

CHRONIC URTICARIA AND THYROID AUTO-IMMUNITY

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SUMMARY: Purpose was to evaluate thyroid auto-immunity and thyroid function in chronic urticaria (CU). Evaluation of antibodies Ab to thyroglobulin (TG) thyroid peroxidase (TPO) and of TSH, FT3, FT4, and of intra-dermal self test with patients own serum in 56 patients presenting chronic idiopathic urticaria and in a matched control group of 56 subjects without CU. Ab to TG positive in 13 (22,2%) to TPO in 15 (26,8%). Overall thyroid antibodies 28,5%. Thyroid function normal in 52 patients, TSH increased in 2, FT3 decreased in 1, TG and TPO Abs and thyroid function results always normal in control group. Self test positive in 4 out of 56 patients. Therapy with thyroid extract was effective in 2 out of 5 cases. CU is associated with thyroid auto-immunity in most cases. Thyroid Ab and function must be evaluated in all the cases of chronic urticaria.

Key-words: Urticaria - Auto-immunity - Thyroid.

Chronic urticaria (CU) is still a challenge for the Immuno-Allergologist. In chronic urticaria, the specific cause is generally determined in no more than 30% of the cases (QUARANTA, ROHR *et al.* 1989).

For many clinicians the search for potential causes of chronic urticaria (CU) is likened to that for the Holy Grail (RUMBYRT, SHOCKET, 2004, BAIGEN, LEIGH, LINCOLN, 1982, PYKNETT, PRINCE, C, 1997, BROWN D, 2003).

In the last few years auto-immunity has gained a growing place in the field of urticaria pathogeny. The term auto-immune urticaria is being increasingly used to define cases where is proposed the role of functional auto antibodies that activate mast cells and basophils through cross-linking the high affinity IgE receptor (FcERI) to secrete histamine (GRATTAN 2004, GREAVES 2001, 2003 KAPLAN 1999, KIKUCHI, KAPLAN 2001, 2003 BLACK AND GREAVES 2003, HIDE *et al.*).

Reports of chronic urticaria linked to auto-immune systemic diseases are common in medical literature (RUMBYRT, SHOCKET). The link between thyroid disease and chronic urticaria is reported from 1950 (CHAPMAN, CADAVATI). In 1971 ISAACS and ERTEL suggested that urticaria in hyperthyroidism could be due to an auto-immune phenomenon. In the last 30 years many other reports on the connection between auto-immune thyroid disease and chronic urticaria have been presented.

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In two large series published in the 80's (SMALL AND LERMAN) thyroid auto-immunity was reported in chronic urticaria patients with greater frequency than other potential causes. LEZNOFF reported 12,1% of elevated thyroid peroxidase antibodies in a series of 140 CU patients. Some of these patients had resolution or improvement of the urticaria after treatment with thyroid hormone. In the middle 80's ERTEL AND MACKENNIE suggest to screen patients with CU for thyroid dysfunction as pruritus and urticaria may be the initial clinical presentation in thyrotoxicosis. Resolution of urticaria symptoms associated with hyperthyroidism has been reported after treatment either with antithyroid medications or radioactive iodine (RUMBYRT, SHOCKET 2004).

The association of hypothyroidism with chronic urticaria was also reported in the same years (LANIGAN 1984). Most of these patients had positive anti-mitochondrial antibodies and some also positive anti-thyroglobulin antibodies.

The prevalence of antithyroid antibodies in the normal population is generally estimated between 3% and 6% (TURNBRIDGE 1997) and frequently associated with other auto immune-conditions, pernicious anemia or vitiligo. LEZNOFF and SUSSMAN (1989) found in 90 patients (14%) positive thyroid auto antibodies in a series of 624 cases of presumed idiopathic CU and angioedema. From these patients 46 were treated with thyroid hormones and eight out of 46 had remission of urticaria within 4 weeks of therapy. Thyroid hormone could suppress the underlying thy-

roid auto-immunity in patients with patent or future hypothyroidism. In 1995 (RUMBYRT, KATZ and SHOCKET) reported resolution of urticaria in CU thyroid patients presenting anti-thyroid antibodies. This observation points to a role of thyroid auto antibodies as an etiologic factor and suggest the usefulness of a larger use of thyroid hormones in such patients.

