

Serum Antithyroid Antibodies in Female Patients with Chronic Urticaria

Iram Saddiqa Aamir, Shoaib Tauheed, Farrukh Majeed and Alina Atif

ABSTRACT

Objective: To determine the frequencies of serum antithyroglobulin and antimicrosomal autoantibodies in female patients with chronic urticaria, and the association between thyroid autoantibodies and chronic urticaria, if any.

Study Design: Non-interventional, case-control analytic study.

Place and Duration of Study: This study was carried out by the Department of Physiology, Dow University of Health Sciences, Karachi, from December 2004 to January 2006 on patients selected from Department of Dermatology and Medical Units of Civil Hospital, Jinnah Postgraduate Medical Centre and The Aga Khan University Hospital, Karachi and from the Community Clinics in Karachi.

Methodology: A total number of 90 subjects were enrolled and divided in three groups consisting of 30 patients each. Group 1 comprised of patients with diagnosis of chronic urticaria, Group 2 of diagnosed cases of hypothyroidism with/without urticaria, and Group 3 of normal age and gender-matched healthy volunteers. In all patients, serum antithyroid autoantibodies (antithyroglobulin and antimicrosomal) and thyroid profile (serum T3, T4 and TSH levels) was carried out. Chi-square test was used to determine significance of proportion of variables at $p < 0.05$.

Results: Elevated titres of antithyroglobulin antibodies were found to be present in 9 (30%) patients in Group 1 (chronic urticaria), 24 (80%) patients in Group 2 (known cases of hypothyroidism) compared to control. Elevated titres of antimicrosomal antibodies were found to be present in 13 (43.3%) patients in Group 1, 27 (90%) patients in Group 2 (known cases of hypothyroidism) compared to control. The association between hypothyroidism and chronic urticaria with regard to autoantibodies titres was highly significance ($p < 0.001$).

Conclusion: A highly statistically significant association was found between chronic urticaria and hypothyroidism with special regard to antithyroglobulin and antimicrosomal autoantibodies. Therefore, assays of these two autoantibodies are justified for the early diagnosis of autoimmune thyroiditis in combination with chronic urticaria for better treatment options.

Key words: *Chronic urticaria. Autoimmune thyroid disease. Thyroid autoantibodies. Autoimmune urticaria. Antithyroglobulin. Antimicrosomal. Autoantibodies.*

INTRODUCTION

Urticaria is a frequent dermatosis observed in 15-25% of general population and 25% of them suffer from Chronic Urticaria (CU).^{1,2} The possible lethal risk of laryngeal edema and the influence of chronic urticaria on quality of life makes this disease a true public health concern.³ Chronic urticaria is a common disorder characterized by the recurrence of transient and itching maculo-popular skin lesions with or without angioedema for more than 6 weeks duration.⁴ Despite extensive investigations, no cause is identified in majority of patients.⁵ However, autoimmunity may be a contributing factor based on two main findings. Antibodies reactive with FcepsilonRI (the high affinity immunoglobulins (IgE receptors), IgE or both are found in sera of 10-40% of patients with chronic urticaria.⁶ Frequency of antithyroid antibodies such as

antithyroglobulin (TGA), antimicrosomal (TMA) or thyroperoxidase antibodies (TPO) is found to be significantly higher in patients with chronic urticaria than in general population.⁷

The term Autoimmune Thyroid Disease (AITD) encompasses all the autoimmune thyroid conditions including Hashimoto's thyroiditis, Graves disease, most cases of silent thyroiditis and postpartum thyroiditis.⁸ Cell mediated immunity, humoral immunity, and genetic pre-disposition all have a role in AITD.⁸ In Hashimoto's thyroiditis, there is a functional defect of suppressor cells. As a consequence, T-helper cells are autoreactive and co-operate with B cells to produce antithyroid antibodies.⁹

An association between hypothyroidism and CU was noted in 1980's, although, CU occurs infrequently in patients with Hashimoto's thyroiditis.⁹⁻¹¹ Previous reports showed that thyroid autoantibodies such as antithyroglobulin antibodies could be found in some patients with CU.^{12,13} In one study,¹⁴ the frequency of CU was higher in patients with thyroid disease and with thyroid autoantibodies than in patients without thyroid autoantibodies. This suggests a relationship between CU and thyroid autoimmunity.

