Prevalence of Thyroid Antibodies in Thai Patients with Chronic Idiopathic Urticaria†

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Abstract

One hundred Thai patients with chronic idiopathic urticaria (CIU) were studied to determine the prevalence of thyroid antibodies in comparison to 100 age- and sex-matched healthy volunteers. It was found that 21 patients (21%) with CIU were positive for thyroid antibodies. Among normal volunteers, only nine cases (9%) had elevated titers of thyroid antibodies. The frequency of thyroid antibodies in the chronic urticaria group was significantly more common than the control group (chi-square = 4.75, p=0.03). Among 21 patients with CIU who were positive for thyroid antibodies, 9 cases were negative for thyroid antibodies when repeating the tests after 3 months. Only 12 patients still had persistent elevation of antibodies after 3 months and thyroid function test was performed in these 12 patients. It was found that 9 cases had autoimmune thyroiditis with euthyroidism. One case had subclinical hyperthyroidism. One case had autoimmune hyperthyroidism. One case had subclinical hypothyroidism.

Key word : Hives, Autoimmune Thyroiditis, Hypothyroidism, Hyperthyroidism

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Chronic urticaria is a common skin disorder. The diagnostic problem is that most patients with urticaria do not have an identifiable cause and are categorized as idiopathic urticaria. Several reports have shown increased frequency of thyroid autoimmunity in patients with chronic urticaria[1-3]. In some patients urticaria improved when thyroid diseases were treated[2-5]. It has been hypothesized that autoimmunity may play a role in the pathogenesis of chronic urticaria. Since there has been racial diffe-

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rence in some autoimmune diseases such as systemic lupus erythematosus (SLE), which was found to be more common among Afro-Caribbians and Asians than among Caucasians[6-9], it is interesting to know whether there is racial difference in the prevalence of thyroid autoimmunity in chronic urticaria patients. The objective of this study was to determine the prevalence of thyroid antibodies in Thai patients with chronic idiopathic urticaria (CIU) in comparison to healthy volunteers.

METHOD

One hundred patients with CIU and 100 age- and sex-matched healthy volunteers were studied at the outpatient clinic of Dermatology Division, Department of Medicine, Ramathibodi Hospital from January to December 1999. The diagnosis of CIU was defined as having symptoms for longer than 6 weeks without identifiable cause. Patients with urticarial vasculitis, physical urticaria (except asymptomatic dermographism), hepatitis B and hepatitis C, and children under 15 years of age were excluded from the study. Complete medical history was obtained and physical examination performed in every patient. Laboratory investigations included complete blood count, urinalysis, stool examination, hepatitis B and hepatitis C antigen and antibody. In certain cases, chest and sinus roentgenograms, antinuclear antibody (ANA), and erythrocyte sedimentation rate (ESR) were obtained and skin biopsy was performed to confirm the diagnosis. All patients and control subjects were tested for the presence of thyroid antibodies, ie. thyroid microsomal antibody (TMA) and thyroglobulin antibody (TGA) using a hemagglutination kit (Murex Biotech Ltd., Dartford, England). In a case that the titer of TMA was $\geq$ 1 : 100 or TGA was $\geq$ 1 : 160, the laboratory test for TMA and TGA would be repeated in the next 3 months. If the antibodies titer remained high, the thyroid function test would be measured as follows : total triiodothyronine (TT3) using chemiluminescence immunoassay, Immulite of Diagnostic Product Corporation (normal : 82-179 ng/dl), free triiodothyronine (FT3) using electrochemiluminescence immunoassay, Ele sys 1010 of Roche-Boehringer (normal : 1.82-4.62 pg/ml), total thyroxine (TT4) using chemiluminescence immunoassay, Immulite of Diagnostic Product Corporation (normal : 4.5-12.5 μg/dl), free thyroxin (FT4) using enzyme immunoassay, Cobas core II of Roche-Boehringer (normal : 0.8-2.0 ng/dl) and thyroid stimulating hormone (TSH) using electrochemiluminescence immunoassay, Ele sys 1010 of Roche-Boeringer (normal 0.1-3.7 μIU/ml). The presence of TMA, TGA in titers equal to or greater than 1 : 100 and 1 : 160 respectively, irrespective of thyroid dysfunction, were the criteria for diagnosis of autoimmune thyroid disease. All patients with thyroid antibodies were examined by an endocrinologist (GP).

