RESEARCH PAPER

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Idiopathic chronic urticaria and thyroid autoimmunity

Experience of a single center

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Urticaria is one of the most frequent dermatosis, being its prevalence in general population estimated about 20%. This prospective case-control study was aimed at determining the prevalence of thyroid autoimmune disorders in a cohort of patients with chronic urticaria (CU), all living within an area with mild-to-moderate iodine deficiency. Fifty four consecutive patients affected by CU were recruited and compared to 108 healthy controls. Assessment of the thyroid function included measurement of serum concentrations of TSH, FT3, FT4, anti-thyreoglobulin (anti-TG) and anti-peroxidase (anti-TPO) antibodies. Ultrasound scan of the thyroid gland was performed in all subjects using a 7.5 MHz linear transducer. All subjects were followed up for 6 months. The prevalence of thyroid antibodies was significantly higher in our cohort of patients with CU than in controls (22% vs. 6.5 %). Hashimoto's thyroiditis was also more frequent in patients than controls (18.5% vs. 1.8%). These frequencies do not differ from those previously reported by some other authors and confirm the association between CU and thyroid autoimmunity also in the area of iodine deficiency. However, presence of antibodies or thyroiditis does not seem to influence clinical course of CU. These results suggest that screening for thyroid function may be useful in all the patients with CU.

Introduction

Urticaria is defined as a widespread, fugacious, itchy cutaneous swelling; it is one of the most frequent dermatosis, being its prevalence in general population estimated about 20%.[1] Urticaria is regarded as idiopathic in approximately 75% of affected patients.[1] Chronic form is defined as at least 6-week history of the disorder and chronic urticaria (CU) was observed in about 25% of the cases.

An increase prevalence of autoimmune diseases was observed in subjects with CU.[2-8] Thyroid autoimmune thyroiditis and Hashimoto's thyroiditis were described among patients with CU, and increased serum levels of antithyroid antibodies were reported with frequency ranging between 12–29% in different studies.[2-5, 7-8]

Although number of authors reported on the association between CU and thyroid autoimmunity, there are not yet available data regarding this association in areas with mild-to-moderate iodine deficiency.[2-9] The present study attempts to address this issue. This prospective case-control study is aimed at determining the prevalence of thyroid autoimmune disorders in a cohort of patients with CU, all living within the province of Naples, Southern Italy.

Results

Thyroid autoantibodies were detected in 12 of the 54 patients, all females (**Table 1**); their mean age was 31.5 years (median: 27 yrs, range: 21–47 years). As shown in **Table 1**, 6 out of these 12 patients had increased levels of anti-TPO antibodies and 6 others had increased both anti-TPO and anti-TG antibodies.

Ten of the 12 patients (18.5%) with positive thyroid autoantibodies were also found as being affected by hypothyroidism. Diagnosis of chronic thyroiditis was confirmed by thyroid ultrasound by a picture of non-homogeneous hypoechoic pattern without nodules.[11] Two of affected patients were sisters. Hypothyroid patients were given replacement therapy with L-thyroxine (100 +/- 12.50 mcg daily).

We did not observed any difference in the clinical features of CU between patients with and without thyroid autoantibodies, when considering the frequency of the crises, association of urticaria with angioedema and resistance to antihistaminic treatments (**Table 2**).

Only 7 controls had detectable anti-thyroid antibodies (**Table 3**); 2 had increased anti-TPO antibodies, other 2 had anti-TG antibodies and 3 other subjects had both anti-TPO and anti-TG antibodies. One of them was hypothyroid.

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Table 1. Thyroid antibodies and thyroid function, C3, C4, immunoglobulin, Rheumatest, ANA, ENA in patients with chronic urticaria

Patients	Sex	Age	FT3	FT4	TSH	Ab-TG	Ab-TPO	C3	C4	RF	ANA	ENA	Diagnosis
2	F	24	2.65	11.8	0.4	463	>8000	N	N	N	neg	neg	Hashimoto's thyroiditis, hypothyroidism
3	F	30	3.13	9.5	7.54	neg	345	N	N	N	neg	neg	Hashimoto's thyroiditis, hypothyroidism
5	F	47	2.01	13.1	5.41	neg	465	N	N	N	neg	neg	Hashimoto's thyroiditis, hypothyroidism
8	F	45	6.1	12.5	1.46	375	461	N	N	N	1/160	Neg	Hashimoto's thyroiditis, hypothyroidism
17	F	21	5.65	10.8	5.21	494	392	N	N	N	1/160	SSB pos	Hashimoto's thyroiditis, subclinical hypothyroidism
27	F	22	5.36	12.9	1.59	neg	229	N	N	N	neg	neg	Isolated positivity of autoantibodies
32	F	22	4.15	11.0	6.01	421	420	N	N	N	1/160	neg	Hashimoto's thyroiditis, subclinical hypothyroidism
36	F	44	2.11	12.3	5.75	441	542	N	N	N	1/160	neg	Hashimoto's thyroiditis, hypothyroidism
42	F	23	4.94	12.8	2.34	neg	357	N	N	N	Neg	neg	Isolated positivity of autoantibodies
49	F	29	2.16	11.2	7.63	neg	327	N	N	N	neg	neg	Hashimoto's thyroiditis, hypothyroidism
52	F	25	2.58	10.2	5.38	585	894	N	N	N	Neg	Neg	Hashimoto's thyroiditis, hypohyroidism
54	F	46	1.97	9.2	5.38	neg	489	N	N	N	Neg	Neg	Hashimoto's thyroiditis, hypothyroidism
normal range			3.7–6.8 pg/ml	9.3–17 pg/ml	0.3–4.2 mUI/ml	<300 IU/ml	<110 IU/ml	70–150 mg/dl	14–40 mg/ml	<20 IUml	<1/80	Neg	

