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Chronic urticaria and thyroid autoimmunity markers

Research Article

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Abstract: The association of chronic urticaria and autoimmune thyroid disease has been well recognized. Some authors observed relationship between thyroid autoimmunity and chronic autoimmune urticaria. Objective. The primary objective was to evaluate thyroid autoimmunity and thyroid function in chronic urticaria. Secondary objective was to correlate results of antibodies to thyroid peroxidase and markers of autoimmune urticaria (autologous serum skin test and CD63 expression). Materials and methods. 128 patients with chronic urticaria were evaluated for antibodies to thyroid peroxidase, autologous serum skin test and donor basophil CD63 expression induced by patients sera. Thyroid-stimulating hormone was performed in all patients with elevated antibodies to thyroid peroxidase and 48 patients with normal level of antibodies. Results. Antibodies to thyroid peroxidase were elevated in 25.0% patients. Thyroid function was abnormal in 28.1% patients with elevated antibodies to thyroid peroxidase and 8.3% patients with normal antibodies level. We did not find the relationship between thyroid antibodies and markers of autoimmune urticaria (autologous serum skin test and CD63 expression). Conclusions. Chronic urticaria was frequently associated with thyroid autoimmunity. We did not observe significant relationship between chronic autoimmune urticaria and thyroid autoimmunity and we suggest these are tangential, parallel autoimmune events.

Keywords: *Chronic urticaria • Antibodies • Thyroid – stimulating hormone • Autologous serum skin test • Basophil activation marker*

1. Background

Chronic urticaria (CU) is a common skin disorder characterized by recurring appearance of wheals and/or angioedema lasting for more than 6 weeks [1]. Recently, it has become clear that 30% to 50% of patients with CU have functional autoantibodies directed against the α-chain of the high-affinity immunoglobulin E (IgE) receptor (FcεRI) or, less commonly, against IgE [2,3]. The only *in vivo* method, an autologous serum skin test (ASST), is a screening test for functional antibodies in CU [4]. The basophil histamine release assay (HRA) is currently the "gold standard" for detecting functional antibodies in the serum of patients with CU [5-7]. Improved screening tests have been sought in the last decade; for instance, flow cytometry used to determine the ability of a CU patient's serum to evoke an expression of CD63 and CD203c on donor basophils is showing some promise [8-13].

In 1983, Leznoff et al. first described an association between CU and autoimmune thyroid disease. Those authors reported that 12% of CU patients (vs. 6% in the control group) had autoimmune thyroiditis (AT) [14]. The frequency of anti-thyroid peroxidase (TPO) or

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anti-thyroglobulin antibodies indicated by other authors is 12% to 33%. The TPOs are found more often [15-19]. O'Donnell at al. investigated 182 CU patients and found that thyroid antibodies were more common in patients with a positive ASST [19]. The same results were obtained by other authors [20,21].

There is no data to suggest that any antithyroid antibody is pathogenic in terms of CU; most likely, these are two separate autoimmune events [22,23]. It has been suggested that autoantibodies serve only as a marker of autoimmunity and that proinflammatory cytokines, which are involved in this condition, decrease the mast cell threshold to endogenous or exogenous stimulants [24].

The majority of patients with CU thyroid autoimmunity have normal thyroid function. Some of these patients are hypothyroid, and less commonly, are hyperthyroid (in the initial phase of thyroid inflammation) [3]. Screening for thyroid autoimmunity and function is advisable for all patients with CU for an early identification of those patients requiring either treatment of their underlying thyroid dysfunction or follow-up [15,18,22,25,26].

The purpose of our study was to assess the incidence of thyroid auto-immunity and thyroid function abnormalities amongst patients with CU and to examine any connection between antibodies to thyroid peroxidase and the markers of chronic autoimmune urticaria (CAU) – an autologous serum skin test and CD63 expression.

2. Study Design

In all, 128 patients with the diagnosis of CU were investigated (26 males and 102 females). The mean age of patients was 43±13 years (range: 20–78 years). The mean duration of disease was 38 ± 70 months (min, 2 months; max, 40 years). The study was performed in Vilnius University Hospital, Center of Pulmonology Allergology in 2006-2008. The study was approved by Lithuanian Bioethics Committee. Written informed consent was obtained from the patients before enrolment in the study.

