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The Prevalence and Characteristics of Allergy in Autoimmune Thyroid Diseases

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Abstract

Objective: The relationship between autoimmunity and allergy is well known. The immunoregulation can be modified towards T helper 2 dominance by cytokines and regulatory T cells, which participate in both diseases. Autoimmune thyroid diseases possess different immunoregulatory and sympathoadrenal activity, whose features can be reflected by their association with allergic attacks and the degree of allergen-specific IgE levels.

Methods: Two-hundred-fifty-nine patients, 149 with Graves' disease (57 had ophthalmopathy), 110 with Hashimoto's thyroiditis and 65 controls with small euthyroid goitre were investigated. Allergen-specific IgE levels to 20 respiratory and 20 food allergens were detected by AllergySreen immunoblot method and given in IU/ml. Thyroid hormones and autoantibodies to thyroid peroxidase (TPO) and thyroglobulin (Htg) were measured in a fully automated way, but TSH receptor antibodies with radioimmunoassay.

Results: The prevalences of respiratory and food allergen-specific IgE levels were higher in Graves' disease in comparison with Hashimoto's thyroiditis and controls. The seasonal allergen-specific IgE levels increased more in Graves' patients without ophthalmopathy, than in patients who had eye symptoms and Hashimoto's thyroiditis. Mugwort- and soybean-specific IgE levels elevated significantly in the absence of anti-Htg and the presence of TSH receptor antibodies, respectively. In turn, the presence of allergen-specific IgE levels was associated with alterations in thyroid hormone and antithyroid antibody levels too.

Conclusion: The elevated prevalences of respiratory and food allergies reflected Th2-derived cytokine productions in autoimmune thyroid diseases. The lower respiratory and food allergen-specific IgE levels highlighted a role of prominent proinflammatory cytokine productions in Graves' ophthalmopathy and Hashimoto's thyroiditis. Allergy due to increased Th2-derived and proinflammatory cytokine productions may aggravate or induce AITDs, as well as via modified thyroid hormone and antithyroid antibody levels may contribute to a slow remission rate of Graves' hyperthyroidism.

Keywords: Graves' disease; Hashimoto's thyroiditis; Allergy; Respiratory; Food; Allergen-specific IgE; Autoimmunity

Introduction

Graves' disease and Hashimoto's thyroiditis are member of autoimmune thyroid diseases (AITDs). Graves' disease is characterized by diffuse goitre, hyperthyroidism and ophthalmopathy in 25-50% of patients [1]. Stimulating TSH receptor antibodies are regarded as factors for hyperthyroidism, and autoantibodies to thyroid peroxidase (TPO) and thyroglobulin (Htg) can produce too. The exact causes, which lead to alterations in both thyroid glands and orbital tissues, have not been cleared yet. In Graves' disease, the immune regulation is characterized by the schift to T helper 2 (Th2) dominance with the productions of cytokines and autoantibodies directing to thyroidal and non-thyroidal antigens [2]. Hashimoto's thyroiditis is characterized by the presence of anti-TPO and anti-Htg autoantibodies, as well as by the rare occurrence of TSH receptor antibodies, in 3-5% only. The immune processes lead to thyroid tissue destruction due to the productions of proinflammatory IL-1, IL-6, IL-17 and TNFα cytokines and the increased apoptosis demonstrating Th1 dominance [3].

Elevated IgE levels in Graves' disease, can be regarded as inducing factors for hyperthyroidism and connect to higher TSH receptor antibody levels [4]. IgE deposits were demonstrated in eye muscle tissue derived from patients with ophthalmopathy [5]. Seasonal allergic attacks showed a strong association with higher prevalence of Graves' hyperthyroidism [6]. Th2-derived IL-5 and IL-13 cytokines were elevated in Graves' disease and also that of IL-5 in Hashimoto's thyroiditis [7-8]. The main regulatory factors of immune responses are mast cells, T cell dysregulation and cytokines, which are involved in both allergy and autoimmunity. Our previous reports highlighted the pathognomic role of serum total IgE, IL-5 and IL-12 cytokine levels, as well as nerve growth factor (NGF) in Graves' ophthalmopathy [9-11].

