ORIGINAL ARTICLE

Significance of antithyroid antibodies and other auto-antibodies in Saudi patients with chronic urticaria. Possible parameters in predicting chronic over three years disease

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KEYWORDS
Chronic urticaria; Autoimmune thyroid disease; Anti-thyroglobulin; Antimicrosomal antibodies

Abstract  Objective: To determine the frequency and significance of thyroid auto-antibodies and antinuclear antibody among Saudi patients with chronic urticaria and to identify markers of chronic urticaria disease.

Materials and methods: Non-interventional, prospective analytical study carried out among consecutive patients with chronic urticaria in the Department of Dermatology, College of Medicine, King Saud University, Riyadh, Saudi Arabia between January 2005 and December 2007. Patients were divided into two groups: Group 1 – with hypothyroidism, Group 2 – without hypothyroidism, both age-matched to normal healthy controls. All patients were investigated for the presence of antithyroglobulin (ATG), antimicrosomal (AMA), antinuclear antibodies (ANA) as well as rheumatoid factor (RF) and antibodies to hepatitis B and C.

Results: A total of 90 participants were included in the study. Significant elevation of anti thyrooglobulin antibodies was found in patients with hypothyroidism than in those without hypothyroidism and in the control group (30.4% vs. 24.4% vs. nil, p = 0.022). Elevated titers of antimicrosomal antibodies were seen in chronic urticaria patients with or without hypothyroidism compared to control group. Positive antinuclear antibodies were detected in all groups. There were no significant
1. Introduction

Urticaria is a common dermatosis observed in 15–25% of the general population and 25% of urticaria is chronic (Leznoff, 1998; Sharma and Miller, 1993). Chronic urticaria is characterized by recurrent, itchy, transient macula-papular rash with or without angioedema lasting for more than 6 weeks (Greaves, 1995; Turktaş et al., 1997). Patients with chronic urticaria have impairment in the quality of life similar to patients with psoriasis, acne and heart disease (O’Donell et al., 1997; Poon et al., 1999; Yosipovitch and Greaves, 2008). The probable lethal risk of laryngeal edema and the influence of urticaria on quality of life make this skin condition a true health concern (O’Donell et al., 1997).

Despite extensive investigations no cause is identified in the majority of patients, thus remains idiopathic (Greaves, 2000; Tong et al., 1997). The prevalence of thyroid function alterations in such patients as well as the efficacy of correcting these alterations has been discussed in many studies but it remains questionable (Zauli et al., 2002).

Furthermore, around 10–40% of patients with chronic urticaria were found to have antibodies to FC epsilon R1 (IgE receptors), IgE or both in the sera of patients (Tong et al., 1997; Zauli et al., 2002; Collet et al., 1995; Grattan et al., 1992; Kaplan and Greaves, 2009). It has been reported in previous studies that the frequencies of antithyroid antibodies, such as antithyroglobulin (TGA), antimicrosomal (TMA) or antithyroxineoxidase antibodies (TPO) were found to be significantly higher in patients with chronic urticaria (Zauli et al., 2001). In addition, an association has been reported between hepatitis C and chronic urticaria (Broussé et al., 1999; Fernandez-Soto et al., 1998).

2. Methods

This non-interventional, prospective analytical study was carried out in the Department of Dermatology, College of Medicine, King Saud University, Riyadh, Saudi Arabia between January 2005 and December 2007 among patients with chronic urticaria of more than six weeks in duration.

Patients were divided into two groups; Group 1 consisted of chronic urticaria patients with hypothyroidism and Group 2 consisted of chronic urticaria patients without hypothyroidism. For comparison, a separate group of patients were recruited which comprised normal healthy age-matched controls. In all patients ANA, TGA and TMA were measured. A hemagglutination technique titer of < 1:10 was considered negative for TGA and < 1:100 was negative for TMA. ANA was positive if titer reads 1:80 or above. TSH and T4 were measured by radioimmunoassay. Hypothyroidism was diagnosed clinically together with a TSH level > 5 mIU/L. All patients including the controls were investigated for the presence of antithyroglobulin, antimicrosomal, antinuclear antibodies as well as antibodies to hepatitis B and C to exclude known causes of urticaria.