Department of Physiology, Dow University of Health Sciences, Karachi.

Correspondence: Dr. Iram Saddiqa Aamir, R-10, PRECHS, Near SMCHS, Gulistan-e-Zafar, Chanesar Halt, Karachi.
E-mail: aamirishi@hotmail.com

Received October 12, 2006; accepted June 20, 2008.

The aim of this study was to determine the frequencies of serum antithyroglobulin and antimicrosomal autoantibodies in female patients with chronic urticaria, and the association between thyroid autoantibodies and chronic urticaria, if any.

METHODOLOGY

It was a case control study conducted by the Department of Physiology, Dow University of Health Sciences, Karachi, from December 2004 to January 2006. A total number of 90 patients were selected from Civil Hospital, JPMC, The Aga Khan Hospital and some community clinics of Karachi who were divided into three groups: Group 1 consisted of diagnosed cases of CU. Group 2 consisted of diagnosed cases of hypothyroidism. Group 3 comprised normal healthy age matched controls.

Urticaria was defined as a papulo-oedematous pruriginous, mobile, fugacious eruption lasting for a maximum of 24 hours. Chronicity was defined as at least three crises a week for at least 6 weeks.

All participants were examined and duly treated by dermatologists and endocrinologists. Most of the patients were referred to dermatology department (Civil Hospital, Karachi) to rule out any allergic etiology.

All patients selected were females and were in stable metabolic condition. The height was measured in centimeters and weight in kilograms. Body mass index was calculated by the following formula:

$$\text{BMI} = \frac{\text{Body weight in kilograms}}{\text{Height in square meters}}$$

In all the patients, total T3, total T4, FT3 and serum TSH were measured by using radioimmunoassay Immulite 2000 analyzer. Immulite 2000 is a continuous random instrument which performs chemiluminescent immunoassay. Thyroid autoantibodies (TGA=negative <1:10, TMA=negative < 1:100) were measured by using haemagglutination method (Thymune M kit and Thymune T kit).¹⁵ The persistent presence of thyroid autoantibodies in references given in addition to thyroid dysfunction or characteristics histopathological abnormality on thyroid aspiration specimen were considered the criteria for diagnosis of autoimmune thyroid disease. The diagnosis of hypothyroidism was made by laboratory criteria of FT3 < 1.8 pg/ml and TSH > 4 µU/ml.

The patients were also screened on the basis of history, medical records and laboratory findings (hemoglobin, haematocrit, complete blood count, erythrocyte sedimentation rate, IgE levels) to exclude known diseases, for example, hepatitis B, hepatitis C and diabetes mellitus, which affect the levels of thyroid autoantibodies and thyroid profile.

The subjects were not funded by any agency. Affording patients were informed about the advantage of laboratory findings and the treatment options and were asked to pay their own expenses. Non affording patients were paid from self funding.

Statistical analysis was performed through SPSS version-10.0.

Age and BMI were presented by mean ± SD. Analysis of variance (F-test) was applied to compare the three groups. Frequencies and percentages were computed to present all categorical variables including chronic urticaria, thyroid status, antithyroglobulin autoantibody titre, antimicrosomal autoantibodies titre and Thyroid Stimulating Hormone (TSH); chi-square test was applied to compare significance of proportions of these variables in order to assess association of chronic urticaria and hypothyroidism with deranged levels of these laboratory parameters. Significance was considered at p < 0.05.

RESULTS

There were 90 patients divided into three groups of 30% each. Overall, the average age of patients was 37±13.07 years ranging from 25 to 60 years in all selected groups. Average BMI of hypothyroid patients (Group 2) was statistically significantly higher than group 1 and 3 (20.41±0.37 vs. 22.70±1.42 vs. 20.19±0.61, p <0.001) (Figure 1).

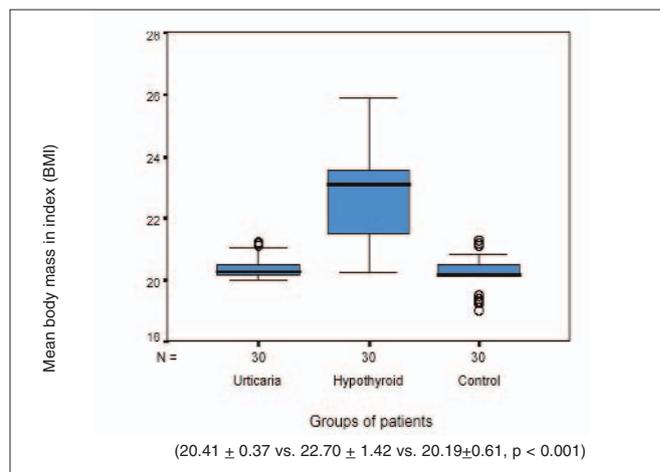


Figure 1: Comparison of body mass index among chronic urticaria, hypothyroid and control group.