The objective of the study was

- To investigate the prevalence of respiratory and food allergic events and the presence of allergen-specific IgE levels in autoimmune and nonimmune thyroid diseases.
- To demonstrate any difference in Graves' disease between the presence and absence of ophthalmopathy.
- To reveal any linkage between allergic events and thyroid status.

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The difference in allergen-specific IgE levels may reflect a distinct immune regulation in AITDs. The results may contribute to a better understanding of the association of thyroid diseases with ophthalmopathy. In turn, the investigations give an answer, whether the presence of allergen-specific IgE levels via modifying effect on thyroid hormone and autoantibody levels can contribute to a slow remission rate of Graves' hyperthyroidism.

Patients and Methods

Patients

Two-hundred-fifty-nine cases formed the patient groups: 149 patients had Graves' disease (mean age of 49 ± 13 years, 57 cases had ophthalmopathy), 110 Hashimoto's thyroiditis (mean age of 50 ± 14 years) and 65 cases with euthyroid goitre were the controls (mean age of 48 ± 13 years) (Table 1). Thirty-eight patients with Graves' disease were hyperthyroid, 87 euthyroid and 24 hypothyroid at the time of the study. Hyperthyroid Graves' patients were treated with thyrostatic therapy (methimazole or propylthiouracil) in 26 cases, radioiodine in 8 cases and surgical removal in 4 cases. In hypothyroid Graves' patients, 3 patients did not receive any therapy, 4 patients were treated with thyrostatic drugs, 12 patients with radioiodine and 5 with surgery treatments. Eleven hypothyroid patients were insufficiently substituted with levothyroxine therapy at the time of the study. Only 7 out of 24 hypothyroid patients had no autoantibodies to thyroid peroxidase and/or thyroglobulin. In Graves' ophthalmopathy, the exact diagnosis based on the investigation of ophthalmologist. All patients with Hashimoto's thyroiditis were treated with levothyroxine supplementation and showed euthyroid state demonstrating autoantibodies to thyroid peroxidase and/or thyroglobulin. Four patients with Hashimoto's thyroiditis had surgical removal in history. The control group consisted of healthy patients without immune, infection, cancer and endocrine diseases in the history, and they had normal biochemical data, but the thyroid ultrasound detected a small (<10 mm) nodule in thyroid glands. None of patients were treated with steroid and antihistamine medications at the time of the study. The diagnosis of seasonal allergies or food sensitivities was based on the physical examination and the typical allergic symptoms in the history with the presence of allergen-specific IgE levels.

Methods

Detection of allergen-specific IgE levels

Allergen-specific IgE levels were detected with AllergyScreen immunoblot method (MEDIWISS Analytic GmbH, Germany) against the following respiratory and food allergens: I. Studied respiratory allergens: D1: House-dust mite I (Dermatophagoides pteronyssinus), D2: House-dust mite II (Dermatophagoides farinae), T2: Alder, T3: Birch, T4: Hazel, Gx: Grass-mixture, G12: Rye pollen, W6: Mugwort, W9: Plantain, W1: Ragweed, E1: Cat, E5: Dog, Ex: Feather mixture, E6: Guinea pig, E82: Rabbit, E84: Hamster, M1: Penicillium notatum, M2: Cladosporium herbarum, M3: Aspergillus fumigatus, M6: Alternaria alternata. II. Studied food allergens: F1: Egg white, F75: Egg yolk, F2: Milk, F78: Casein, F4: Wheat flour, F5: Rye flour, F17: Hazelnut, F13: Peanut, F256: Walnut, F31: Carrot, F85: Celery, F258: Tomato, F14: Soya bean, F35: Potato, F33: Orange, F49: Apple, F3: Cod fish, F23: Crab, F10: Sesame seed, F20: Almond. The strips were handled with 250 µl nondiluted sera at room temperature for 45 minutes and shaked. After washing buffer (TRIS/NaCl, pH=7.5), 250 µl of biotinylated detector antibodies were added for 45 minutes. The strips were washed and 250 µl of streptavidin conjugates were measured into the membranes for 20 minutes. After washing, 250 µl of substrate solutions were added for 20 minutes in dark and terminated by briefly rising under flowing water. The membranes were dried and evaluated with Kodak camera. The results were given in IU/ml. The sensitivity and specificity of AllergenScreen were the following according to the instruction manual in comparison with Prick and ELISA tests: 95.1% and 81.2% for skin-Prick test; 84.3% and 95% for ELISA system, respectively.