Comparing patients to controls, thyroid autoantibodies were more frequently found in patients (22.2%, p = 0.0074). Moreover, patients with CU developed hypothyroidism more frequently than controls (18.5%, p = 0.0001).

Significantly increased ANA levels were observed in 4 out of 10 patients affected by Hashimoto's thyroiditis (**Table 1**). One of them developed lupus erythematous discoid (LED) during the 6-month period of observation. No other abnormality in the biochemical tests was revealed among our patients with autoimmune thyroid disorders.

In 10 patients without thyroid autoimmunity, an increase in total IgE and/or specific IgE was revealed. In particular, 6 patients had an increase in total IgE; one patient had IgE antibodies directed against some inhalant and/or food allergens and 3 patients had an increase in both total IgE and some specific IgE antibodies.

Iodine urinary excretion was similar in patients and healthy controls; they were both in the lower third of the normal range. Median urinary iodine excretion was below 55 mcg/l that was found by Aghini-Lombardi et al. in an iodine-deficient area of Southern Italy.[12]

Discussion and Conclusions

In this prospective, case-control study we evaluated the association between CU and thyroid autoimmunity in an area with mild-to-moderate iodine deficiency. The prevalence of thyroid antibodies was significantly higher in our cohort of patients with CU than in controls (22% vs. 6.5 %). Hashimoto's thyroiditis was also more frequent in patients than controls (18.5% vs. 1.8%). These frequencies do not differ from those previously reported by some other authors and confirm the association between CU and

thyroid autoimmunity also in the area of iodine deficiency.2-5, 7-8 However, presence of antibodies or thyroiditis does not seem to influence clinical course of CU, as suggested by similar frequencies and features of the crises among patients with or without thyroid autoimmune disorders.

According to other reports, both CU and thyroiditis occurred more frequently in women than men; therefore, also the association of these two disorders was more frequent in women. However, we can not exclude a gender-related bias.[3,7]

Thyroid autoimmune disorders in patients with CU may appear with variable features, ranging from a simple positivity of thyroid autoantibodies to a lymphocytic thyroiditis or Hashimoto's thyroiditis with or without hypothyroidism.[2-9] Such an association was first described by Leznoff et al. in 1983 who observed that 12% of patients with CU were also affected by autoimmune thyroiditis.[8] Since then, the prevalence of positive thyroid autoantibodies ranged from 12 to 29% in patients with CU in different studies.[2-5, 7-8] Interestingly, no case of Graves disease was described among patients with urticaria.

The role of geographical area has never been investigated regarding this issue, in particular, there are no literature data regarding the frequency of the association in areas of mild-to-moderate iodine deficiency, such as Southern Italy.[13] In these areas, a higher prevalence of antithyroid antibodies occurs in general population.[14] This may be related to a prolonged TSH-stimulated release of thyreoglobulin with increased immunogenicity in the bloodstream. Indeed, a variable degree of thyreoglobulin iodination may account for different immunological properties with the generation of new epitopes that provide greater immunogenicity to the molecule.[15] The only data regarding the association of thyroid autoimmunity and CU in the province of Naples were provided by Aversano et al.[9] However, these authors evaluated the effects of L-thyroxine on the CU outcome in patients affected by autoimmune thyroiditis, and their study was not aimed at evaluating the prevalence of thyroid disorders among patients with CU.

The effects of replacement treatment for hypothyroidism on clinical symptoms of urticaria are still controversial. Leznoff et al. reported that the L-thyroxin therapy improved clinical symptoms of CU.[7] Some studies confirmed this observation, while other authors failed to find any influence of L-thyroxine on the course of urticaria.[9,16,17] In our patients with thyroiditis, the treatment with L-thyroxine had no influence on the clinical course of urticaria.

Mechanisms that link thyroid autoimmunity and CU are still unknown and are object of controversies.[18] It was shown that thyroid autoantibodies do not induce urticaria and are only an epiphenomenon. CU may have autoimmune basis, since as many as 5–69% of the patients have autoantibodies to the high affinity receptor for IgE (anti FcεRI) on mast cells and basophils, these antibodies may be pathogenetic in the onset of CU.[18-20] No other etiology of CU except for the autoimmune one was revealed among our patients.

Other biochemical tests that were carried out in our patients were aimed at evaluating of association with other autoimmune disorders, in particular, diseases of the connective tissue. Positivity of ANA (>1:160) that was found in 4/10 patients with Hashimoto's thyroiditis and development of lupus erythematous discoid in one of them further confirms the autoimmune pathogenesis of CU.