Table I describes comparison of chemical variables (serum T3, T4 and TSH, antithyroglobulin and antimicrosomal autoantibodies) in selected groups. Serum T3 and T4 were low in statistically significant proportions (p < 0.001) in hypothyroid group compared to the control and the CU groups. Elevated levels of serum TSH and titres of TGA and TMA were found to be present in group 2 compared to control group (p-value < 0.001).

Table I: Comparison of chemical variables (mean±sem of T3, T4 and TSH, antithyroglobulin, antimicrosomal antibodies in chronic urticaria, hypothyroid and control groups, (n=90).

	Groups of patients		
	CU** (n=30)	HYPO*** (n=30)	Control**** (n=30)
T3 (nm/l)	1.7±0.07	0.95±0.04a	1.8±0.065
T4 (ug/dl)	7.11±0.26	4.5±0.22b	9.2±0.27
TSH***** (uIU/ml)	1.8±0.069	1±0.00c	2±0
TGA *****	1.30±0.089	1.80±0.074d	1.10±0.056
TMA*****	1.43±0.092	1.90±0.074e	1.13±0.063

N*=Number of Patients, CU**=Chronic Urticaria, HYPO*** =Known Cases Of Hypothyroidism, CONTROL**** =Age And Sex Matched Normal Healthy Volunteers, TSH*****=Thyroid stimulating hormone, TGA*****=Antithyroglobulin antibodies, TMA*****=Antimicrosomal antibodies, a=p value<0.001, b=p-value<0.001, c=p-value<0.001, d=p-value 0.001, e=p-value<0.001.

Table II describes the comparison of frequencies of TGA and TMA between the three groups. Elevated titres of antithyroglobulin antibodies were found to be positive in 9 (30%) patients in group 1 (chronic urticaria) and 24 (80%) patients in group 2 (known cases of hypothyroidism) compared to the controls (p < 0.001). Elevated titres of antimicrosomal autoantibodies were detected in 13 (43.3%) patients in group 1 and 27 (90%) patients in group 2 with hypothyroidism compared to the control group p < 0.001.

Among 30 patients with diagnosis of hypothyroidism, 17 (56.7%) were found to have chronic urticaria > 6 weeks compared to age matched healthy controls.

Among 30 cases of chronic urticaria, 3 (10%) were found to be hypothyroid compared to age and sex matched healthy controls. Out of a total 47 patients with chronic urticaria with or without hypothyroidism, elevated titres of TGA and TMA were found to be positive in 42.5% and 57.6% patients, respectively (Table III).

Table II: Comparison of frequencies of antithyroglobulin and antimicrosomal autoantibodies in chronic urticaria, hypothyroid and control groups, (n=90).

Thyroid autoantibodies	Groups of patients		
	CU*: (n=30)	HYPO** (n=30)	CTRL*** (n=30)
Antithyroglobulin antibodies (>1:10 positive)	9 (30%)	24 (80%)	0
Antimicrosomal antibodies (>1:100 positive)	13	27	0

P-Value <0.001. (Statistically highly significant), CU*= Chronic urticaria HYPO**= Known cases of hypothyroidism, CTRL***= Normal age and sex matched healthy control.

Table III: Comparison of frequencies of antithyroglobulin and antimicrosomal antibodies in patients having chronic urticaria > 6 weeks duration among chronic urticaria, hypothyroid and control groups.

Thyroid autoantibodies	Chronic urticaria > 6 weeks	
	Cases: (n=47)	Control: (n=30)
TGA* (>1:10 positive)	20 (42.5%)	0
TMA** (1>1:100, positive)	27 (57.4%)	0

TGA*= Antithyroglobulin antibodies, TMA**= Antimicrosomal antibodies, P < 0.001, statistically highly significant.