Detection of thyroid hormone and anti-thyroid autoantibody levels

Thyroid hormone serum levels (TSH, FT4 and FT3), anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Htg) antibodies were measured with chemiluminescence method (Immulite, USA) in a fully automated way, in Kenézy Hospital laboratory. The outpatient sera were sampled, stored at 4°C and measured within 24 hours. The normal ranges were the following: 0.35-4.94 µU/ml for TSH, 0.7-1.48 ng/dl for FT4, 1.45-3.48 pg/ml for FT3, 0-115 IU/ml for anti-TPO antibodies and 0-65 IU/ml for anti-Htg antibodies. TSH receptor antibody detection was carried out with radioimmunoassay (Brahms, Germany), the normal range was below 1.5 U/l.

Statistical analysis

The data were exhibited as mean ± standard error (SE). The distribution of data was non-normally, therefore Chi-squared with Yates' correction and nonparametric Mann-Whitney tests were applied for comparison of two groups.

Results

Clinical parameters, thyroid hormone and antithyroid antibody levels in the studied patient groups

The clinical parameters: Age, gender and duration of thyroid diseases in the studied patient groups are exhibited in Table 1.

TSH levels were as follows: 1.46 ± 0.2 µU/ml for controls; 4.54 ± 1.06 µU/ml for Graves' disease; 6 ± 1.02 µU/ml for Hashimoto's thyroiditis. FT4 and FT3 levels were as follows: 0.98 ± 0.02 ng/dl and 2.6 ± 0.06 pg/ml for controls, 1.23 ± 0.05 ng/dl and 3.76 ± 0.34 pg/ml for Graves' disease, 1.02 ± 0.02 ng/dl and 2.51 ± 0.06 pg/ml for Hashimoto's thyroiditis, respectively. In Graves' disease, TSH receptor antibody levels were 6.35 ± 0.99 U/l. Anti-TPO and anti-Htg antibody levels were as follows: 58.41 ± 18.28 IU/ml and 44.76 ± 7.93 IU/ml for controls; 315.02 ± 30.48 IU/ml and 237.04 ± 54.48 IU/ml for Graves'disease; 564.6 ± 40.2 IU/ml and 622.17 ± 104.2 IU/ml for Hashimoto's thyroiditis, respectively.

Respiratory allergen-specific IgE levels in patients with autoimmune thyroid diseases

The prevalences of allergic symptoms: rhinitis, conjunctivitis, urticaria and asthma were studied in all patients (Table 2).

Clinical parameters	Graves'disease n=149	Hashimoto's thyroiditis n=110	Controls n=65
Age (years)	49 ± 13	50 ± 14	48 ± 13
Gender (male/women)	28/121	6/104	4/61
Duration of thyroid disease (months)	71 ± 81	44 ± 57	38 ± 45

Table 1: Clinical parameters (age, gender, duration of thyroid diseases) in the studied patient groups.