3. Materials and methods

All 128 patients with CU were evaluated for antibodies to thyroid peroxidase (TPO). A thyroid-stimulating hormone test (TSH) was performed for all patients with elevated TPO and 48 patients with a normal level of antibodies. Both tests were performed by using immunochemiluminescence technique (ABBOTT Diagnostics, USA). The autologous serum skin test was done under the recommendations of EAACI [27].

Donor basophil CD63 expression induced by the patients' sera was performed with a standard BD FastImmune set (Becton Dickinson, USA). The test was performed on heparinized blood within 3 to 4 hours after drawing the donor's blood. Aliquots of the donor's heparinized whole blood (100 µl) were incubated for 20 minutes at 37ºC with 100 µl sera from patients with CU or normal controls and 20 µl BSB. For controls, 100 µl PBS was added and used as the negative control, and 100 µl 1-µM fMLP was used as the positive control. The reactions were stopped by placing the tubes on ice for 5 min. Cells were stained with 20 µl CD63FITS/ CD123PE/ Anti-HLA DR PerCP antibodies cocktail at room temperature in the dark for 30 minutes. Red cells were lysed with 2 ml FACS Lysing Solution. The cells were washed with 2 ml PBS and fixed in 0.5% paraformaldehyde. The cells were then analyzed on a FACSCalibur flow cytometer (BD). Data on at least 1000 basophils were acquired, and the percentage of CD63-expressing basophils was calculated.

116 patients answered the European Academy of Allergology and Clinical Immunology/ European Union–funded network of excellence/ European Dermatology Forum (EAACI/GA²LEN/EDF) urticaria questionnaire; disease activity was evaluated by using urticaria activity score.

Statistical analysis of results was performed with SSPS 15 program.

Statistical significance was determined by using the Wilcoxon matched pairs test, the Man-Whitney test, or χ^2 test, where appropriate. A p value < 0.05 was considered significant.

4. Results

Antibodies to thyroid peroxidase were elevated in one-quarter (25%) of the study patients.

Thyroid hypofunction (elevated TSH) was observed only in patients with elevated TPO (12.5%). Thyroid hyperfunction (reduced TSH) was found in both elevated and normal TPO groups, 15.6% and 8.3%, respectively. TSH results subject to TPO are shown in Figure 1 and Table 1.

ASST was positive in 33.6% patients with CU. Positive CD63 expression test was observed in 36.7% of CU patients using a 10% cut-off value, according to receiver operator characteristic (ROC) curve analysis. The results of the TPO correlation with CAU tests (ASST, CD63 expression test) are presented in Tables 2 and 3.

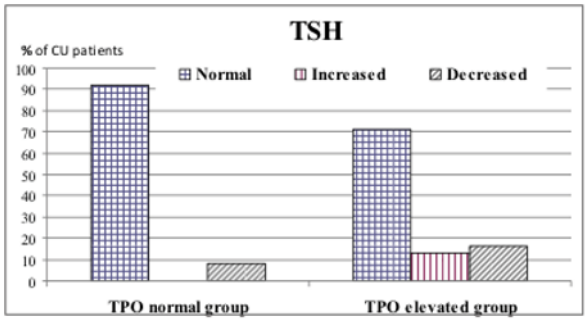
We found significant correlation between CD63 expression and ASST (r=0.282, p=0.001), but no significant connection between elevated TPO and positive ASST

Table 1. Relation of TPO and TSH results

	TPO				Total	
	Normal		Elevated			
TSH:	N	%	N	%	N	%
Normal	44	91.7	23	71.9	67	83.8
Elevated	0	0.0	4	12.5	4	5.0
Reduced	4	8.3	5	15.6	9	11.3
Total	48	100.0	32	100.0	80	100.0

TSH - thyroid-stimulating hormone, TPO - anti-thyroid peroxidase antibodies.

Figure 1. TSH results in different TPO groups of CU patients.



