria patients in this environment with predominantly dark-skinned population.

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Materials and Methods

This study was carried out at dermatology outpatient clinic of Lagos University Teaching Hospital (LUTH), Idi Araba Lagos and all consecutive patients presenting with CSU with or without angioedema between May 2017 and April 2018 were recruited into the study. LUTH is a government hospital and the larger of the two teaching hospitals in the state that provides multidisciplinary tertiary care services to the inhabitants of Lagos and its surrounding states. Lagos State is unarguably the most economically important state in the nation and the

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former capital of Nigeria. The clinic attends to an average of about one hundred and fifty patients weekly and a third of these are newly referred dermatology patients.

The procedures carried out agreed with the ethical standards of the committee on human research (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000 with ethical approval granted by the hospital after thorough appraisal of study design and methodology by the health research and ethics committee of LUTH prior to commencement of recruitment into the study (ADM/DCST/HREC/APP/1249).

The study was descriptive, and the procedures associated (blood draws) were procedures that are routinely conducted during standard clinical practice and risk exposures were negligible. Informed consent was obtained from all participants without undue influence or coercion, and the right to withhold participation or withdraw at any time, confidentiality was communicated clearly. No cost related to the study was borne by participants. All data were de-identified using study identification numbers, and personal data to enable follow-up and tracking of participation were securely kept.

CSU was defined as spontaneous wheals lasting greater than six weeks. Sixty patients (15–69 years) were enrolled in the study after a written informed consent was obtained. A thorough clinical history and physical examination was carried out to assess for features suggestive of an autoimmune disease and thyroid disease. Complete blood counts (CBC), erythrocyte sedimentation rate (ESR), and antithyroid peroxidase (anti-TPO) were carried out in all patients with chronic urticaria. ASST was performed on all the 60 chronic urticaria patients and 30 age- and sex-matched controls as there was difficulty recruiting controls because they considered the test invasive, and they were not ill. Pregnant and lactating women, patients with history of allergic diseases like asthma, patients with chronic illnesses like diabetes mellitus and hypertension were all excluded from the study.

The serum for ASST was extracted by taking venous blood in a plain glass tube and allowed to stand at room temperature for 30 min. Care was taken to label each patient's serum properly and procedure was done under strict asepsis. Serum was then gotten after centrifuging this at 2000 rpm for 10 min. ASST was performed by injecting 0.05 ml (with a 1 ml insulin syringe) of each patient's serum intradermally on the proximal part of the volar aspect of the forearm for positive control and equal amount of normal saline distally as negative control with a gap of 5 cm between the two. The two areas injected were marked with a pen and labelled as test (T) and control (C) respectively. The wheal reaction was assessed at 30 min and the recorded diameter was measured as the average of the maximum horizontal and vertical diameters. The response was graded from 0 to + 3 as follows; diameter as 0 = negative control; +1 = wheal 1.5 mm > negative control, mm; +2 = wheal 3-5 mm > negative control, +3 = wheal 6–10 mm > negative control.[9,10] Only the wheal reaction was assessed as erythema in serum skin testing is not easily appreciable in pigmented skin and histamine which is supposed to be used as positive control can be omitted in patients with dark skin without affecting the results.[11] Antihistamines and steroids were stopped at one week and two weeks prior to ASST respectively. The ASST does not induce a systemic reaction as the serum being injected is the patient's own. Resuscitative materials such as hydrocortisone, adrenaline and normal saline were however available during the procedure in case of any systemic reaction. No systemic reaction occurred as each patient's serum was properly labelled and crosschecked before injection.

The Statistical Package for Social Sciences version 22.0 (SPSS Chicago Inc. Illinois USA) was utilized for statistical analysis. Categorical variables were expressed as percentages while continuous variables were expressed as means and standard deviation. The Chi square test was utilized for comparison of percentages while the student's *t*-test was used to compare means. $P < 0.05$ was considered statistically significant.

Results

A total of 68 patients with urticaria presented to the clinic during the one-year period of this study, and 60 eligible patients were enrolled in the study. Among the patients recruited, 43 (71.7%) were females while 17 (28.3%) were males. The controls recruited consisted of 21 females (70%) and 9 males (30%). The mean age of cases (at presentation) and controls was 37.1 ± 13.7 and 36.7 ± 12.9 years respectively ($P = 0.88$). The average age at onset of urticaria was 31.1 ± 13.3 years (females 32.7 ± 13.7; males 27.3 ± 11.7, $P = 0.16$) and peak age at onset was in the third decade of life for both genders. There was no history or clinical findings suggestive of autoimmune or thyroid disease in all the patients and controls. A personal history of atopic dermatitis was documented in 9 (15.0%) and a history of asthma in 4 (6.7%) patients respectively however this was not significant when compared to a positive ASST result ($P = 0.7$, $P = 1$).