PURPOSE

The purpose of our study was to evaluate the relation between thyroid disease and urticaria. Research of thyroid auto antibodies, systemic non organ specific auto antibodies and evaluation of thyroid function have been done in a group of idiopathic chronic urticaria patients.

In this paper we intend to review in a series of 56 CU patients thyroid auto-immunity and function.

MATERIAL AND METHODS

56 patients (10 male, 46 female, 21 to 63) presenting idiopathic chronic urticaria have been evaluated by intradermo self test with autologous serum, research of auto-antibodies to thyroglobulin (TG) and thyroid peroxidase (TPO), ANA, antibodies to SSA, SSB, Sm, ds DNA, RA-Test and complement fractions C3, C4 assay. Thyroid function was evaluated by assay of TSH, FT3, T3, T4. A matched control group without CU of 56 patients has been also studied.

RESULTS

Autologous serum test was positive only in 4 patients. ANA was positive in 4 patients. Antibodies to SSA, SSB, Sm, dsDNA and RA-Test always negative, C3 and C4 complement factors normal in all the cases. Thyroid auto antibodies were found in 15 (28,5%) out of 54 patients. 13 patients (23,2%) presented auto antibodies to TG and TPO, 2 only to TPO, one only to TG. Results were always negative in control group. Overall antibodies to TG were present in 14 patients (25,0%) and to TPO in 15 (26,8%). Thyroid function was normal in 52 patients. TSH was increased in 2 patients both with thyroid auto antibodies, FT3 decreased in one patient with increased TSH and increased in another one. FT4, T3, T4 were always in the normal range. In 2 euthyroid patients, as well as in the patient with low thyroid function and high TSH, therapy with low dosage thyroid hormone was tried with good clinical response with complete remission of urticaria and in the patient with low thyroid function normalisation of TSH and FT3.

DISCUSSION

These results confirm that a large number of so-called chronic idiopathic urticarias are associated to thyroid auto-immunity with presence of thyroid auto antibodies in most of the patients (28,5% in our series). Treatment with low dosage thyroid extract can be effective in some urticarias even in euthyroid patients. Research of thyroid auto-antibodies and evaluation of thyroid function could therefore be useful in most cases of chronic urticaria.

The potential mechanisms of chronic urticaria in thyroid diseases are controversial. To certain authors including KAPLAN the presence of auto antibodies in chronic urticaria is only the reflection of a more generalized autoimmune state (KIKUCHI, FANN and KAPLAN 2003). From this point of view the occurrence of antithyroid antibodies are collateral to the main mechanism of urticaria. However the clinical results obtained by other authors including some of our own cases leads to consider that at last in certain patients thyroid glandular inflammation can be a central feature of this association (RUMBYRT, SCHOCKET 2004). These authors propose that when the thyroid gland is inflamed because of spontaneously occurring or virally induced auto-antibodies, thyroid antigens normally sequestered, are released into the local and systemic circulation, stimulating a sustained immune response.

This immune response is characterized by the occurrence of auto antibodies to thyroid components - antithyroglobulin (TG) and/or antimicrosomal particularly antiperoxidase (TPO) antibodies. The involvement of these auto antibodies in the pathogenesis of urticaria is controversial (RUMBYRT and SCHOCKET 2002). Disease remission is not correlated to the level of antibodies. However, their occurrence can only be a marker of immunoactivation and other thyroid dependent mechanisms not yet determined be involved. Treatment success with thyroid extracts can be related to the suppression of thyroiditis. This suppression has been obtained with thyroid hormone (PELTZ *et al.* 1995) antithyroid medication (ERTEL, 1985, Mac KECNIEE 1985, PACE and GARRETS 1995, HENDERSON 1995) and surgery (AMOROSO *et al.* 1997). In euthyroid patients presenting anti-thyroid antibodies treatment with suppressive hormone replacement although it is not based in an abnormal thyroid function has been used with clinical success in some patients (RUMBYRT, KATZ, SHOCKET 1995). These authors suggest that these patients can have a subclinical autoimmune thyroiditis and have been treated before showing any evidence of hyperthyroidism or hypothyroidism. SHOCKET has successfully treated with thyroid extracts two patients with a family history of hypothyroidism and without thyroid auto antibodies. Non humoral immunefactors can therefore have also a role in this disease (RUMBYRT and SHOCKET).

