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CHRONIC IDIOPATHIC URTICARIA;
SUGGESTED/HYPOTHETICAL ROLE OF ELEVATED SERUM TSH IN PATHOGENESIS OF CHRONIC IDIOPATHIC URTICARIA

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ABSTRACT… Objectives: Urticaria is a condition in which itchy red bumps or wheals appear on the skin unexpectedly. There are two main types ,acute condition which last for up to six weeks while chronic idiopathic urticaria (CIU) last for more than six weeks. There are multiple factors in causation of chronic idiopathic urticaria (CIU) and therefore association with elevated thyroid stimulating hormone (TSH) was evaluated in this study. **Study Design:** Prospective case control. **Setting:** Department of Physiology Dow University of Health Sciences Karachi. **Period:** December 2004 to January 2006. **Subjects / Patients and Methods**: A total number of ninety subjects/patients were enrolled. They were divided in three groups having 30 subjects/ patients in each group. Group A consist of diagnosed cases of chronic urticaria. Group B consist of diagnosed cases of hypothyroidism and group C consist of age and sex matched healthy subjects. In all selected patients/subjects, serum antithyroid autoantibodies and thyroid profile (serum TSH, T3 and T4), complete blood count, IgE levels, ESR were done. All patients were selected from dermatology and medical units of civil hospital, Agha Khan Hospital, JPMC and community health clinics in Karachi. **Results:** Out of 90 patients, 47(78%) were found to have chronic urticaria compared to control. Out of 47 patients , serum TSH (thyroid stimulating hormone) was found to be elevated in 20(42.6%) patients with or without hypothyroidism compared to control group.($P < 0.001$) **Conclusion:** Statistically significant association was found between elevated serum TSH and chronic urticaria symptoms.

Key words: Thyroid autoimmunity, chronic idiopathic urticaria, autoimmune urticaria.

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INTRODUCTION

Chronic idiopathic urticaria (CIU) is a disabling disorder usually having a prolonged waxing and waning course.[1] Chronic urticaria (CU) is defined as wheals persisting daily or almost daily for more than six weeks durtation.[1, 2] The pathophysiology of CIU is not completely understood and proven, many researchers agree that the activation of cutaneous mast cells has the key role in its pathogenesis.[2,3,4] Clinically CIU patients do not have any identifiable trigger and constitute largest subgroup of this disorder. [5,6]

According to previous researches, it has been suggested that the pituitary gland plays an important role in integration of immune and endocrine system.[7] The pituitary gland regulates neuroendocrine activities by producing various hormones like Thyroid stimulating hormone, Adrenocorticotrophic hormone, Prolactin and Growth hormone.[7,8] Thyroid stimulating hormone is polypeptide in nature secreted from pituitary gland.[7] Now a days, it has been proposed that serum thyroid stimulating hormone can act as a cytokine altering the immune response mainly by activation of T lymphocyte, B lymphocytes and dendritic cell.[8] This effect is potentiated in autoimmune thyroid disorders for example Hashimotos thyroiditis and determines the continual release of interleukins (Interleukin-2) and cytokines by immune cells of both inflamed and normal thyroid tissue responsible for

inflammation of target tissues for example skin, nervous system, muscles, heart, joints, eyes and bone marrow.[9,10] Around 40 % of chronic idiopathic urticaria (CIU) patients have autoimmune basis of their symptoms and signs and studies have suggested an association between thyroid autoimmunity and CIU.

Keeping in mind this hypothetical approach, serum TSH has been implemented in pathogenesis of CIU.

According to one theory, [11] it has been suggested that serum TSH regulates thyroid gland secretory activity and causes exaggerated inflammatory response even in susceptible euthyroid patients. Thyroid autoantibodies (antimicrosomal and antithyroglobulin antibodies) can cause inflammation of thyroid tissues leading to disruption of normal architecture and release of stored antigens. These antigens are taken as non self and are responsible for autoimmune reactions. The mediators of autoimmune phenomenon affects cutaneous mast cell activation or mediator release threshold. Other products for example autoimmune complexes of thyroid protein can activate classical complement pathway causing the formation of C5a and C3a which can bind to receptors in skin mast cells; and trigger degranulation leading to symptoms and signs of chronic urticaria.

OBJECTIVE

The objective of present research was to test a hypothesis that serum TSH is a hormone and as a cytokine is responsible for immune response alteration leading to symptoms and signs of chronic idiopathic urticaria (CIU).

METHODOLOGY

This case control study was carried out by the Department of Physiology, Dow Medical College Karachi from December 2004 to January 2006. A total number of 90 patients were enrolled from Agha Khan Hospital, Civil hospital, Abbasi Shaheed Hospital, and General practitioners in Karachi. All subjects underwent a complete investigation of history and physical examination to rule out diagnosis of chronic urticaria and autoimmune thyroid disease (AT).They were divided in three groups having thirty patients/ subjects in each group.