Allergic symptoms	Graves'disease (n=149)	Hashimoto's thyroiditis (n=110)	Controls (n=65)	Total
No	94 (63, 1%)	63 (57, 3%)	54 (83, 1%)	211 (65, 1%)
Rhinitis*	11^{a} (7, 4%)	20^{a} (18, 2%)	10 (15, 4%)	41 (12, 7%)
Conjunctivitis	37^{b} (24, 8%)	21^{c} (19, 1%)	0^{b,c}	58 (17, 9%)
Urticaria	7 (4, 7%)	5 (4, 5%)	1 (1, 5%)	13 (4%)
Asthma	0	1 (0, 9%)	0	1 (0, 3%)
Total	149	110	65	324

^{a}P<0.014, ^{b}P<0.0001 and ^{c}P<0.0004 after yates' correction

*P<0.0007 after Yates' correction between Graves' patients with (n=57) and without (n=92) eye signs:32 (9, 9) vs 5 (1, 5%)

Table 2: The prevalence of allergic symptoms in patients with autoimmune thyroid diseases and controls.

Rhinitis allergic attacks were more frequent in Hashimoto's thyroiditis compared to those in Graves' disease (20 cases, 18.2% vs. 11 cases, 7.4%, P<0.01). Allergic conjunctivitis was more frequent in AITDs in comparison with controls, but it was higher in Graves' disease (37 cases, 24.8% vs. not any in controls, P<0.0001). The concordance between the seasonal allergic attacks and the month of thyroidal onset was higher in Graves' disease showing significant increase compared to those in Hashimoto's thyroditis (17 cases, 18.2% vs. 7 cases, 7.2%, P<0.04; odds ratio (OR): 2.506, CI95%: 1.089-5.766) (Table 3).

Month for thyroidal onset and seasonal allergic attack is common	Graves' disease	Hashimoto's thyroiditis	Controls	Total
No	77 (81, 9%)	90 (92, 8%)	48 (78, 7%)	215 (85, 3%)
Common	17^{a} (18, 1%)	7^{a,b} (7, 2%)	13^{b} (21, 3%)	37 (14, 7%)
Total	94	97	61	252

^{a}P<0.04 and ^{b}P<0.02

*no exact data were given in 72 cases.

Table 3: The concordance between the month of thyroidal onset and seasonal allergic attacks.

The prevalence of respiratory allergen-specific IgE levels was subgrouped according to the main allergen subgroups, such as dust-mites, trees, weeds, grass-mixture, animal epithelias and moulds (Table 4).

Allergen groups	Graves' disease (n=149)	Hashimoto's thyroiditis (n=110)	Controls (n=65)	Total
D (dust mite I-II)	33 (22, 1%)	25 (22, 7%)	7 (10, 8%)	65 (20, 1%)
T (alder, birch, hazel)	25^{a} (16, 8%)	7^{a} (6, 4%)	6 (9, 2%)	38 (11, 7%)
W (mugwort, plantain, ragweed)	35^{b} (20, 1%)	12^{b} (10, 9%)	10 (10, 8%)	57 (15, 7%)
G (grass-mixture)	30 (26, 8%)	1 4(12, 7%)	7 (10, 8%)	51 (15, 7%)
E (cat, dog and other epithella, feather-mixture)	40 (26, 8%)	23 (20, 9%)	19 (29, 2%)	82 (25, 3%)
M (molds*)	10 (6, 7%)	4 (3, 6%)	4 (6, 2%)	18 (5,6%)
Total	149	110	65	324

^{a}P<0.02 and ^{b}P<0.015 *Alternaria, Aspergillus, Cladosoporium, Penicillium

Table 4: The prevalence of respiratory allergen-specific IgE levels in patients with autoimmune thyroid diseases and controls.

Graves' patients showed increased prevalences of tree and weed allergen-specific IgE levels compared to those in Hashimoto's thyroiditis (25 cases, 16.8% vs 7 cases, 6.4%, P<0.02 for trees and 35 cases, 23.5% vs 12 cases, 10.9%, P<0.02 for weeds). In comparison with controls, the prevalences of allergen-specific IgE levels were higher in Graves' disease (30 cases, 20.1% vs 5 cases, 7.7%, P<0.02 for dust-mite II and 24 cases, 16.1% vs 4 cases, 6.2%, P<0.05 for alder) and Hashimoto's thyroiditis (23 cases, 20.9%, P<0.02 for dust-mite II) (Figure 1).

