

Remission and Recurrence of Hyperthyroid Graves' Disease during and after Methimazole Treatment When Assessed by IgE and Interleukin 13

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We analyzed the relationship between serum IgE concentrations and the remission or recurrence of Graves' disease. One hundred seven patients with Graves' disease were treated with methimazole (MMI). Serum IgE concentration greater than 170 IU/ml was found in 41 of 107 untreated patients (38.3%). However, the presence of TSH-binding inhibiting immunoglobulin or thyroid-stimulating antibody did not correlate with the IgE concentrations. Remission was found in 20 of 41 patients with elevated IgE concentrations (48.8%) after 18 months of MMI treatment, as opposed to 53 of 66 patients with normal concentrations (80.3%) ($P = 0.0014$). MMI treatment was discontinued in 73 patients who were followed for 26–48 months. The recurrence of Graves' disease was found in 13 patients, whereas the remaining 60 were still in remission.

The rate of long-standing remission was lower in patients with elevated than normal IgE concentration (34.1% vs. 69.7%, $P = 0.0007$). We also analyzed serum levels of interleukin (IL)-13. Although IL-13 was not detected in all patients, the detection rate was higher in patients without remission and in those with recurrence than in those with long-standing remission (47.1%, 38.5%, and 13.3%, respectively; $P = 0.0012$). More patients with elevated IgE were positive for allergic diseases and for family history of allergic diseases in their first-degree relatives. We conclude that the elevation of IgE and the higher detection rate of IL-13 are associated with both remission and recurrence of Graves' disease. (*J Clin Endocrinol Metab* 86: 3540–3544, 2001)

PREVIOUS STUDIES HAVE found that 30–40% of hyperthyroid patients with Graves' disease have an elevation of serum IgE concentrations (≥ 170 IU/ml) (1). In contrast, the prevalence of IgE elevation was significantly less in autoimmune Hashimoto's thyroiditis (1). Interestingly, decreases in TSH-binding inhibiting immunoglobulin (TBII) and thyroid-stimulating antibody (TSAb) in response to antithyroid drugs were less pronounced in patients with than without IgE elevation (1). However, the role on IgE in autoimmune Graves' disease is not known.

Quite interestingly, interleukin (IL)-4 and IL-13 in the lungs of asthmatic patients stimulate IgE secretion (2–5). It has also been shown that IL-13 stimulates secretion of IgG, IgM, and IgE (6). Thus, one may expect an elevation of IL-4 and/or IL-13 in patients with Graves' disease who have an increase in IgE synthesis. Although abnormalities of intra-thyroidal lymphocytes are not reflected in circulating lymphocytes (7, 8), circulating IL-4 and/or IL-13 may stimulate the synthesis of IgE as well as IgG (TBII or TSAb). To better define the role of ILs in the pathophysiology of Graves' disease, we measured circulating ILs (IL-4, IL-6, IL-10, and IL-13) and analyzed the relationship between IL concentrations and the remission or recurrence of Graves' disease during and after the discontinuation of methimazole (MMI) treatment.

Abbreviations: AITD, Autoimmune thyroid disorder; IL, interleukin; IL4R, IL-4 receptor; IFN- γ , interferon γ ; MMI, methimazole; TBII, TSH-binding inhibiting immunoglobulin; Tg, thyroglobulin; TSAb, thyroid-stimulating antibody;

Patients and Methods

One hundred seven patients with Graves' disease (17 men and 90 women, ages 17–67) were treated with MMI for 18 months. Thirty-four of 107 patients were in a euthyroid state; however, because of continuous elevation of thyroglobulin (Tg), TBII, and/or TSAb concentrations, MMI treatment could not be discontinued as reported previously (group I) (9, 10). In the remaining 73 patients (groups II and III), MMI treatment was discontinued because of normalization in serum concentrations of T_4 , Tg, TBII, and TSAb (9, 10); those patients were followed for 26–48 months. During follow-up, the recurrence of Graves' disease was noted in 13 patients within 8–26 months after MMI withdrawal (group III), whereas the remaining 60 patients were still euthyroid at 26–48 months (group II). Patients who had allergy to MMI were excluded from this study, because MMI treatment could not be continued for a long period. We analyzed the presence of allergic diseases (atopy, allergic rhinitis, and asthma) in patients with Graves' disease and allergic diseases and autoimmune thyroid disorders (AITDs) in their first-degree relatives.