KET 2004). The authors propose a theory to unify these data. Thyroid stimulation by thyroid stimulating hormone (TSH) enhances the activity of thyroid gland and can potentially increase inflammation even in euthyroid patients. In some patients hypothyroidism is detected suggesting that a part of the gland has been already destroyed. Inflammation caused by the presence of auto antibodies disrupt the normal architecture of the gland and leads to the release of sequestered antigens which are preserved as non self and induce a low-grade immune response. The products of this autoimmune response affect cutaneous mast cell activation or mediator release threshold. Products such as thyroid protein immune complexes could be formed that activates the classical complement pathway leading to the generation of complement split products C3a and C5a which can bind to the receptors in skin mast cells and trigger degranulation. Histamine releasing factors could also be generated as a result of autoimmune response lowering the mast cell release threshold and leading to the release of mediators (RUMBYRT and SCHOCKET, 2004).

When threshold of mast cell mediators release is reduced these cells become susceptible to continuous stimulation by physiologic levels of endogenous components such as substance P. This mechanism may be similar to the mechanism of exercise induced anaphylaxis. Thyroid gland suppression is ultimately accomplished with thyroid hormone. This suppression can be due to the suppressive effect of thyroxine on TSH production. Thyroxine can also directly act on the function of altered thyroid peroxidase functionally modified by auto antibodies. When TSH is reduced to sub normal levels thyroid gland inflammation decreases leading to a reduced release of sequestered antigens which triggers a reduction in autoimmune response and a reduction of normal threshold of mast cell release (RUMBYRT and SCHOCKET 2004).

These considerations lead to consider the role of l. thyroxine in the treatment of chronic urticaria. Selected patients must have thyroid auto antibodies and therapy being initiated with low doses (0.1 mg/a). In patients under thyroid hormone treatment doses are increased by 0,025 and slowly increased step by step every 3 to 4 weeks (RUMBYRT AND SCHOCKET 2004). An anti-histamine could be used simultaneously to control disease. After sustained improvement, 3 to 6 months gradual reduction of l. thyroxine can be tried (RUMBYRT and SCHOCKET 2004).

CONCLUSIONS

In conclusion the role of thyroid auto immunity must be considered in most cases of chronic urticaria and the research of thyroid auto-antibodies and thyroid

function mandatory in so called idiopathic chronic urticaria. Thyroid auto-immunity could be linked to chronic urticaria.

