

Frequency of Autoimmune Thyroid Disease in Chronic Urticaria

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ABSTRACT

Objective: To determine the frequency of autoimmune thyroid disease in diagnosed cases of chronic urticaria (CU) and the association between hypothyroidism and chronic urticaria if any.

Study Design: Non-interventional, descriptive study.

Place and Duration of Study: Department of Physiology, Dow University of Health Sciences, Karachi, from December 2004 to January 2006.

Methodology: The patients were selected from Department of Dermatology and Medical Units of Civil Hospital, Jinnah Postgraduate Medical Centre, the Aga Khan Hospital and community clinics. A total number of 60 patients were enrolled in this study. In all patients, serum antithyroid autoantibodies (antithyroglobulin and antimicrosomal/thyroperoxidase), thyroid profile (serum TSH, T3 and FT4), complete blood count, erythrocyte sedimentation rate and IgE levels were carried out. The proportions were compared using chi-square test with significance at $p < 0.05$.

Results: Forty seven (78%) patients were found to have chronic urticaria (history and laboratory reports). Out of 47 patients with diagnosis of CU, elevated titres of antithyroglobulin (TGA) and antimicrosomal antibodies (TMA) were found to be present in 20 (42.6%) and 27 (57.4%) patients respectively. Serum TSH level (thyroid stimulating hormone) was increased and T3, FT4 were decreased in 20 (42.6%) patients ($p < 0.001$). A total number of 20 (42.5%) patients were found to be hypothyroid with chronic urticaria of greater than 6 weeks duration.

Conclusion: This study shows a statistically significant association between hypothyroidism and chronic urticaria. Full thyroid profile (serum thyroid autoantibodies, serum TSH, T3 and FT4) is highly recommended in patients with diagnosis of chronic urticaria.

Key words: *Chronic urticaria. Hypothyroidism. Thyroid autoantibodies. Autoimmune urticaria. Autoimmune thyroid disease.*

INTRODUCTION

Chronic urticaria (CU) is defined as the presence of urticaria (hives) for at least 6 weeks duration with the assumption that it occurs daily or close to it.¹ Keeping in view the autoimmune basis, chronic urticaria can be divided into autoimmune chronic urticaria (45%) and idiopathic chronic urticaria (55%).² The autoimmune sub-group is associated with the IgG anti-IgE receptor alpha sub-unit in 35-40% of patients and IgG anti-IgE in an additional 5-10%.² These autoantibodies have been shown to activate blood basophils and cutaneous mast cells *in vitro* with augmentation of basophil activation by complement and release of C5a.³

Autoimmune thyroid disease is the most common organ specific autoimmune disorder usually resulting in dysfunction (hyper function, hypofunction or both) of thyroid gland.⁴ Hashimoto's thyroiditis is an autoimmune disease characterized by defects in suppressor T-lymphocytes.⁵ As a consequence, T-helper cells cooperate with B cells to produce antithyroid antibodies.

The first study of autoimmunity in patients with CU reported that patients with CU have increased frequency of Hashimoto's thyroiditis.⁶ This association was studied with presence of antibodies to thyroglobulin or microsomal driven antigen (peroxidase) even in euthyroid patients.⁷

The role of thyroid autoantibodies in physiological derangements of CU is highly debatable. One theory postulates that antithyroid autoantibodies in CU are only reflection of a more generalized autoimmune state.⁸ Another theory suggested that thyroid stimulation by thyroid stimulating hormone drives the glandular activity and potentially exacerbates inflammation even in euthyroid patients.⁸ The postulated pathogenetic mechanism is that inflammation caused by thyroid autoantibodies disrupt the normal architecture of thyroid gland and leads to release of sequestered antigens which are perceived as non-self and induce a low grade immune response. The product of this autoimmune response such as thyroid protein immune complexes could be formed that activate classical pathway leading to generation of C3a and C5a, which can bind to receptors in skin mast cells and trigger degranulation leading to symptoms and signs of CU.⁸

This article focuses to search for an association between CU and hypothyroidism (positive antithyroglobulin (TGA) and antimicrosomal (TMA) autoantibodies, elevated levels of serum TSH, and decreased levels of T3 and

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FT4). The main thyroid autoantigens are thyroglobulin, thyroid peroxidase and thyroid stimulating hormone receptor. Antimicrosomal/antiperoxidase (TMA) and antithyroglobulin (TGA) are the routinely tested antibodies in clinical practice today and can be demonstrated in serum in population surveys.⁹

The objective of this study was to determine the frequency of autoimmune thyroid disease in diagnosed cases of chronic urticaria and the association between hypothyroidism and chronic urticaria if any.