Serum T_4 , TSH, TBII, TSAb, Tg, and IgE concentrations were measured monthly (1, 9, 10). IFN- γ and IL-4, IL-6, IL-10, and IL-13 concentrations were measured at the time of MMI treatment, at the time of recurrence, or at the latest follow-up. The detection limit for TSH was 0.02 mIU/liter. Concentrations of IgE and cytokines were confirmed by ELISA (Mitsubishi Kagaku Bio-Chemical Laboratory Inc., Tokyo, Japan). Fresh sera from hyperthyroid patients were used for cytokine measurement. A normal IgE concentration was defined as less than 170 IU/ml, because mean serum IgE level was 61.6 IU/ml (range, 27.54–138.34) obtained from 43 normal subjects without history of allergic diseases and negative for specific antibodies against 16 common antigens (1, 11). The intra- and interassay coefficients of variation for IgE were 7.2% ($n = 8$) and 6.8% ($n = 8$), respectively. The minimal detectable levels were 1.56 pg/ml for IFN- γ , 15 pg/ml for IL-4, 0.15 pg/ml for IL-6, 0.5 pg/ml for IL-10, and 3.12 pg/ml for IL-13. The intra-assay coefficients of variation for IFN- γ , IL-4, IL-6, IL-10, and IL-13 were 4.5% ($n = 6$), 3.9% ($n = 8$), 2.9% ($n = 20$), 4.5% ($n = 16$), and 4.1% ($n = 6$), respectively. The interassay coefficients of variation for IFN- γ , IL-4, IL-6, IL-10, and IL-13

were 5.7% (n = 6), 6.7% (n = 8), 10.9% (n = 20), 7.8% (n = 16), and 5.0% (n = 6), respectively. Serum T₄, T₃, TBII, TSAb, and Tg concentrations were measured as reported previously (1). Under normal conditions, TBII is less than 10% and TSAb is less than 180% (12). Statistical analysis was performed by ANOVAs, χ^2 test with Yate's correction, or Fisher's exact probability test using StatView software (SAS Institute, Inc., Cary, NC). A P value less than 0.05 was considered statistically significant.

Results

Remission and recurrence rates during and after MMI treatment in Graves' disease with or without IgE elevation

The elevation of serum IgE was found in 41 of 107 untreated hyperthyroid patients with Graves' disease (38.3%) (Table 1). After 18 months of treatment, concentrations of T₄, TSH, TBII, TSAb, and Tg normalized in 73 of 107 patients (68.2%, remission; groups II and III). Furthermore, the remission occurred in 20 of 41 patients with elevated concentrations of IgE (48.8%) and in 53 of 66 patients with normal IgE concentrations (80.3%, $P = 0.0014$) (Table 1). During follow-up (26–48 months), 60 of 73 patients had a long-standing remission (group II). The long-standing remission rate was significantly lower in patients with elevated than normal IgE (34.1% vs. 69.7%, $P = 0.0007$). However, no difference in the recurrence rate was seen between group III patients with elevated IgE and with normal IgE (30.0% vs. 13.2%, $P = 0.1721$), because of the limited number of patients (Table 1).

TBII (or TSAb) and IgE levels during and after MMI treatment in patients with Graves' disease

As shown in Table 2, 34 patients without remission (group I) were euthyroid after 18 months of treatment. However, TBII and/or TSAb did not normalize regardless of the IgE level. In 60 patients with long-standing remission for the follow-up period (group II), TBII and TSAb normalized, but not IgE concentrations in the majority of those patients (Table 3). Recurrence was found in 13 patients within 8–24 months after discontinuation of MMI treatment (group III). As ex-

pected, concentrations of T₄, TBII, and TSAb were increased at the time of recurrence (Table 2).