In conclusion, results from the present study confirms the high prevalence of thyroid autoimmune disorders in patients with CU and extends the finding on the population with mild-to-moderate iodine deficiency. Indeed, in the province of Naples, an area with iodine deficiency, the prevalence of antithyroid autoantibodies and Hashimoto's thyroiditis in patients with CU were 22% and 18.5%, respectively. These results suggest that screening for thyroid function may be useful in all the patients with CU. Non symptomatic positivity of antithyroid antibodies is a serological markers for chronic thyroiditis that represents a risk factor for development of hypothyroidism. Predictive value of this association remains to be elucidated.

Table 2. Clinical features of the urticaria in patients according to the presence of anti-thyroid autoantibodies

	Patients without antibodies (n=42)	Patients with antibodies (n=12)	*P* value
N. patients with crises less than once a day more than 3 times a week	28	8	0.99
N. patients with less than crises 3 times a week	14	4	0.99
Association with angio-edema	18	4	0.74
Resistance to antihistamines	34	7	0.13

Table 3. Clinical features of the urticaria in patients according to the presence of anti-thyroid autoantibodies

	Patients with chronic urticaria(n= 54)	Controls (n=108)	*P* value
Positivity of thyroid antibodies	12 (22.2 %)	7 (6.5 %)	0.99
N. patients with less than crises 3 times a week	10 (18.5 %)	2 (1.8 %)	0.0005
Association with angioedema	10 (18.5%)	1 (0.9%)	0.0001
Resistance to antihistamines	8 (15%)	0 (0%)	0.0002
Subclinical hypothyroidism	2 (3.7%)	1 (0.9%)	0.53

Patients and Methods

Patients. This is a prospective case-control study that enrolled patients and controls during 6 months, from December to July 2007, and followed all of them for further 6 months.

Fifty-four consecutive patients affected by CU were recruited at the outpatient clinic of Allergological Dermatology; there were 42 females and 12 males, with a median age of 36 years (range, 15–58 years), all were living in the province of Naples.

For each patient enrolled, two control subjects matched for age and gender were selected among the population of usual blood donors and included in the data analysis. Indeed, the control group consisted of 108 healthy individuals (84 females and 24 males, median age 35 years (range, 18-59 years); without history of urticaria. All control subjects lived within the same geographic area.

None of the 162 subjects were taking any drugs or had history of other autoimmune diseases.

The study was performed according to the procedures indicated by the Helsinki II Declaration. All enrolled subjects gave their informed consent to participate in the study.

Methods. All the patients underwent a complete medical and pharmacological anamnesis, a complete physical examination, a dermatological objective examination to reveal eventual presence of other skin disorders.

Biochemical evaluation included a routine laboratory screening with complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Antistreptolysin O titre, glucose levels, liver and kidney function tests, electrophoresis of serum proteins), Rheumatoid factor (RF), C3 and C4 components of the complement system, immunoglobulin, cryoglobulin, HBsAg, HCV-Ab, VDRL, antinuclear antibodies (ANA), anti-extractable nuclear antigens (ENA), total IgE, IgE antibodies directed towards mixed food and inhalant allergens and parasitological evaluation of the stool (on 3 samples collected in 3 days). Assessment of the thyroid function included measurement of serum concentrations of TSH, FT3, FT4, anti-thyreoglobulin (anti-TG) and anti-peroxidase (anti-TPO) antibodies.

Ultrasound scan of the thyroid gland was performed in all subjects using a 7.5 MHz linear transducer.

The patients were followed up for 6 months after the study entry to observe the course of urticaria and eventual appearance of other autoimmune diseases.

All controls underwent the same evaluation at the study entry; their medical history, physical examination and biochemical tests excluded any previous or current urticaria. They were also followed for 6 months after their initial evaluation, in order to exclude any new onset of urticaria or other disorder.

Assays. Determinations of thyroid hormones, TSH and antibodies were performed with the same commercial kits for the whole study period. Serum TSH was measured using an immunoradiometric assay (Delfia, Wallac, Inc. Finland) and free thyroid hormones were determined by radioimmunoassay Lisophase kits (Technogenetics, Milan, Italia). Anti-TG antibodies were measured with an Ares Serono kit (Milan, Italy) and anti-TPO antibodies by a DiaSorin kit (Saluggia, Italy). Iodine urinary excretion was measured in extemporaneous morning samples using the colorimetric ceric ion arsenious acid wet ash method based on the Sandell-Kolthoff reaction (10) and spectrophotometer equipped with an automatic sipper. The intra-assay variation coefficient was <3.6% and the inter-assay one <7.8% for all the measurements.

Blood chemistry profile, blood count, and liver and kidney function were analyzed using a standard autoanalyzer.

Statistical analysis. All statistical procedures were performed using a Statistical Package for Windows (Sigma-Stat). The differences between patients and controls were compared by using the Pearson's chi-square test for categorical variables. All results are given as percentage, media, median, standard deviation and range. Statistical significance was set at 5%.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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