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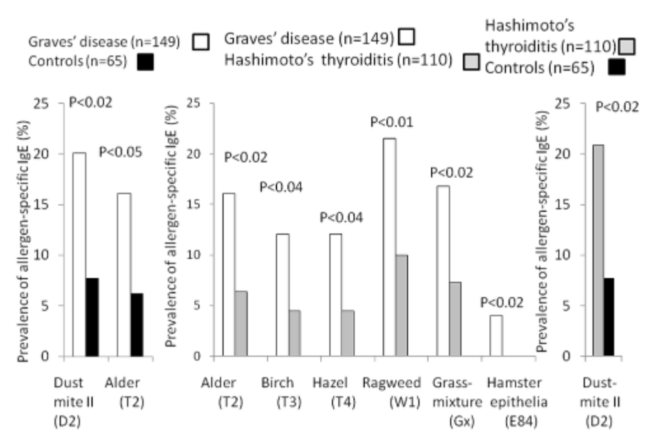

Figure 1: Significant differences in respiratory allergen-specific IgE levels among Graves' disease, Hashimoto's thyroiditis and controls.

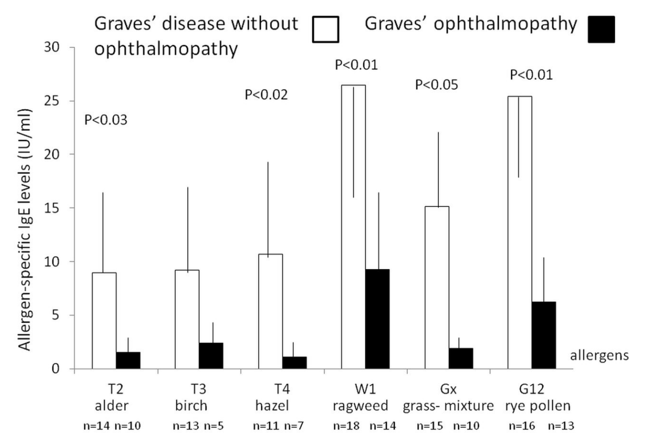

Figure 2: Significant differences in seasonal allergen-specific IgE levels between Graves' disease without and with ophthalmopathy.

Significant differences among seasonal allergen-specific IgE levels could be demonstrated between Graves' patients without and with ophthalmopathy [8.98 ± 7.02 IU/ml (n=12) vs. 1.55 ± 0.9 IU/ml (n=10), P<0.03 for alder; 10.68 ± 8.94 IU/ml (n=11) vs. 1.11 ± 0,66 IU/ml (n=7), P<0.02 for hazel; 26.48 ± 9.57 IU/ml (n=18) vs. 9.23 ± 7.01 IU/ml (n=14), P<0.01 for ragweed; 15.12 ± 6.95 IU/ml (n=15) vs. 1.91 ± 0.69 IU/ml (n=10), P<0.05 for grass-mixture; 25.39 ± 8.13 IU/ml (n=16) vs. 6.22 ± 2.64 IU/ml (n=13), P<0.01 for rye pollen] (Figure 2).

In Graves' disease, thyroid function, particularly hyperthyroidism did not connect to relevant increased IgE levels. TSH receptor antibodies were associated with elevated cladosporium-specific IgE levels [1.87 ± 0.88 IU/ml (n=3) vs 0.67 ± 0.09 IU/ml (n=4), P<0.03]. None of significant elevations in IgE levels could be detected with respect to anti-TPO levels. The mugwort-specific IgE levels were higher in patients with the absence of anti-Htg antibodies than with the presence of them [2.41 ± 1.52 IU/ml (n=6) vs 0.49 ± 0.06 IU/ml (n=2), P<0.05].