TPO- anti- thyroid peroxidase antibodies,
TSH- thyroid-stimulating hormone,
CU- chronic urticaria

(χ^2=0.292, p=0.589). Similarly, no statistically significant correlation was found between TPO and CD63 expression (χ^2 =1.894, p=0.169). We also found no correlation between disease activity and chronic autoimmune CAU markers (ASST (χ^2= 5.962, p=0.310), CD63 (χ^2=4.155, p=0.527)), duration of disease and CAU markers (ASST (p=0.470), CD63 (p=0.786)).

5. Discussion

The incidence of thyroid antibodies in the total population as estimated by Monge et al. is between 3% and 6% [27]. The level of TPO in our CU patients was considerably higher than that in the total population. The prevalence of thyroid antibodies that we and other investigators have detected in CU patients is similar [15-19]. Our study confirms the apparent association between CU and thyroid autoimmunity.

Abnormalities of thyroid function were observed in one-third of our patients with elevated TPO, close equally hypo- or hyperthyroidism. Several studies reported that hypothyroidism is more frequent in CU patients with thyroid autoimmunity [3,28]. Surprisingly, hyperthyroidism was also found in 8.3% of patients with normal TPO, and this incidence was considerably higher than the 2.2% reported in the general population [29]. We think that all patients with CU should be tested for thyroid function without a reference to thyroid antibodies. There is some evidence that TSH has many cytokine-like qualities and can regulate the immune response, mainly by a direct T cell, B cell and dendritic cell activation. Aversano et al

Table 2. Relation of TPO and ASST results

	TPO				Total	
	Normal		Elevated			
ASST:	N	%	N	%	N	%
Negative	65	67.7	20	62.5	85	66.4
Positive	31	32.3	12	37.5	43	33.6
Total	96	100.0	32	100.0	128	100.0

TPO - anti-thyroid peroxidase antibodies, ASST - autologous serum skin test.

Table 3. Relation of TPO and CD63 expression results

	TPO				Total	
	Normal		Elevated			
CD63	N	%	N	%	N	%
Negative	64	66.7	17	53.1	81	63.3
Positive	32	33.3	15	46.9	47	36.7
Total	96	100.0	32	100.0	128	100.0

TPO - anti-thyroid peroxidase antibodies

[30] hypothesized that inflammatory status inflicted by TSH lead to flares of urticaria and also production of antithyroid antibodies.

Unlike some investigators [19-21], we did not find a significant correlation between elevated TPO and positive ASST or CD63 expression. The finding in the present study is comparable with the study of Nettis et al., who did not detect a statistically significant difference between thyroid antibodies in either ASST positive or negative groups [31].

The association between CAU and thyroid autoimmunity remains a subject of debate; further studies with larger sample sizes are needed. The mechanism of these associations is not known. Confino-Cohen et al. assume that this might result from a shared susceptibility to autoimmune or chronic inflammatory processes; this hypothesis is supported by the additional findings that all other autoimmune diseases they investigated were more common in patients with CU [28]. A role for thyroid antibodies in mast cell activation in CU needs to be proven.

Recent data from Altrichter and al. show that a sizeable subgroup of patients with CU has IgE-anti-TPO autoantibodies. These autoantibodies, when they bound to and activate mast cells, could cause "autoallergic" mast cell degranulation, a novel pathogenic pathway of CU induction. The patients with positive IgG –anti-TPO are more likely to potentially express urticaria-inducing IgE – anti-TPO [32]. The authors also speculate that IgE antibodies directed against other autoantigens also may exist and act as mast cell activators.

Some studies have reported the presence of CAU autoantibodies that indicated a subset of patients with more severe CU [33,34]. However, other studies did not support this observation [31]. We also found no correlation between disease activity, duration of disease and CAU markers (ASST, CD63 expression). Identification of patients with autoimmune urticaria is of some importance because immunomodulating therapy can be used in severely affected conventional – treatment-resistant patient [4].

In conclusion, CU is likely an autoimmune disease. In our study, we have shown that thyroid autoimmunity is significantly more prevalent in CU patients than in the general population. Thyroid function is often abnormal in patients with CU, even in cases where the patient has normal levels of thyroid antibodies. We did not observe a significant connection between CAU tests and thyroid autoimmunity, and we assume that further studies will be necessary to investigate the role of thyroid antibodies in the pathogenesis of CU.

6. Acknowledgements

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7. Conflict of interest

None.

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