Group (A) consisted of diagnosed cases of chronic urticaria.

Group (B) of patients who are known cases of hypothyroidism.

Group (C) of normal subjects without diagnosis of chronic urticaria or hypothyroidism.

All subjects/patients were diagnosed by history, physical examination and appropriate tests. Consent was taken and confidentiality was maintained. 5 ml of venous blood was collected ascetically from each patient consecutively using a disposable syringe. All blood samples were kept at 40 degree centigrade until serum was separated. Sera were then kept at -70 degree centigrade until assayed.

In selected subjects, total T3 (72-170 mg/dl), total T4 (4.5 to 12.5), FT3 (1.8-4.2) and serum TSH (0.40-4.00 ulu/ml) by using Immulite 2000. Thyroid autoantibodies, antithyroglobulin antibodies (TGA) and antimicrosomal autoantibodies (TMA) were measured by using haemagglutination method (Thymune-M Kit and Thymune-T kit).[12] As far as work up of CU is records and laboratory findings to exclude the known diseases for example Hepatitis B, C, Diabetes mellitus which may affect the level of auto antibodies.

In order to assess the association between chronic urticaria and hypothyroidism, chi square test was applied. Significance was considered at $p < 0.001$.

RESULTS

There were 90 patients divided into three groups of 30 each. Overall, mean age of the patients was 38.55 $\pm$ 1.76, ranging from 25 to 60 years in all selected groups. All selected patients were females. Out of total 90 patients, 47 (52.2%) patients were found to have chronic urticaria with or without hypothyroidism. Serum TSH (thyroid stimulating hormone) was found to be elevated in 20(42.6%) patients with or without hypothyroidism compared to control group.($P < 0.001$) A total

number 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. No patient was found to be hyperthyroid (Table-I).

SERUM TSH	CHRONIC URTICARIA > 6 WEEKS	
	PRESENT	ABSENT
> 4.00 ELEVATED	20 (42%)	0
< 4.00 NORMAL	27 (57.4%)	43 (47.7)

Table-I. Elevated titers of Serum TSH in Chronic urticaria patients (n=47)

Elevated titers of Antithyroglobulin (TGA) and antimicrosomal autoantibodies (TMA) were found to be present in 2O (42.5%) and 27 (57.4 %) of chronic urticaria patients respectively compared to control (p <0.001) (Table-II)

	TGA (antithyroglobulin antibodies)	TMA (antimicrosomal autoantibodies)	TOTAL
Patients	20 (42.5%)	27 (57.4%)	47

Table-II. Frequency of Antithyroid Auto Antibodies in Chronic Urticaria Patients (n=47)

DISCUSSION

The association between thyroid autoimmunity and chronic idiopathic urticaria (CIU) has been a subject of controversy. The prevalence of antithyroid autoantibodies and deranged thyroid profile has also been documented in allergic subjects.[13] In our study elevated levels of Thyroid stimulating hormone (TSH) was found in diagnosed cases of chronic urticaria. Although many theories have proposed that serum TSH is a hormone, it can also act like a cytokine activating immune system of body leading to symptoms and signs of CU; but still it is hypothesis.

The regulatory axis between immune and neuroendocrine system is already documented in literature review.[14] One study revealed that the immune and endocrine systems are coordinated to each other via hormones, cytokines and receptors.[15]

Regarding the role of serum TSH in pathogenesis of chronic idiopathic urticaria, several authors have documented the following facts:

1. The receptors of Thyroid stimulating hormone, Thyroid releasing hormone and human prolactin are expressed on the cells of immune system.[7,8]

2. The human mononuclear cells, monocytes and splenocytes are able to release considerable concentration of serum TSH when treated with Thyroid releasing hormone from hypothalamus. [1,2,4]

3. The cytokine receptors particularly of IL-1,2,6, tumor necrosis factor alpha are expressed on hypothalamic pituitary loop leading to inhibition of Thyroid releasing hormone induced thyroid stimulating hormone release.[9,10]

4. According to one study, it has been seen that serum thyroid stimulating hormone has dose dependant effect in release of interleukin 1, 2,6 and 12 from lymphocytes and dendritic cells.[16]

According to these studies, it has been proposed that serum TSH can act as a cytokine and can modify the immune axis by different cellular constituents leading to symptoms and signs of chronic urticaria[16]. A prospective, case-control study evaluated the association between CU and thyroid autoimmunity and found significantly high values in patients with CU than in controls.[17]

CONCLUSION

Statistically significant association was found between elevated serum TSH and chronic urticaria symptoms.