Food allergen-specific IgE levels in patients with autoimmune thyroid diseases

The prevalences of seven food allergen-specific IgE levels were significantly higher in Graves' disease compared to those in Hashimoto's thyroiditis: 13 cases, 8.7% vs one case, 0.9%, P<0.01 for hazelnut; 16 cases,10.7% vs 3 cases, 2.7%, P<0.03 for potato; 24 cases, 16.1% vs 5 cases, 4.5%, P<0.01 for celery; 25 cases, 16.8% vs 6 cases, 5.5%, P<0.01 for carrot; 10 cases, 6.7% vs one case, 0.9%, P<0.03 for tomato; 17 cases, 11.4% vs 3 cases, 2.7%, P<0.02 for orange; 22 cases, 14.8% vs 4 cases, 3.6%, P<0.01 for wheat flour (Table 5).

Allergen groups	Graves'disease (n=149)	Hashimoto's thyroiditis (n=110)	Controls (n=65)	Total
F17(hazelnut)	13[a] (8, 7%)	1[a] (0, 9%)	2 (3, 1%)	16 (4, 9%)
F35 (potato)	16[b,c] (10, 7%)	3[b] (2, 7%)	1[c] (1, 5%)	20 (6, 2%)
F85 (celery)	24[d] (16, 1%)	5[d] (4, 5%)	4 (6, 2%)	33 (10, 2%)
F31(carrot)	25[e] (16, 8%)	6[e] 95, 5%)	4 (6, 2%)	35 (10, 8%)
F25 (tomato)	10[f] (6, 7%)	1[f] (0, 9%)	0	11 (3, 4%)
F33(Orange)	17[g,h] (11, 4%)	3[g] (2, 7%)	1[h] (1, 5%)	21 (6, 5%)
F4 (wheat flour)	22[i] (14, 8%)	4[i] (3, 6%)	1 (4, 6%)	29 (9%)
Total	149	110	65	324

[a]P<0.01, [b]P<0.03, [c]P<0.04, [d]P<0.01, [e]P<0.01, [f]P<0.03, [g]P<0.02, [h]P<0.03, and [i]P<0.01, with Yates' corrections.

Table 5: The prevalence of food allergen-specific IgE levels in patients with autoimmune thyroid diseases and controls.

IgE levels for potato and orange allergens were also increased in Graves' disease compared to those in controls (one case, 1.5%, P<0.04 for potato; one case, 1.5%, P<0.03 for orange). The differences in celery and carrot allergen-specific IgE levels increased, but in walnut-specific IgE levels decreased remarkably in AITDs compared to those in controls [5.53 ± 3.6 IU/ml (n=24) vs. 0.63 ± 0.3 IU/ml (n=4), P<0.02 for celery; 5.82 ± 3.94 IU/ml (n=25) vs. 0.39 ± 0.14 IU/ml (n=4), P<0.002 for carrot in Graves' disease and 0.44 ± 0.07 IU/ml (n=3) vs. 0.62 ± 0.02 IU/ml (n=3), P<0.03 for walnuts in Hashimoto's thyroiditis] (Figure 3).

Graves' patients without ophthalmopathy showed higher potato- and carrot-specific IgE levels than those with ophthalmopathy [6.42 ± 5.01 IU/ml (n=9) vs 0.76 ± 0.14 IU/ml (n=7), P<0.04 for potato and 8.96 ± 6.52 IU/ml (n=15) vs 1.11 ± 0.3 IU/ml (n=10), P<0.03 for carrot]. No relevant elevation or decrease was demonstrated with respect to thyroid function and the presence of anti-TPO or anti-Htg antibodies. In Graves' ophthalmopathy, a strong relationship was detected between increased soybean-specific IgE levels and the presence of TSH receptor antibodies compared to those with the absence of them [0.6 ± 0.07 IU/ml (n=7) vs 0.43 ± 0.02 IU/ml (n=3), P<0.05].