References

1. Amoroso A., Garzia P., Pasquarelli C., Sportelli G., Afeltra A. - Hashimoto's Thyroiditis associated with urticaria and angioedema: Disappearance of cutaneous and mucosal manifestations after thyroidectomy. *J Clin Pathol* 1997;50(3):254-6.
2. Asero R., Lorini M., Tedeschi A. - Association of chronic urticaria with thyroid autoimmunity and Raynaud phenomenon with anticontromere antibodies. *J Allergy Clin Immunol* 2003;111(5):1129-30.
3. Baigent M., Leigh R., Lincoln H. (1982) - Holy Graail, Holy Blood. Jonathan Cape, London.
4. Bar-Sela S., Reshef T., Mekori Y.-A. - IgE antithyroid microsomal antibodies in a patient with chronic urticaria. *J Allergy Clin Immunol* 1999;103(6):1216-7.
5. Black A.-K., Greaves M.-W. - Urticaria and angioedema. 1997; pp1586-1607. In: Allergy and Allergic diseases Kay, AB (ed) Blackwell Science, Oxford.
6. Bressler R.-B. - Pathophysiology of chronic urticaria. *Immunol Allergy Clin N Am* 1995;15:659-678.
7. Brown D. - The DaVinci Code 2003 Doubleday, New York.
8. Caravati C.-M., Richardson D.-R. Wood B.-T., Cawley E.-P. - Cutaneous manifestations of hyperthyroidism. *South Med J* 1969;62:1127.
9. Chapman E.-W., Maloof F. - Bizarre clinical manifestations of hyperthyroidism. *N Engl J Med* 1956;254:1.
10. Charlesworth E.-N. - The spectrum of urticaria. *Immunol Allergy Clin N Am* 1995;15:641-658.
11. Claveau J., Lavoie A., Brunet C., Bedard P.-M., Hebert J. - Chronic idiopathic urticaria : possible contribution of histamine-releasing factor to pathogenesis. *J Allergy Clin Immunol* 1993;92(1 Pt 1):132-7.
12. Costa A.-C., Pedro E., Sousa A.-V., Barbosa M.-P., Palma-Carlos A.-G. - Treatment of chronic urticaria with thyroxine in euthyroid patients with thyroid antibodies. Abstract Book XXIII. EAACI Congress Amsterdam, pp.198.
13. Dagher H.-N., Aboujaoude Z.-C., Jabbour S.-A. - Chronic urticaria: an unusual initial manifestation of primary hyperparathyroidism. *Endocr Pract* 2002;8(1):47-9.
14. Dibern D.-A., Dreskin S.-C. - Urticaria and angioedema: an overview. *Immunol Allergy Clin N Am* 2004;24:41-162.
15. Ertel N.-H. - Hyperthyroidism and urticaria. *JAMA* 1985;254(18):2553-2554.
16. Gaig P., Garcia-Ortega P., Enrique E., Richart C. - Successful treatment of chronic urticaria associated with thyroid autoimmunity. *J Investig Allergol Clin Immunol* 2000;10(6):342-5.
17. Grattan CEH. - Auto immune urticaria. *Immunol Allergy Clin N* 2004;24:163-182.
18. Greaves M.-W. - Chronic idiopathic urticaria. *Curr Opin Allergy Clin Immunol*. 2003;3:363-368.
19. Greaves M.-W. - Chronic urticaria as a new auto-immune disease. In: Hertl M (ed) Autoimmune diseases of the skin 2001 Springer New York Wien pp 283-302.
20. Hall R. - Immunologic aspects of thyroid function. *N Eng J Med* 1962;266:1204-1208.
21. Henderson C.-A., Highet A.-S. - Urticaria associated with thyrotoxicosis. *Clin Exp Dermatol* 1995;20(2):173-4.
22. Heymann W.-R. - Chronic urticaria and angioedema associated with thyroid autoimmunity: review and therapeutic implications. *J Am Acad Dermatol* 1999;40(2 Pt 1):220-32.
23. Henderson C.-A., Highet A.-S. - Urticaria associated with thyrotoxicosis. *Clin Exp Dermatol* 1995;20(2):173-4.
24. Hide M., Francis D.-M., Grattan CEH., Hakimi J., Kochan M.-W. - Anti-bodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993;328(22):1599-604.