Urticaria occurred with angioedema in 28 patients (46.7%) while a positive family history was recognized in 18 (30%) patients [Figure 1]. The average age at onset of urticaria did not differ significantly between those with (29.4 ± 14.6) and without (31.6 ± 12.9) a documented family history of urticaria ($P = 0.57$). The frequency of a positive family history was 34.9% (15/43) in females and 17.6% (3/17) in males (Fischer's exact $P = 0.23$).

ASST was positive in 68.3% (41/60) chronic urticaria participants compared to 16.7% (5/30) controls, and this difference was significant statistically ($P = 0.0001$) [Figures 2 and 3]. The distribution of responses on ASST is also shown in Table 1. The frequency of positive ASST was comparable between males and females ($P = 0.32$). Patients with a ASST positivity of + 2 were more likely to have symptoms lasting more than one year ($P = 0.02$). Patients with positive ASST also had a higher prevalence of angioedema (23/28 patients with angioedema) with symptoms lasting more than 24 h ($P = 0.04$). ASST was positive in (13/18)

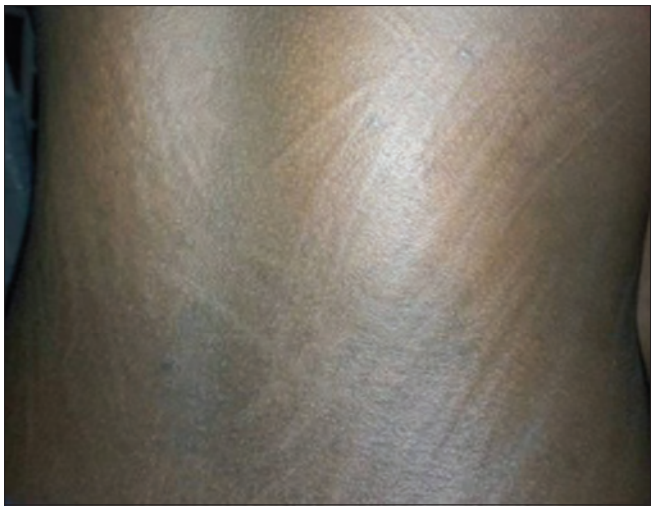

Figure 1: Wheals on the back of a patient with chronic urticaria

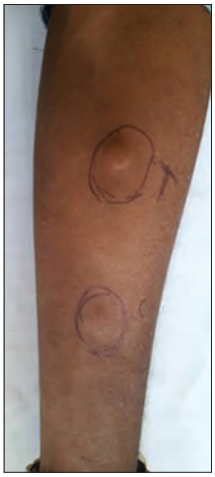

Figure 2: Positive autologous serum skin testing on the left forearm

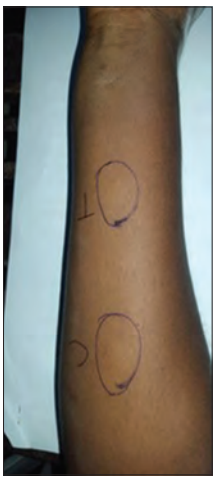

Figure 3: Negative autologous serum skin testing on the right forearm

of those with a family history of urticaria in first degree relatives although compared to the percentage of those without a positive family history and were also ASST positive, this was not significant statistically ($P = 0.49$).

Table 1: Autologous serum skin testing in chronic urticaria patients and controls

ASST	Degree of intensity	Chronic urticaria ($n=60$)	Controls ($n=30$)
Positive test*		41 (68.3)	5 (16.7)
Wheal size			
+1 (wheal 1.5- <3 mm>NC)	Mild	3 (5)	1 (3.3)
+2 (wheal 3-5 mm >NC)	Moderate	26 (43.3)	3 (10)
+3 (wheal 6-10 mm >NC)	Severe	12 (20)	1 (3.3)

*P for intergroup difference in frequency=0.0001, Wheal size measured in mm and compared to a standard saline NC. NC: Negative control, ASST: Autologous serum skin testing

The CBC was normal and the median ESR was 21.50 (12.25-39.75). Anti-TPO was positive in 3/60 (5%) and this did not show any association with a positive ASST ($P = 0.24$).