Statistical method

The chi-square test was used to evaluate the proportions of subjects with thyroid antibodies. Significance was set at $p<0.05$.

RESULTS

Of the 100 patients with CIU, 19 (19%) were male and 81 (81%) were female, the male to female ratio was 1 : 4.3. The age ranged from 15 to 64 years (mean $\pm$ SD = 33.5 $\pm$ 11.4 years). Most female patients (85%) were aged from 21 to 50 years (Fig. 1). There was no increased prevalence in males with respect to the age group. (Fig. 1, Table 1). The duration of symptoms ranged from 6 to 520 weeks (mean $\pm$ SD = 58.2 $\pm$ 93.1 weeks).

The control group consisted of 100 healthy volunteers, aged 15-67 years (mean $\pm$ SD = 33.6 $\pm$ 11.2 years), 19 (19%) were male, 81 (81%) were female, male to female ratio = 1 : 4.3.

Twenty-one CIU patients (21%) were positive for thyroid antibodies initially, 16 (16%) had TMA titers ranged from 1 : 100-1 : 6400, 12 (12%) had TGA titer ranged from 1 : 160-1 : 640. Nine cases had high titers of TMA only, while 5 cases had high titers of TGA only (Table 2).

Nine cases (9%) in the control group had elevated titers of thyroid antibodies (Table 3). In comparison to control group, the frequency of thyroid antibodies in the chronic urticaria group was significantly more common (chi-square = 4.75, p=0.03).

Nine patients were negative for thyroid antibodies on repeating the tests 3 months thereafter and therefore thyroid function test was done in only 12 patients. Among these 12 patients with persistent elevation of TMA and/or TGA, 9 cases had autoimmune thyroiditis with euthyroidism (Table 4) and were treated with antihistamines. One patient with subclinical hyperthyroidism (no. 3), was treated only with antihistamines. She still had subclinical hyperthyroidism and urticaria 6 months later. One patient with autoimmune hyperthyroidism (no. 19) was treated with methimazole and antihistamine. She became euthyroid 5 weeks after initiation of an antithyroid

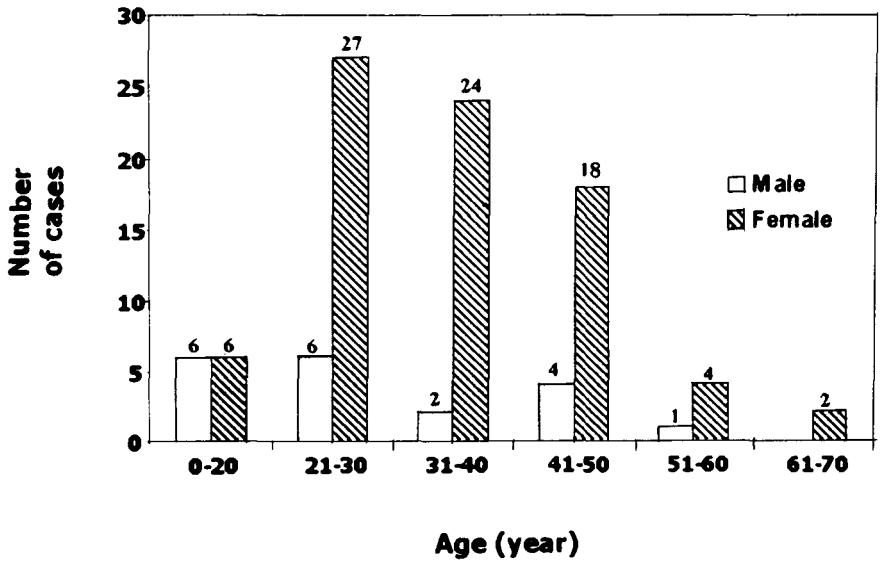

Fig. 1. Age and sex distributions of 100 patients with chronic urticaria.