Data were collected and analyzed using Predictive Analysis Software version 18 (PASW, SPSS Inc., IBM-SPSS, Chicago, Illinois, USA). Demographic frequencies were expressed as mean ± standard deviation (SD) or as percentage distribution. The group statistics were assessed using students’ t-test for paired samples or Fisher’s exact test as appropriate. The relationship between urticaria duration, family history and auto-antibodies was evaluated using Fisher’s exact test or Chi-square test, when appropriate. Two-tailed p value of < 0.05 was considered statistically significant.

3. Results

There were 23 patients with chronic urticaria with hypothyroidism (Group 1) and 43 patients with chronic urticaria without clinical or biochemical hypothyroidism (Group 2). Twenty-two participants comprised the normal healthy age-matched controls. Patients with chronic urticaria without hypothyroidism were significantly younger compared to those with hypothyroidism (37.9 ± 15.6 years vs. 46.2 ± 12.6 years, p = 0.03). There is significant preponderance to the female gender in both study groups (100% and 84.4%, p = 0.047). The mean duration of urticaria was relatively longer in patients with hypothyroidism than in those without hypothyroidism (6.3 ± 6.0 years, range: 6 months to 25 years vs. 4.4 ± 4.4 years, range: 2 months to 25 years, p = 0.138).

Table 1 describes the comparison of frequencies of TGA, TMA and ANA between the study groups and the control group. There were 30.4% of patients in Group 1 who had elevations of TGA, 24.4% of Group 2 and none among the healthy controls (χ² = 0.022). There were no significant differences in the mean TGA titers observed in between study groups (p > 0.05), however, significant elevations of TGA titers were observed among the study patients compared to the healthy group (18/68 or 26.5% vs. none, p < 0.0001). There were 26.1% of patients in Group 1 who had elevations of TMA, 26.7% of Group 2 and 4.5% among the healthy controls (χ² = 0.09). There were no significant differences in the mean TMA titers observed in between study groups (p > 0.05), however, significant elevations of TMA titers were observed among the study patients compared to the healthy controls.
group (18/68 or 26.5% vs. 4.5%, \( p < 0.0001 \)). There were 4.3% of patients in Group 1 who had elevations of ANA, 24.4% of Group 2 and 18.2% among the healthy controls \( (x^2 = 0.004) \). A significantly higher percentage of patients without hypothyroidism had elevations of ANA compared to those with hypothyroidism \( (p = 0.037) \), however, there were also a significant percentage of normal healthy controls who had elevations of ANA \( (18.2\%, p = 0.047) \). There were no significant differences in the percentage of patients who had elevations of ANA between the study group and the control group \( (p = 0.823) \).

Thirty-eight patients had the disease for more than 3 years. Of these, 4 (of 23 patients in Group 1 or 25%) and 13 (of 45 patients in Group 2 or 29.4%) had elevations of ANA \( (18.2\%) \), indicating more female predominance in patients of chronic urticaria with hypothyroidism, which is consistent with the published data \( (Lezoff and Sussman, 1989) \). The findings of a significantly younger age population of chronic urticaria patients without hypothyroidism are understandable since thyroid autoimmunity and hypothyroidism may appear several years after the onset of urticaria \( (Levy et al., 2003) \).

The elevated titers of antithyroglobulin antibodies and AMA in patients with chronic urticaria and hypothyroidism in both study groups when compared to controls were consistent with the findings of Turktas et al. \( (1997) \) \( (O'Donell et al., 1997; Broussolle et al., 1999) \) where elevations of TGA and TMA were as much as 11.7% and 9.6% of patients \( (O'Donell et al., 1997; Broussolle et al., 1999) \). In another study, elevated titers of TGA were also found in as much as 30% of patients with chronic urticaria and as much as 80% in patients with hypothyroidism. Elevated titers of AMA were likewise found in 43.3% with chronic urticaria and as much as 90% in patients with hypothyroidism, with or without urticaria \( (O'Donell et al., 1997; Aamir et al., 2008) \). These elevations in TGA and TMA represent an abnormal thyroid function in chronic urticaria patients; however, the pathogenesis in the context of chronic urticaria associated to thyroid autoantibodies remains vague. The significance of the association lies in the different autoimmune mechanisms found in both disorders \( (O'Donell et al., 1997; Greaves, 2000) \).

Table 2 Comparison of frequencies of antithyroid and antinuclear antibodies in chronic urticaria patients with or without hypothyroidism among those with more than 3 years of disease duration.