25. Hermes B., Prochazka A.-K., Haas N., Jurgovsky J., Sticherling M., Henz B.-M. - Upregulation of TNF- α and IL-3 expression in lesional and uninvolved skin in different types of urticaria. *J Allergy Clin Immunol* 1999;103 (2 Pt 1):307-14.
26. Irani C., Gordon N.-D., Zweiman B., Levinson A.-I. - Chronic urticaria/angioedema and Grave's disease: coexistence of 2 antireceptor antibody-mediated disease. *J Allergy Clin Immunol* 2001;108(5):874.
27. Isaacs N.-J., Ertel N.-H. - Urticaria and pruritus: uncommon manifestations of hyperthyroidism. *J Allergy Clin Immunol* 1971;48(2):73-81.
28. Kennard C.-D. - Evaluation and treatment of urticaria. *Immunol. Allergy Clin N Am* 1995;15:785-802.
29. Kaplan A.-P., Fin A. - Auto immunity and the aetiology of chronic urticaria. *Can J. Allergy Clin Immunol* 1999;4:286-293.
30. Kikuchi Y., Kaplan A.-P. - Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol* 2001;107(6):1056-62.
31. Kikuchi Y., Fann T., Kaplan A.-P. - Antithyroid antibodies in chronic urticaria and angioedema. *J Allergy Clin Immunol* 2003;112(1):218.
32. Kim S.-H., Lee B.-J., Chang Y.-S., Kim Y.-K., Cho S.-H., Min K.-U. *et al.* - A case of hereditary angioedema associated with idiopathic hypoparathyroidism. *Korean J Int Med* 2001;16(4):281-3.
33. Lanigan S.-W., Adams S.-J., Gilkes J.-J., Robinson T.-W. - Association between urticaria and hypothyroidism. *Lancet* 1984;1(8392):1476.
34. Leznoff A., Josse R.-G., Denburg J., Dolovich J. - Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol.* 1983;119(8):636-40.
35. Leznoff A., Sussman G.-L. - Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989;84(1):66-71.
36. Liechty R.-D., Firminger H.-I. - Hyperparathyroidism and urticaria. *JAMA* 1983; 250(6):789-90.
37. MacKennie H.-L. - Chronic urticaria and hyperthyroidism. *JAMA* 1985;253(19):2894.
38. Nsoulie T.-M., Nsouli S.-M., Bellanti J.-A. - Neuroimmunoallergic Inflammation : new pathogenic concepts and future perspectives of immediate and late allergic reactions. *Part II, Ann Allergy* 1988;60(6):483-92.
39. Pace J.-L., Garretts M. - Urticaria and hyperthyroidism. *Br J Dermatol* 1975; 93(1):97-9.
40. Peltz S., Barchuk W., Oppenheimer J., Druce H., Bielory L. - Chronic angioedema of the tongue associated with pernicious anemia and Hashimoto's thyroiditis. *Clin Exp Dermatol* 1995;20(4):351-2.
41. Picknett L., Prince C. - The Templar revelation, 1977, Bantam Press, London.
42. Quaranta J.-H., Rohr A.-S., Rachelsfsky G.-S., Siegel S.-C., Katz R.-M. - The natural history and response to therapy of chronic urticaria and angioedema. *Ann Allergy* 1989;62(5):421-424.
43. Rumblyrt J.-S., Katz J.-L., Schocket A.-L. - Resolution of chronic urticaria in patients with thyroid autoimmunity. *J. Allergy Clin Immunol* 1995;96(6 Pt 1):901-5.
44. Rumblyrt JHS., Shocket A.-L. - Chronic urticaria and thyroid disease. *Immunol. Allergy Clin N Am* 2004;24:215-224.
45. Sabroe R.-A., Grattan CEH., Francis D.-M. - The antillogous serum skin test. A screening test for auto antibodies in chronic idiopathic urticaria. *Br J Dermatol.* 1999;140:446-452.
46. Said Y.-S., Harfi H.-A. - Prevalence of thyroid autoantibodies and response to thyroid idiopathic urticaria. *Allergy Clin Immunol Int: J World Allergy Org* 2003, suppl. 1, 226.
47. Sheikm J. - Advances in the treatment of chronic urticaria. *Immunol Allergy Clin N Am* 2004;24:317-335.
48. Small P. - Hyperthyroidism and polycythemia vera with chronic urticaria. 1979, pg 715-7156 in *Advances in Allergology and applied Immunology*, Oehling A, Glazer I, Mathov E, Arbeman C. Eds. Pergamon Press, Oxford.
49. Small P., Lerman S. - Hyperthyroidism and polycythemia vera with angioedema chronic urticaria and angioedema. *Ann Allergy* 1981;46(5):256-9.
50. Tunbridge W.-M., Evered D.-C., Hall K. - The spectrum of thyroid disease in a community: the Wickham survey. *Clin Endocrinol* 1977;7(6):481-93.
51. Turktaş I., Gokcora N., Demirsoy S., Cakir N., Onal E. - The association of chronic urticaria and angioedema with autoimmune thyroiditis. *Int J Dermatol.* 1997;36(3):187-90.
52. Vaughn M.-P., De Walt A.-C., Diaz J.-D. - Urticaria associated with systemic disease and psychological factors. *Immunol Allergy Clin N Am* 1995;15:725-744.
53. Zauli D., Deleonardi G., Fedoraro S., Grassi A., Bortolotti R., Ballardini G. *et al.* -Thyroid autoimmunity in chronic urticaria. *Allergy Asthma Proc* 2001;22(2): 93-5.
54. Zauli D., Grassi A., Ballardini G., Contestabile S., Zucchini S., Bianchi F.-B. - Thyroid autoimmunity in chronic idiopathic urticaria: implications for therapy. *Am J Clin Dermatol* 2002;3(8):525-528.
55. Wai Y.-C., Sussman G.-L. - Evaluating chronic urticaria patients for allergies, infections, or auto-immune disorders. *Clin Rev Allergy Immunol* 2000;23:185-193.