Table 1. Age and sex distribution of 100 patients with chronic urticaria.

Age (years)	Number of cases		Total
	Male	Female	
0-20	6	6	12
21-30	6	27	33
31-40	2	24	26
41-50	4	18	22
51-60	1	4	5
61-70	0	2	2
Total	19	81	100

drug, and urticaria disappeared 5 weeks after the patient became euthyroid. One case (no. 7) had subclinical hypothyroidism; she was treated only with antihistamine, and urticaria resolved within 3 months.

DISCUSSION

Some cases of chronic idiopathic urticaria of unexplained cause may be associated with autoimmune thyroiditis. Leznoff et al[5] were the first to demonstrate the association of chronic urticaria with thyroid autoimmunity. They found that 12.1 per cent of 140 chronic urticaria patients had elevated titers of thyroid microsomal antibodies, while only 5.6 per cent of 477 control persons had thyroid microsomal antibodies. Eight patients in the urticarial group had a goiter or thyroid dysfunction. In another study, Leznoff and Sussman[2] reported that 14.4 per cent of 624 idiopathic chronic urticaria and angioedema patients had evidence of thyroid autoimmunity. They expected that <6 per cent of normal subjects had thyroid autoimmunity, so there was significant association between urticaria and angioedema and autoimmune thyroid disease. In a study reported by Lanigan, Short and Moult[10], 28 per cent of 50 patients had thyroid diseases with elevated titers of thyroid microsomal and thyroglobulin antibodies were found to have a history of chronic urticaria, while only 4 per cent of 50 patients who had only thyroid diseases without any evidence of thyroid autoimmunity, and only 6 per cent of 50 control persons who had no history of thyroid disease had history of chronic urticaria. They concluded that there was significant association between thyroid autoimmunity and chronic urticaria by comparing these 3 groups of patients. Turktas et al[1] studied 94 patients who had chronic urticaria and angioedema and found elevated titers

Table 2. Initial positive thyroid antibody results in 21 patients with chronic idiopathic urticaria.

No.	TMA ≥ 1 : 100	TGA ≥ 1 : 160
1	1 : 100	negative
2	1 : 100	negative
3	1 : 1,600	negative
4	1 : 6,400	1 : 320
5	1 : 1,600	1 : 640
6	1 : 100	1 : 160
7	1 : 1,600	1 : 160
8	negative	1 : 160
9	negative	1 : 160
10	1 : 400	negative
11	1 : 400	1 : 160
12	1 : 400	negative
13	negative	1 : 160
14	1 : 100	negative
15	1 : 400	negative
16	1 : 100	negative
17	1 : 400	1 : 320
18	1 : 100	negative
19	1 : 1,600	1 : 320
20	negative	1 : 160
21	negative	1 : 160

Table 3. Positive thyroid antibody results in 9 control subjects.

No.	TMA ≥ 1 : 100	TGA ≥ 1 : 160
1	1 : 400	negative
2	1 : 100	1 : 160
3	1 : 1,600	neg
4	1 : 1,600	1 : 640
5	1 : 400	negative
6	negative	1 : 160
7	1 : 400	negative
8	1 : 400	negative
9	1 : 400	1 : 320

of thyroglobulin and thyroid microsomal antibodies in 11.7 per cent and 9.57 per cent of the patients respectively. Both antibodies were detected in only 3.7 per cent of 80 age- and sex-matched healthy volunteers. The association between thyroid antibodies and chronic urticaria and/or angioedema was statistically significant. In agreement with the aforementioned reports, the authors found Thai patients with chronic urticaria had elevated titers of thyroid antibodies more frequently than the age-and sex-matched healthy volunteers, i.e. 21 per cent *vs* 9 per cent (chi-square = 4.75, p=0.03). The prevalence of thyroid antibodies in Thai patients in the present study was significantly higher than those in Canada[2] and Turkey[1] (chi-square, p=0.048 and 0.040 respectively). The higher prevalence of thyroid antibodies in the present study might be due to racial difference or population selection or methodological difference of laboratory tests for the antibodies. Further study should be done to explain this finding.