METHODOLOGY

This descriptive study was conducted at Dow University of Health Sciences, Karachi, in the Department of Physiology, from December 2004 till January 2006. A total number of 60 patients were enrolled with history of hives and female gender: gender was favoured by known frequency in literature. The selected patients were not supported or funded by any agency. The affording patients were told about the significance of laboratory tests and treatment options. The non-affording patients were paid by self-funding. Cases of acute urticaria and angioedema, asthma, Hepatitis B, Hepatitis C and Diabetes mellitus, which may affect the levels of thyroid autoantibodies and thyroid profile were excluded.

All participants were examined and treated by dermatologists and endocrinologists. Most of the patients were referred by a general practitioner to dermatology department (Civil Hospital, Karachi) to rule out any allergic aetiology. In addition, all the biochemical analyses were performed at the Aga Khan Hospital Laboratory because of availability of instrument Immulite 2000 and the suggestions of kit suppliers.

All patients selected were females and were in stable metabolic condition. Their height was measured in centimeters and weight in kilograms and body mass index (BMI) was calculated.

In all the patients, total T3 (normal values being 72-170 ng/dl, 1.1-2.6 nm/litre), FT4 (normal values being 0.93-1.7 ng/dl) and serum TSH (normal values being 0.40-4.0 uIU/ml) were measured by using radioimmunoassay Immulite-2000 analyzer. Thyroid autoantibodies (TGA=negative < 1:10, TMA=negative < 1:100) were measured by using haemagglutination method (Thymune-M kit and Thymune-T kit).¹⁰ The diagnosis of autoimmune thyroid disease was made by detection of auto antibodies to antigenic components of thyroid tissue.

The diagnosis of hypothyroidism was made by laboratory criteria of FT4 < 0.93, and TSH > 4 uIU/ml. (Elevated TSH and decreased FT4).

Table III: Thyroid hormone levels and thyroid status in study group (n=47).

| | Hypothyroid n (%) | Euthyroid n (%) | Hyperthyroid n (%) | T3* Mean±SD | FT4** Mean±SD | TSH*** Mean±SD |
|--------------|----------------------|--------------------|-----------------------|----------------|------------------|-------------------|
| Patients**** | 20 (42.5) | 27 (57.4) | 0 | 1.44±0.50 | 4.63±1.37 | 1.57±0.49 |
| P-value | 0.000 | - | - | 0.001 | 0.217 | 0.000 |

T3* Free trii-iodothyronine; FT4**Free thyroxine; TSH*** Thyroid stimulating hormone; Patients**** with diagnosis of chronic urticaria > 6 weeks duration.

Statistical analysis was performed through SPSS version -10.0. Age and BMI were presented by mean ± SD. Frequencies and percentages were computed to present all categorical variables including anti-thyroglobulin autoantibody titre, anti-microsomal auto-antibodies titre, serum thyroid stimulating hormone (TSH), T3, and FT4 in order to assess association of chronic urticaria and hypothyroidism with deranged levels of these laboratory parameters. Chi-square test was applied. Statistical significance was taken at p < 0.05.

RESULTS

During the study period, a total number of 60 patients were enrolled. Overall, the average age of patients was 38.55±1.76 years (ranging from 21-65 years). All patients selected were females. The average BMI (kg/m²) of patients was 21.22±0.17 (Table I).

Table II describes frequencies of thyroid autoantibodies (anti-thyroglobulin and anti-microsomal auto-antibodies) in patients with diagnosis of chronic urticaria > 6 weeks duration. Out of the 47 patients with CU > 6 weeks duration, elevated titres of antithyroglobulin and antimicrosomal antibodies were found to be positive in 20 (42.6%) and 27 (57.4%) patients.

Table III describes thyroid hormone levels and auto-immune thyroid status in selected patients. In all antibody positive patients, serum TSH was raised and T3 and FT4 were decreased (statistically highly significant).

A total of 20 (42.5%) patients were found to be hypothyroid out of 47 patients with diagnosis of chronic urticaria. Out of 20 hypothyroid patients, 6 (30%) were on replacement therapy with thyroxine. No patient was found to be hyperthyroid.

Table I: Physical variables in study population (n=47).

| Physical variables | Patients with diagnosis of chronic urticaria > 6 weeks duration (n=47) |
|-----------------------|--|
| Age (years) | 38.55 ± 1.76 |
| BMI kg/m ² | 21.22 ± 0.17 |

Values are represented as mean± sem

Table II: Frequency of antithyroid autoantibodies in study group (n=47).

| | TGA* | TMA** | Total |
|-------------|------------|------------|-------|
| Patients*** | 20 (42.5%) | 27 (57.4%) | 47 |

TGA* Antithyroglobulin autoantibodies; TMA** Antimicrosomal autoantibodies;

Patients*** with chronic urticaria > 6 weeks duration.