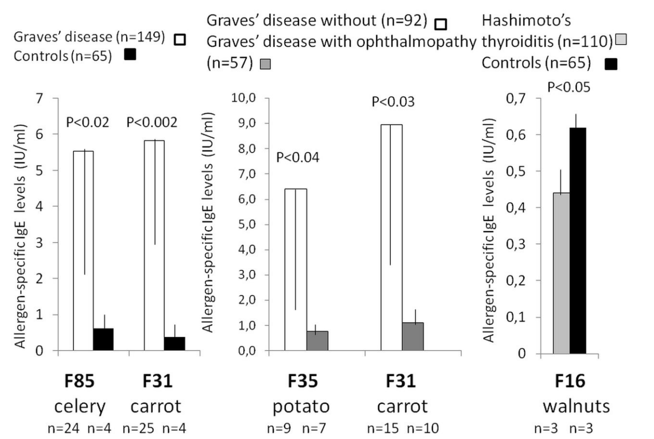

Figure 3: Significant differences in food allergen-specific IgE levels among Graves' disease, Hashimoto's thyroiditis and controls.

Modifying effects of allergen-specific IgE levels on thyroid hormone and antithyroid antibody levels in Graves' disease

The relationship between the presence of allergen-specific IgE levels and thyroid hormone or anti-thyroid antibody levels highlighted that respiratory and food allergens can influence the thyroid immunoregulation in Graves' disease. Three food and 4 seasonal allergen-specific IgE levels were associated with increased TSH [5.18 ± 2.42 µU/ml (n=9) vs. 4.49 ± 1.12 µU/ml (n=140), P<0.02 for casein; 25.05 ± 18.85 µU/ml (n=5) vs. 3.82 ± 0.86 µU/ml (n=144), P<0.003 for Penicillium; 17.93 ± 13.79 µU/ml (n=7) vs. 3.88 ± 0.88 µU/ml (n=142), P<0.01 for Cladosporium]; TSH receptor antibody [7.76 ± 2.04 U/l (n=8) vs. 6.26 ± 1.04 U/l (n=139), P<0.02 for mugwort]; anti-TPO antibody [567.33 ± 82.88 IU/ml (n=24) vs. 266.57 ± 30.97 IU/ml (n=125), P<0.001 for soybeans; 612.22 ± 89.78 IU/ml (n=9) vs. 295.91 ± 31.29 IU/ml (n=140), P<0.004 for walnuts] and anti-Htg antibody levels [263.23 ± 132.35 IU/ml (n=24) vs. 231.97 ± 59.99 IU/ml (n=124), P<0.007 for soybeans], as well as with decreased FT4 levels [0.73 ± 0.01 ng/dl (n=5) vs. 1.25 ± 0.06 ng/dl (n=144), P<0.01 for Penicillium; 0.83 ± 0.09 ng/dl (n=7) vs. 1.25 ± 0.06 ng/dl (n=142), P<0.03 for Cladosporium] (Figure 4).

Discussion

Our results highlighted that the increased prevalences of respiratory and food allergen-specific IgE levels were connected rather to Graves' disease. In this study, the manifestation of allergic conjunctivitis (and not rhinitis) was more frequent in Graves' disease suggesting that the seasonal allergic attacks can play as aggravating or inducing role in hyperthyroidism. The relationship between Graves' disease and allergy is not surprising, because thyroid autoimmunity and hyperthyroidism is characterized by Th2 dominance. The prevalence of asthma increased in women with elevated anti-TPO antibodies [12]. Th2 dominance associating with elevated nerve growth factor (NGF) levels represents an increased sympathoadrenal activity and connects to hyper- and hypothyroidism [10]. The orbital tissues are special sources for NGF release and these regions are densely innervated by sympathetic nerve fibers [13]. Ocular tissues are targets for systemic anaphylaxis or allergy due to the increased number of resident mast and eosinophil cells. The concomitant release of vasoactive amines leads to the cosecretion of NGF [14,15]. AITDs can be regarded as two endpoints of thyroid autoimmunity [16]. The difference in allergen-specific IgE levels between Graves' patients without and with ophthalmopathy highligthed that the absence of eye symptoms was associated with higher increased IgE serum levels, particularly in seasonal allergy. IL-10 elevation via influencing immunoregulation can be responsible for the stronger immunosuppressive effect in patients with ophthalmopathy [17]. In another way, the elevated levels of IL-17 and IL-6 proinflammatory cytokines can contribute to lower allergen-specific IgE levels in Graves' ophthalmopathy [18,19]. Increased IL-17 levels are also present in allergic events, Hashimoto's thyroiditis and smoking induced inflammatory processes [20-22]. IL-33 is another cytokine, which is involved in both allergic and autoimmune diseases [23]. Activation of IL-33 receptor - expressed on dendritic cells, T and B lymphocytes, natural killer (NK), mast, basophil, eosinophil and macrophage cells - leads to Th2- and NGF-mediated cytokine productions [24]. IL-33 serum levels increase significantly and correlate positively with thyroid hormone levels in Graves' disease in comparison with Hashimoto's thyroiditis and controls [25]. In house dust mite allergy, the airway inflammation was induced by Treg cells and IgA production,which immune responses could be attenuated by probiotics [26].