IFN- γ and ILs in sera of patients with Graves' disease during and after MMI treatment

IFN- γ was detected in only four patients with elevated IgE concentrations, whereas IL-4 was not detected in any patients at any time of follow-up. The detection rate of IL-6 varied from 85–100%. IL-10 was detected in all patients studied at any time of follow-up. We analyzed the concentration of IL-6 and IL-10 quantitatively, and no specific relationship was found in IL-6 and IL-10 concentrations between patients with normal and those with elevated IgE concentrations (data not shown). Recurrence did not induce any significant changes in IL-6 concentrations, as was the case with IL-10, except the highest IL-10 concentration was found at recurrence (data not shown).

The detection rate of IL-13 varied from 8.7–83.3%, and in all patients studied the detection rate of IL-13 was higher in those with elevated IgE than with normal IgE ($P < 0.0001$) (Fig. 1). The detection rate was higher in patients with elevated than normal IgE in each group, but statistical significance was found only for group III patients ($P = 0.025$). The detection rate of IL-13 in patients with remission (groups II and III) was higher in those with elevated than normal IgE ($P = 0.0048$, Fig. 1). Moreover, the detection rate was lower in patients with long-standing remission than in those without remission and with recurrence (13.3%, 38.5%, and 47.7%, respectively; $P = 0.0012$).

Presence of allergic diseases in patients with Graves' disease and allergic diseases and AITDs in their first-degree relatives

More patients with elevated IgE were positive for allergic diseases, and for family history of allergic diseases and AITDs in the first-degree relatives (Table 4). Compared with patients with normal IgE, those with elevated IgE had high frequency of allergic diseases ($P = 0.0017$) and family history of allergic diseases ($P < 0.0001$). Allergic rhinitis was the most frequent both in patients with elevated IgE (29.3%) and in the first-degree relatives of those with elevated IgE (41.5%). However, we could not find that attack of allergic rhinitis preceded the recurrence of Graves' disease.

Discussion

The study indicates that 38.3% of patients with Graves' disease have elevated serum IgE concentrations (≥ 170 IU/ml). If an IgE concentration of 100 IU/ml or greater was considered abnormal, then 50% of patients with untreated Graves' disease had abnormal concentrations of IgE. This high prevalence of elevated concentrations of IgE was comparable with that found in patients with bronchial asthma (70%) (13). Our previous study indicated that the decrease in TBII that occurred in response to antithyroid drug treatment was less pronounced in patients with elevated than normal IgE (1). In concordance with this, we found that normalization of TBII and/or TSAb during 18 months of treatment occurred less frequently in patients with elevated IgE than

TABLE 1. Remission and recurrence rates during and after MMI treatment in Graves' disease with or without IgE elevation

	Patients with elevated IgE	Patients with normal IgE	$P (\chi^2)^a$
Group I			
No. of patients	21	13	
Groups II and III			
No. of patients	20	53	
Remission rate	48.8% (20/41)	80.3% (53/66)	0.0014 (10.196)
Group II			
No. of patients	14	46	
Remission rate (long-standing)	34.1% (14/41)	69.7% (46/66)	0.0007 (11.573)
Group III			
No. of patients	6	7	
Recurrence rate	30.0% (6/20)	13.2% (7/53)	0.1721 (1.780)

Values are expressed as number or percentage.

^a χ^2 test between patients with and without elevated IgE. MMI was discontinued in 73 of 107 patients. They were then followed for more than 26 months. Recurrence was found in 13 of 73 patients (17.3%). Group I, Without remission during 18-month treatment; Group II, without recurrence during 26- to 48-month follow-up; Group III, with recurrence during 26- to 48-month follow-up.