DISCUSSION

The association between chronic urticaria and thyroid disorders has been a subject of controversy. Some reports link CU with hyperthyroidism or hypothyroidism.^{10,16} It is also documented that some patients may respond to the administration of thyroid hormones.¹⁷ In France, thyroid hormones are often routinely assayed in patients with chronic urticaria.¹⁸

More recently, some studies have suggested that there may be a link between CU and thyroid autoimmunity.^{9,12,13} In one of the early researches by Leznoff *et al.* in 1983, 12% of patients with urticaria had elevated titres of thyroid antibodies and of these 88.2% were females.⁹ Later on, in a larger study Leznoff then reported the results of a survey of 624 patients by chronic idiopathic urticaria and angio-oedema, 90 (12.1%) of these had high titres of thyroid microsomal antibodies and 44 presented other clinical and laboratory findings suggestive of autoimmune thyroiditis.¹²

With regard to the present results, elevated titres of antithyroglobulin antibodies are found to be positive in 9 (30%) patients with CU, 24 (80%) of the known cases of hypothyroidism with or without antibodies, compared to control. There was significantly high frequencies of TMA and TGA (57.8% and 42.5%) among a total 47 patients with CU with or without thyroid disorders. These results are similar to those reported in literature.

Verneuli and colleagues compared the frequencies of thyroid autoantibodies in 45 patients with chronic urticaria and 30 healthy volunteers.¹⁹ Their results showed that the frequencies of antithyroid antibodies was significantly higher in patients with CU than in healthy subjects (26.7% vs. 3.3%, p-value < 0.01).

Similarly Gaig and colleagues reported 25 (14.7%) out of 170 consecutive patients with CU had an antithyroglobulin and antimicrosomal antibody level >180 IU/ml and all were females.²⁰

In another study by Turktas and colleagues, it was shown that out of a total 94 CU patients, 11 (11.7%) were found to have TGA and 9 (9.57%) TMA ranging from 150-1340.37 and 165.73 - 8000 IU/ml, respectively.²¹

In another research, elevated titres of antimicrosomal and antithyroglobulin antibodies were found to be positive in 35.4% and 30.7% of the patients and it was thought that these thyroid autoantibodies might take part in the mechanism of chronic relapsing urticaria.²²

Bakos and Hillander investigated 48 patients with chronic urticaria on the basis of autologous serum testing and found that the prevalence of antithyroid antibodies were different in two groups (42.3% in autoimmune group versus 13.6% in control p=0.03).²³

In agreement with previously reported studies, a female prevalence was noted for urticaria with thyroid autoantibodies;^{12,13,24} therefore, we also included all female subjects because of high prevalence of thyroid autoantibodies in females.

The present work shows that TGA and TMA are found in statistically significant proportion $p < 0.001$ in patients with chronic urticaria with or without thyroid disorders than in general population. These results suggest the need for systematically including TGA and TMA in the assessment of chronic urticaria, particularly in females. Zauli *et al.* suggested to screen for serum thyroid autoantibodies and thyrotropin levels especially in women and in patients with thyroid autoimmune disease of any type.²⁵

No data exists to suggest that antithyroid antibodies have a pathogenic role in CU. To certain authors including Kaplan, the presence of autoantibodies in CU is the only reflection of a more generalized autoimmune state.²⁶ However, the clinical results obtained by other authors including some of the present cases leads to consider that at least in certain patients thyroid glandular inflammation can be a central feature of this association.¹⁹ Guidelines have been published by a joint task force of allergists suggesting that screening of patients with chronic idiopathic urticaria, especially women, for both thyroid autoantibodies should be highly recommended.²⁷

CONCLUSION

There was a significant association found between thyroid autoimmunity and urticaria, although the underlying mechanism was not clear. It is, however, still controversial whether screening for thyroid autoimmunity is advisable in all chronic idiopathic urticaria cases.

Acknowledgement: I am highly obliged to my respected senior colleagues, Dr. Naeem-ul-Haq (Endocrinologist) and Dr. Asif Ali Imam (Immunologist) for their great cooperation in the conduct of this study.

I am also highly thankful to Dermatology Department (Civil Hospital, Karachi) for providing subject material for this article.