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Chronic Urticaria with hypothyroidism ( n = 16 )</th>
<th>Chronic Urticaria without hypothyroidism ( n = 22 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>Antithyroid antibodies</td>
<td>4 (25%)</td>
<td>13 (59.1%)</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>0 (0%)</td>
<td>10 (45.5%)</td>
</tr>
</tbody>
</table>

4. Discussion

Our study showed that most of our patients had chronic urticaria \( (duration > 3 \text{ years}) \) with greater preponderance to the female gender which is in concordance with the report of Lezoff and Sussman \( (1989) \) which female to male percentages in Groups 1 and 2 were \((100:0\%) \) and \((84:15.6\%) \), respectively, indicating more female predominance in patients of chronic urticaria with hypothyroidism, which is consistent with the published data \( (Lezoff and Sussman, 1989) \). The findings of a significantly younger age population of chronic urticaria patients without hypothyroidism are understandable since thyroid autoimmunity and hypothyroidism may appear several years after the onset of urticaria \( (Levy et al., 2003) \).

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Our study confirms the relationship between chronic urticaria and thyroid autoimmunity as suggested in previous studies \( (O'Donell et al., 1997; Aamir et al., 2008) \). These elevations in TGA and TMA represent an abnormal thyroid function in chronic urticaria patients, however, the pathogenesis in the context of chronic urticaria associated to thyroid autoantibodies remains vague. The significance of the association lies in the different autoimmune mechanisms found in both disorders \( (O'Donell et al., 1997; Greaves, 2000) \).

Elevated AMA antibodies were likewise found in 43.3% with chronic urticaria and as much as 90% in patients with hypothyroidism, with or without urticaria \( (Toubi et al., 2004) \). In this study positive antinuclear antibodies \( (ANA > 1:80) \) were detected in one patient \( (4.35\%) \) in Group 1; 11 patients \( (24.4\%) \) in Group 2 and four patients \( (18.18\%) \) in the control group which may indicate higher incidence of ANA positivity among chronic urticaria patients without hypothyroidism, thus more apt to be a marker of autoimmunity \( (Gurber et al., 1988; Sabroe et al., 1999; Godse, 2004) \).
In our study, we found no significant differences in the severity of the disease in between study groups. This suggests that whether chronic urticaria patients present with or without hypothyroidism, the severity of the condition is unaffected. These findings conform to the previous study which stated that patients may still suffer from chronic urticaria after 3 years or even more, despite the absence of hypothyroidism. Although we found no significant associations between duration of urticaria with family history of hypothyroidism or the disease severity, there might be other confounding factors that in one way or the other correlate the existence of such unique factor in a particular patient and makes it peculiar sometimes. Furthermore, in this study, among patients of chronic urticaria of more than 3 years duration, the frequency of antithyroid antibodies positivity increases significantly. Our findings suggest a strong association between the duration of urticaria with the significant elevations of antithyroid antibody titers and also positivity to ANA. Thus, early identification of patients whose urticaria is expected to be chronic warrants an immunological work-up. If TGA and TMA are present in high titers, this may support the diagnosis of chronic immunologic urticaria. The plasma levels of thyrotropin may help in the screening for thyroid dysfunction.

Urticaria is one of the extra hepatic manifestations of hepatitis B and C (Reichel and Mauro, 1990). It might occur as part of the prodromal phase of hepatitis B infection along with fever and arthralgia. In a study conducted by Chen et al. (2009) (19.3%) of their 150 patients of chronic urticaria were found to have higher incidence of positive HbsAb as compared to controls (10%) (Broussolle et al., 1999; Fernandez-Soto et al., 1998; Chen et al., 2009).

Chronic urticaria associated with HCV infection could make a distinct clinical entity characterized by older age group (53 years), longer lasting eruption, detectable HCV RNA and abnormal liver function test with an indication for interferon therapy (Broussolle et al., 1999; Fernandez-Soto et al., 1998; Chen et al., 2009).

In recent reports thyroid dysfunction and elevated Thyroperoxidase antibodies were the most frequently reported untoward side effects among patients receiving interferon therapy for hepatitis C reaching as high as (6%) (Dusheik, 1997). Screening patients for hepatitis B and C might be of significance to exclude other underlying causes of thyroid disease, auto-antibodies and urticaria.

Because of the associations between thyroid dysfunction and chronic urticaria, thyroid function screening, detection of auto-antibodies, and ANA titers may be advisable to determine an underlying autoimmune disorder. This may serve as an adjunct in the diagnosis of patients with chronic urticaria for early identification and detection of the underlying thyroid dysfunction and autoimmunity.

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References


Significance of antithyroid antibodies