In the present study, high titer of TMA was found more frequently than high titer of TGA (16% *vs* 12%), which is consistent with the report by Leznoff et al[2]. However, in the study by Turktas et al[1], TGA was more frequently found than TMA (11.7% *vs* 9.57%). The reasons for this discrepancy are not clear. There might be some methodological difference of laboratory tests for the antibodies. Racial difference may be another factor to be considered, although there has been no previous mention in the literature.

It remains unclear why there is a high prevalence of thyroid antibodies in patients with chronic urticaria. Rumbyrt et al[3] proposed that antithyroid antibodies are not pathogenic, but only indicates that there is autoimmunity. They postulated that the mediators released from inflammatory cells - i.e. histamine releasing factors, proinflammatory cytokines, and autoantibodies - not only perpetuate a chronic inflammatory state but also decrease the mast cell threshold to endogenous peptides or exogenous allergens or other stimulants.

There have been many reports of remission of urticaria in patients who had thyroid autoimmunity that were treated with thyroid hormone; however, these reports were not control trial studies[2-5]. The mechanism of thyroid hormone in resolving urticaria is still unknown[11], urticaria has been found to be occasionally associated with hyperthyroidism [5,12-14]. In the present study, one patient had autoimmune hyperthyroidism, and another one had subclinical hyperthyroidism.

Of interest, in the present study as well as the studies by Leznoff et al[2] and Turktas et al[1] there was a high prevalence of urticaria in females (male : female ratio is 1 : 4.3, 1 : 7 and 1 : 2.6, respectively). Autoimmune thyroiditis is also common in females[15].

In conclusion, the present study agreed with previous studies[1,2,5,10] that there is a high prevalence of thyroid antibodies among patients with

Table 4. Results of thyroid function tests in 12 patients with persistent elevation of thyroid antibody tests after 3 months.

Case no.	Thyroid function tests			
	T3 (ng/dl)	T4 (μg/dl)	FT4 (ng/dl)	TSH (μIU/ml)
1	113	7.1	0.9	1.35
3*	179	10.4	1.7	0.005
4	129	9	0.9	4.3
5	120	7.2	0.9	1.4
7**	126	8.5	0.8	4.78
10	109	9.7	1	2.3
11	120	9	1.1	1.7
12	115	8	1.1	1.5
15	88	7.2	1.2	1.6
17	128	7.8	0.8	3.8
18	110	8.7	1	2.5
19***	236	12	3.8	<0.005

Normal valueT3 = 82-179 ng/dl, T4 = 4.5-12.5 μg/dl, FT4 = 0.8-2.0 ng/dl, TSH = 0.1-3.7 μIU/ml

* Subclinical hyperthyroidism
** Subclinical hypothyroidism
*** Hyperthyroidism

chronic idiopathic urticaria. In addition the present study performed on Thai patients had a higher prevalence of thyroid antibodies than other studies ($p< 0.05$). Eventhough most patients with elevated titers of thyroid antibodies were euthyroid, some may have either hypothyroidism or hyperthyroidism. Most of the patients with autoimmune thyroiditis in this study and the study done by Turktas[1] were asymptomatic, however they should be closely followed-up since some may ultimately develop overt hypothyroidism. The authors recommend routine TMA and TGA tests in patients with chronic idiopathic urticaria. For patients with persistent positive TMA or TGA, thyroid function tests should be performed.