REFERENCES

1. Leznoff A. Chronic urticaria. *Can Family Physician* 1998; **44**:2170-6.
2. Sharma JK, Miller R. Chronic urticaria: review of the literature. *J Cutan Med Surg* 1999; **3**:221-8.
3. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997; **136**:197-201.
4. Greaves MW. Chronic urticaria. *N Engl J Med* 1995; **332**:1767-72.
5. Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000; **105**:664-72.
6. Collet E, Petit JM, Lacroix M, Bensa AF, Morvan C, Lambert D.

- Chronic urticaria and autoimmune thyroid diseases. *Ann Dermatol Venerocol* 1995; **122**: 413-6.
7. Rumbly JS, Schocket AL. Chronic urticaria and thyroid disease. *Immunol Allergy Clin N Am* 2004; **24**: 215-23.
8. Davies TF, Amino N. A new classification for human autoimmune thyroid disease. *Thyroid* 1993; **3**: 331-3.
9. Yoshikawa N, Morita T, Resetkova E, Arreanza G, Carayon P, Volpe R. Reduced activation of suppressor T-lymphocytes by specific antigens in autoimmune thyroid disease. *J Endocrinol Invest* 1992; **15**:609-17.
10. Leznoff A, Josse RG, Denburg J, Dolovich J. Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol* 1983; **119**:636-40.
11. Lanigan SW, Adams SJ, Gilkes JJ, Robinson TW. Association between urticaria and hypothyroidism. *Lancet* 1984; **1**:1476.
12. Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. *N Engl J Med* 1996; **335**: 99-107.
13. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema and thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; **84**: 66-71.
14. Lanigan SW, Short P, Moul P. The association of chronic urticaria and thyroid autoimmunity. *Clin Exp Dermatol* 1987; **12**:335-8.
15. Witebsky E, Rose NR. Studies on organ specificity. IV. Production of rabbit thyroid antibodies in the rabbit. *J Immunol* 1956; **76**:408-16.
16. Mullin GE, Eastern JS. Cutaneous signs of thyroid disease. *Am Family Physician* 1986; **34**:93-8.
17. Heymann WR. Chronic urticaria and angioedema associated with thyroid autoimmunity: review and therapeutic implications. *J Am Acad Dermatol* 1999; **40** (2 pt 1):229-32.
18. Question of the month: what evaluation is needed in chronic urticaria in adults? *Ann Dermatol Venereol* 1993; **120**:652-6.
19. Verneuli L, Leconte C, Ballet JJ, Coffin C, Laroche D, Izard JP, *et al.* Association between chronic urticaria and thyroid autoimmunity: a prospective study involving 99 patients. *Dermatology* 2004; **208**:98-103.
20. Gaig P, Garcia-Ortega P, Enrique E, Richard C. Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity. *J Investig Allergol Clin Immunol* 2000; **10**:342-5.
21. Turktas I, Gokcora N, Demirsoy S, Cakir N, Onal E. The association of chronic urticaria and angioedema with autoimmune thyroiditis. *Int J Dermatol* 1997; **36**:187-90.
22. Sibgatulina NA, Kuzmina NS, Raklmatullina NM, Gevarzieva VB. Autoantibodies to thyroid gland antigens in chronic relapsing urticaria. *Zh Mikrobiol Epidemiol Immunobiol* 2002 Sept-Oct; (5): 69-71.
23. Bakos N, Hillander M. Comparison of autoimmune urticaria with chronic idiopathic urticaria. *Int J Dermatol* 2003; **42**:613-5.
24. Zauli D, Deleonardi G, Foderaro S, Grassi A, Bortolotti R, Ballardini G, *et al.* Thyroid autoimmunity in chronic urticaria. *Allergy Asthma Proc* 2001; **22**:93-5.
25. Zauli D, Grassi A, Ballardini G, Contestabile S, Zucchini S, Binachi FB. Thyroid autoimmunity in chronic idiopathic urticaria. *Am J Clin Dermatol* 2002; **3**:525-8.
26. Kikuchi Y, Fann T, Kaplan AP. Antithyroid antibodies in chronic urticaria and angioedema. *J Allergy Clin Immunol* 2003; **112**: 218.
27. Joint Task Force on practice parameters. The diagnosis and management of urticaria; a practice parameter. Part I: acute urticaria/angioedema. Part II: chronic urticaria/angioedema. Joint Task Force on practice parameters. *Ann Allergy Asthma Immunol* 2000; **85**(6 pt 2):521-44.

.....★.....