Discussion

Several factors working synergistically have been implicated in the pathogenesis of chronic urticaria.[1,12] Crucial to the pathophysiology of urticaria is an inappropriate stimulation and mast cell degranulation with release of preformed intermediates like histamine and newly formed mediators like leukotriene C4, D4 and prostaglandin D2.[13,14] Various pathogenetic mechanisms have been noted to be involved in chronic urticaria and these include immunologic, autoimmune, coagulative, complement mediated and cytokine driven mechanisms. These mechanisms are likely to be synergistic in the pathophysiology rather than being involved independently. There is an altered cytokine and chemokine expression subsequent to immune dysregulation.[13] The extrinsic coagulation pathway has also been noted to play a role and severe attacks of urticaria have been associated with the release of fibrin degradation products. The role of platelets in immune mediated disorders like atopic dermatitis, psoriasis and urticaria has been documented.[15]

More recently, autoimmunity has been implicated to play a considerable role in chronic urticaria.[1,16] Clustering of autoimmune diseases such as Type 1 diabetes mellitus, rheumatoid arthritis, Sjogren syndrome, coeliac disease among others have been documented in individuals with urticaria further supporting the autoimmune basis of chronic urticaria.[17-19] The autoimmunity in urticaria is directed toward the IgE (FCERI) receptor or toward IgE.[9,20] Basophil histamine releasing assay is the ideal *in vitro* test to assay for these functional antibodies; however because of the cumbersome nature of the tests, *in vivo* skin reactivity tests such as ASST and APST are often used as a replacement for this.[6,9] The prevalence of ASST positivity from previous studies ranges from 30% to 78% which resonates with the 68.3% in this study while that of APST ranges between 14% and 97% although both have been documented to suffice for *in vivo* skin reactivity testing.[21-24] Kocatürk *et al*. found the sensitivity of ASST to be higher in distinguishing patients with

CSU and controls although specificity of APST and ASST was similar.[25] Kumaran *et al*. noted that APST had a higher sensitivity, specificity and positive predictive value compared to ASST although this was not statistically significant.[22]

The demographic distribution of patients with urticaria and positive ASST in this study is also in agreement with previously done studies with a female preponderance.[10,22,26] Patients with moderate ASST positivity were likely to present with a longer duration of disease greater than one year as noted in this study. Angioedema occurred more often significantly in patients with ASST positive results. Kumaran *et al*. also documented a more severe intensity of angioedema in patients with ASST positivity although the prevalence of angioedema was similar when compared to those with ASST negative results.[22] This may be indicative of the fact that patients with ASST positive chronic urticaria may have a more severe course. It is not surprising in this study that people with more symptomatic disease would present in the clinic as the study site is a tertiary hospital and people with milder symptoms would have been seen by general practitioners. The significant prevalence of ASST positivity in our study may also be attributed to the fact that patients with more severe symptoms are likely to present to the teaching hospital.

Asero *et al*. documented a positive family history in 7% of patients in a large study of patients with urticaria.[27] Although in our study, patients with ASST had a higher incidence of urticaria in first degree relatives, this was not significant when compared with patients with negative ASST results. Other parameters that demonstrated no significant association with ASST include gender, personal history of atopy and asthma similar to some previous studies.[22]

The high percentage of positive ASST in patients in this study highlights the possible role of autoimmunity in chronic urticaria in this environment that has not been previously explored. Supporting the plausible role of autoimmunity is the high percentage of young women affected by chronic urticaria. Closely interacting with autoimmunity is a likely background genetic susceptibility to the development of urticaria. This may be the reason patients have long standing symptoms.

Limitations

The study site is a tertiary hospital and as such, the results may not be characteristic of the general populace, but it would serve as a baseline for further studies regarding the role of autoimmunity in chronic urticaria in black patients. Antinuclear antibody was also not done in the patients, and this may have supported the findings from the skin reactivity test.

Conclusion

Autoimmunity may be contributory in chronic urticaria in black patients as shown by the response to ASST. Patients with positive ASST may have an extended period of disease, and recalcitrant disease as evidenced by the greater prevalence of angioedema in patients with ASST positivity. More studies especially community-based ones should be explored in future.

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Conflicts of interest

There are no conflicts of interest.

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