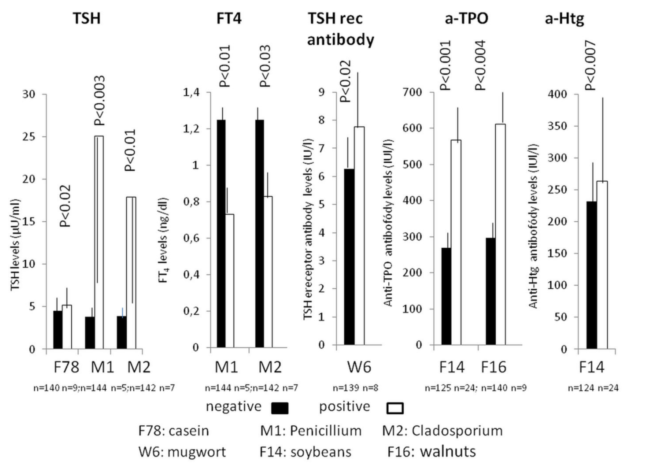

Figure 4: Modifying effect of respiratory and food allergen-specific IgE levels on thyroid hormone and antithyroid antibody levels in Graves' disease.

The prevalences of food allergic sensitizations and the degrees of allergen-specific IgE levels were similarly high in Graves' disease, particularly in patients without eye symptoms, but lower in Hashimoto's thyroiditis and Graves' ophthalmopathy. Carrot- and potato-specific IgE levels showed significant differences between Graves' patients without and with ophthalmopathy. The presence of TSH receptor antibodies was associated with elevated soybean-specific IgE levels in Graves' ophthalmopathy. Food allergy represents mucosal immunity against food allergens [27]. The role of IL-17 cytokine was demonstrated in food allergy too [28]. Gastrointestinal autoimmunity, such as coeliac disease and autoimmune gastritis were associated with Graves' ophthalmopathy rather than Graves' patients without eye symptoms [29]. Estrogenic isoflavones in soyabeans possess goitrogenic activity inhibiting iodine uptake via decreasing its organification [30]. Genistein inhibits thyroxine hormone synthesis and acts as a potent stimulator for T and B cell-mediated immune processes [31]. In our study, the immune effects of genistein may be explained by the increased anti-TPO and anti-Htg serum levels in patients with soybean-specific IgE levels. The clinical importance of modifying effect of respiratory or food allergen-specific IgE levels on thyroid hormone or antibody levels needs futher investigations. This fact highlights, that allergy similarly to smoking can contribute to a slow remission rate of Graves' hyperthyroidism.

Summarizing, the prevalences and the degrees of food and respiratory allergen-specific IgE levels increased significantly in Graves' disease highlighting the dominance of Th2-derived cytokines. In turn, the elevation of proinflammatory cytokines can be responsible for the lower degree of allergen-specific IgE levels in Graves'ophthalmopathy and Hashimoto's thyroiditis. Surprisingly, Hashimoto's thyroiditis has also Th2-derived feature with respect to respiratory allergy but failed for food allergy. Some allergen-specific IgE level had modifying effect on thyroid hormone and antithyroid antibody levels contributing to a slow remission rate in Graves' disease.

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