LIMITATION OF STUDY

Our study is not a population based study. Because of limited resources especially due to financial constraints and cost effectiveness, we have just performed hormonal assays and levels of antithyroid antibodies in patient's serum with chronic urticaria. How these antibodies lead

to chronic urticaria is not studied. Large scale and population based studies are required to find out association between chronic urticaria and thyroid autoantibodies. Also because of our limited budget, we have included patients who were diagnosed cases of chronic urticaria and hypothyroidism.

REFERENCES

1. S Yadav, AJ Kanwar, D Parsad, RW Minz. **Chronic idiopathic urticaria and thyroid autoimmunity: Perplexing association**. Indian J Dermatol 2013. July-Aug; 58(4):325

2. Tong LJ, Balakrishnan G, Kochan JP, Kinét JP, and Kaplan AP. **Assessment of autoimmunity in patients with chronic urticaria**. J Allergy Clin Immunol. 1997; 99:461–5.

3. Fiebiger E, Maurer D, Holub H, Reininger B, Hartmann G, Woisetschläger M, et al. **Serum IgG autoantibodies directed against the α chain of FcRI: Selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients**. J Clin Invest. 1995; 96:2606–12.

4. Zweiman B, Valenzano M, Atkins PC. **Modulation of serum histamine releasing activity in CIU. Immunopharmacology**. 1998; 39:225–34.

5. George M, Balachandran C, Prabhu S. **Chronic idiopathic urticaria: Comparison of clinical features with positive autologous serum skin test**. Indian J Dermatol Venereol Leprol. 2008; 74:105–8.

6. Vohra S, Sharma NL, Mahajan VK, Shanker V. **Clinicoepidemiologic features of chronic urticaria in patients having positive versus negative autologous serum skin test: A study of 100 Indian patients**. Indian J Dermatol Venereol Leprol. 2011; 77:156 –9.

7. Komorowski J, Zylinska K, Pawlikow-ski M, Stepienn H. **Stimulatory effect of thyrotropin (TSH) on intnerleukin-2 (IL-2) release from human peripheral blood lymphocytes. A dose response study in vitro**. Horm Metab Res 1993;25:598-9

8. Chikanza IC, Panayi GS. **Hypothalamic-pituitary mediated modulation of immune function: Prolactin as neuroimmune peptide**. Br J Rheumatol 1991;30:203

9. Bagriacik EU, Klein JR. **The thyrotropin (thyroid stimulatory hormone) receptor is expressed on murine dendritic cell and on a subset of CD45RBhigh lymph node T- cells: functional role for thyroid stimulating hormone during immune activation**. J Immunol 2000;164;6158-65

10. Melmed S. **Cytokine regulation of somatotrope function. Topical endocrinology**. (Supple)1998;4:4

11. Rumbyrt JS, Schoket AL. **Chronic urticaria and thyroid disease**. Immunol Allergy Clin North Am 2004;24:15-24

12. Witebsky, Rose NR, Terplan K. Paine K, Egan RW. **Chronic thyroiditis and autoimmunization**. JAMA 1957;164:1439

13. Aversano M, Caiazzo P, Lorio G, Ponticiello L, Lagana B, Leccese F. **Improvement of chronic idiopathic urticaria with L-thyroxine: a new TSH role in immune response?**. Allergy 2005:60:489-493

14. Delevaux I, Andre M, Tridon A, Aumaitre O. **Chronic urticaria and Hashimoto- Hashimotos thyroiditis: report of 6 cases**. Rev Med Interne 2001;22:232-237

15. Turktas I, Gokcora N, Demirsoy S, Cakir n, Onal E. T**he association of chronic urticaria and angioedema with autoimmune thyroiditis**. Int J Dermatol 1997;36:187-190

16. Saunier B, Tournier C, Jacquemin C, Pierre M. Stimulation of mitogen activated protein kinase by thyrotropin in primary cultured human thyroid follicles. J Biol Chem 1995;270:40539-40546

17. Vincenzo Nuzzo, 1 Libuse Tauchmanova, Paola Colasanti. **Alfonso Zuccoli and Annamaria Colao Idiopathic chronic urticaria and thyroid autoimmunity Dermatoendocrinol**. 2011 Oct-Dec; 3(4): 255–258.

"In order to succeed,
we must first believe that we can."

Nikos Kazantzakis

PREVIOUS RELATED STUDY

Muhammad Afzal, Wasim Ahmed, Anjum Iqbal. FEXOFENADINE HYDROCHLORIDE IN THE MANAGEMENT OF CHRONIC IDIOPATHIC URTICARIA (CIU) PATIENTS IN KARACHI (Original) Prof Med Jour 10(3) 166 - 171 Jul, Aug, Sep, 2003.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
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2	Dr. Shazia Shakoor	Data collection	
3	Dr. Khalid Siddiqui	Statistical analysis of data	
4	Dr. Usama Khalid Choudary	Critical revision of article especially of results and discussion	
5	Dr. Alina Atif	Draft of articla	