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REFERENCES

1. 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.
2. Leznoff A, Sussman GL. Syndrome of idiopathic urticaria and angioedema with thyroid autoimmunity : A study of 90 patients. J Allergy Clin Immunol 1989; 84 : 66-71.
3. Rumbyrt JS, Katz JL, Schocket AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. J Allergy Clin Immunol 1995; 96 : 901-5.
4. Dreyfus DH, Schocket AL, Milgrom H. Steroid-resistant chronic urticaria associated with antithyroid microsomal antibodies in a nine-year-old boy. J Pediatr 1996; 128: 576-8.
5. Leznoff A, Josse RG, Denburg J, Dolovich J. Association of chronic urticaria and angioedema with thyroid autoimmunity. Arch Dermatol 1983; 119: 636-40.
6. Siegel M, Holley HL, Lee SL. Epidemiologic studies on systemic lupus erythematosus. Comparative data for New York City and Jefferson County, Alabama, 1956-1965. Arthritis Rheum 1970; 13: 802-11.
7. Hart HH, Grigor RR, Caughey DE. Ethnic difference in the prevalence of systemic lupus erythematosus. Ann Rheum Dis 1983; 42: 529-32.

8. Serdula MK, Rhoads GG. Frequency of systemic lupus erythematosus in different ethnic groups in Hawaii. Arthritis Rheum 1979; 22: 328-33.
9. Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Arthritis Rheum 1995; 38: 551-8.
10. Lanigan SW, Short P, Moult P. The association of chronic urticaria with thyroid immunity. Clin Exp Dermatol 1987; 12: 335-8.
11. Heymann WR. Chronic urticaria and angioedema associated with thyroid autoimmunity : Review and therapeutic implications. J Am Acad Dermatol 1999; 40: 229-32.
12. Small P. Hyperthyroidism and polycythemia vera with chronic urticaria and angioedema. Ann Allergy 1981; 46: 256-9.
13. Isaacs NJ, Ertel NH. Urticaria and pruritus : Uncommon manifestations of hyperthyroidism. J Allergy Clin Immunol 1971; 48: 73-81.
14. Pace JL, Garetts M. Urticaria and hyperthyroidism. Br J Dermatol 1975; 93: 97-9.
15. Lamberton P, Jackson I. Thyroiditis. In : Becker KL (ed). Principles and Practice of Endocrinology and Metabolism, Vol. 1, 2nd edn. Philadelphia: J B Lippincott Company, 1995: 412-21.

อุบัติการณ์การเกิดแอนติบอดีย์ต่อต่อมธัยรอยด์ในผู้ป่วยไทยที่เป็นลมพิษโดยไม่ทราบสาเหตุ†

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ได้ศึกษาหาอุบัติการณ์การเกิดแอนติบอดีย์ต่อต่อมธัยรอยด์ในผู้ป่วยไทย 100 รายที่เป็นลมพิษโดยไม่ทราบสาเหตุ เปรียบเทียบกับคนปกติที่มีอายุและเพศเหมือนกันกับกลุ่มผู้ป่วยพบว่า ผู้ป่วย 21 ราย (21%) ที่เป็นลมพิษเรื้อรังมีแอนติบอดีย์ต่อต่อมธัยรอยด์ ในขณะที่ตรวจพบแอนติบอดีย์ต่อต่อมธัยรอยด์ในคนปกติเพียง 9 ราย (9%) ความแตกต่างนี้มีนัยสำคัญทางสถิติ (chi-square = 4.75, p=0.03) ในผู้ป่วยลมพิษ 21 รายที่มีแอนติบอดีย์ต่อต่อมธัยรอยด์ เมื่อตรวจเลือดซ้ำอีกครั้งห่างจากครั้งแรก 3 เดือน 9 รายตรวจไม่พบแอนติบอดีย์นี้อีก มีเพียง 12 รายที่ยังมีระดับแอนติบอดีย์สูงอยู่ ซึ่งได้ตรวจหาการทำงานของต่อมธัยรอยด์ในผู้ป่วย 12 รายนี้ พบว่า 9 รายเป็นต่อมธัยรอยด์อักเสบจากออโตอิมมูนซึ่งยังมีการทำงานของต่อมธัยรอยด์อยู่ในเกณฑ์ปกติ 1 รายเป็นโรคต่อมธัยรอยด์ทำงานมากกว่าปกติแต่ยังไม่แสดงอาการ 1 รายเป็นโรคต่อมธัยรอยด์เป็นพิษและมีอาการแสดงด้วย 1 รายมีต่อมธัยรอยด์ทำงานน้อยกว่าปกติแต่ยังไม่แสดงอาการ

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