DISCUSSION

Chronic urticaria is a frequent pathology characterized by the presence of hives and/or angioedema lasting longer than 6 weeks.¹² In an important number of patients, it behaves as an autoimmune illness frequently associated with alterations in thyroid functions and thyroid antibodies.¹³

A great number of publications have shown a significant association between CU and thyroid autoimmunity with a prevalence of female success cases.^{6,14,15} The frequencies of antibodies to thyroglobulin, thyroperoxidase or both is estimated at between 12–29%, although the prevalence of autoimmune thyroid antibodies in normal population is generally estimated between 3 and 6%.¹⁶ Many patients with antithyroid antibodies have thyroid hormone levels within normal range. However, some patients have hyperthyroidism or hypothyroidism resulting from Hashimoto's thyroiditis.¹⁷

The first report of an association between CU and thyroid autoimmunity was published by Leznoff and Sussman in 1983.⁶ They found thyroid microsomal antibody in 12% of 140 patients. Eight of those patients had goiter or thyroid dysfunction. Some years later, they found these antibodies in 14% of a larger survey of similar cases.⁷

Zauli *et al.* observed 35 of 122 patients with antithyroid antibodies (29%).¹⁴ Thyroid disease or altered serum thyroid stimulating hormone levels requiring treatment were present in 14 patients.

Asero *et al.* studied 257 patients with CU.¹⁸ Of those patients, 66 (26%) were found to have circulating antithyroid antibodies. Additionally, 46 of these subjects had normal thyroid functions, 16 showed reduced thyroid functions (decreased free T4, increased TSH or both).¹⁵

In a prospective case control study, Verneuil *et al.* compared the frequency of antithyroid antibodies in 45 patients with CU with 30 healthy controls.¹⁵ The frequency of antithyroid antibodies was significantly higher in patients with CU than in healthy controls (26.7% vs. 3.3%; $p < 0.001$). All patients with antithyroid antibodies had thyroid concentration within normal limits.

Carlos *et al.* evaluated antibodies to thyroglobulin, thyroperoxidase, TSH, FT4, FT3 in 56 patients with CU and in a matched control group of 56 patients without CU.¹⁹ Antithyroid antibodies were positive in 28.5% of all patients. Thyroid function was normal in 52 patients.

Collet *et al.* examined 45 patients (29 men and 16 women) with CU.¹¹ Eight of those patients (all women) had laboratory evidence of autoimmune thyroid disease; Greaves disease juvenile chronic thyroiditis in one patient each and autoimmune thyroid disease in the remaining 6 patients.

Keeping in mind the above mentioned finding about association of CU and thyroid autoimmunity, the presently reported study was conducted. Out of 60 patients, 47 (78%) patients were found to have chronic urticaria for more than 6 weeks duration. According to these results, elevated titres of TGA and TMA were found to be positive in 20 (42.6%) and 27 (57.4%) of 47 patients with CU. In all those patients, serum TSH was raised and T3 and FT4 were decreased. A total number of 20 (42.5%) patients were found to be hypothyroid and 6 (30%) were on thyroid replacement therapy.

These results are consistent with those reported in literature. However, there are differences in values due to differences in study population (Asians including Pakistani population) and laboratory techniques. To find out validity and authenticity of our results, a broad based study is required.

In agreement with previously reported studies,^{14,15} a female prevalence was noted for urticaria with thyroid autoantibodies; therefore, it would seem to be interesting to test for thyroid autoimmunity particularly in women.⁶ So this study included all female subjects because of high prevalence of thyroid autoantibodies in females.

No data exists to suggest that thyroid antibodies (TGA or TMA) have a pathogenic role in CU. CU and thyroid autoimmunity are likely parallel autoimmune events.¹⁵ These considerations lead to consider a significant association between thyroid autoimmunity and urticaria, although the underlying mechanism is not clearly understood. The role of thyroid autoimmunity must be considered in most cases of CU and search for thyroid autoantibodies and thyroid functions mandatory in CU.

CONCLUSION

This study shows a statistically significant association between hypothyroidism and chronic urticaria. Full thyroid profile (serum thyroid autoantibodies, serum TSH, T3 and FT4) is highly recommended in patients with diagnosis of chronic urticaria.

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