TABLE 2. Clinical parameters during and after MMI treatment in patients with Graves' disease

	Group I		Group II		Group III	
	Elevated IgE	Normal IgE	Elevated IgE	Normal IgE	Elevated IgE	Normal IgE
Age (yr)	39 ± 15	42 ± 14	36 ± 14	47 ± 14	47 ± 19	39 ± 12
Gender (M/F)	4/17	2/11	2/12	4/42	2/4	2/5
T ₄ (nmol/L)						
Before MMI treatment	337 ± 75	346 ± 85	324 ± 86	282 ± 63	331 ± 64	227 ± 23
18 Months after MMI treatment	109 ± 26	111 ± 28	109 ± 22	106 ± 21	116 ± 19	121 ± 18
At latest point of follow-up or at the time of recurrence			106 ± 26	113 ± 19	227 ± 30	227 ± 48
TSH (mU/L)						
Before MMI treatment	0.02 ± 0 ^a	0.02 ± 0	0.02 ± 0	0.02 ± 0	0.02 ± 0	0.02 ± 0
18 Months after MMI treatment	2.14 ± 2.82	1.58 ± 2.24	2.18 ± 1.61	2.35 ± 2.33	2.95 ± 3.14	1.61 ± 1.44
At latest point of follow-up or at the time of recurrence			1.14 ± 1.01	1.52 ± 1.42	0.02 ± 0	0.02 ± 0
TBII (%)						
Before MMI treatment	59.4 ± 19.7	68.4 ± 16.9	32.3 ± 13.0	36.5 ± 16.4	39.6 ± 18.9	34.8 ± 18.2
18 Months after MMI treatment	34.1 ± 17.3	38.4 ± 19.8	6.9 ± 2.7	6.9 ± 3.2	8.0 ± 2.3	5.4 ± 2.6
At latest point of follow-up or at the time of recurrence			6.9 ± 4.0	6.0 ± 3.8	19.2 ± 7.2	20.7 ± 9.6
TSAb (%)						
Before MMI treatment	579 ± 438	856 ± 681	436 ± 418	370 ± 186	303 ± 75	354 ± 278
18 Months after MMI treatment	317 ± 287	437 ± 360	164 ± 30	157 ± 20	143 ± 20	143 ± 34
At latest point of follow-up or at the time of recurrence			156 ± 34	139 ± 32	199 ± 59	203 ± 58

Data are reported as the mean ± SD or number. Group I, Without remission during 18-month treatment; Group II, without recurrence during 26- to 48-month follow-up; Group III, with recurrence during 26- to 48-month follow-up.

^a The detection limit for TSH was 0.02 mU/L.

TABLE 3. Profile of serum IgE levels before, during, and after MMI treatment in patients with Graves' disease

	Group I		Group II		Group III	
	Elevated IgE	Normal IgE	Elevated IgE	Normal IgE	Elevated IgE	Normal IgE
IgE (IU/mL)						
Before MMI treatment	916 ± 970	48 ± 35	620 ± 936	55 ± 41	1780 ± 1975	76 ± 38
18 Months after MMI treatment	740 ± 938	31 ± 22	256 ± 156 ^a	43 ± 38	877 ± 1296	57 ± 32
<i>P</i> (paired <i>t</i> test) ^b	0.0176	0.0810	0.1794	0.6594	0.2429	0.0712
At latest point of follow-up or at the time of recurrence			260 ± 191 ^c	42 ± 41	797 ± 1087	67 ± 38

Data are reported as the mean ± SD. Group I, Without remission during 18-month treatment; Group II, without recurrence during 26- to 48-month follow-up; Group III, with recurrence during 26- to 48-month follow-up.

^a *P* = 0.0029 *vs.* Group I with elevated IgE.

^b *P* value is between before MMI and 18 months after MMI treatment in each group.

^c *P* = 0.2831 *vs.* Group III with elevated IgE (ANOVA).

with normal IgE. As a result, the rate of remission (normalization of T₄, TSH, Tg, TBII, and TSAb) was lower in the patients with elevated than normal IgE. Interestingly, it was reported that allergic rhinitis could be an aggravating factor of Graves' disease and increased eosinophils could be a predictive indicator of recurrence of Graves' disease (14). Allergic response should be considered as a cofactor to change the process of Graves' disease. Thus, in addition to IgG-TBII (TSAb), IgE-TBII (TSAb) should be included in the evaluation of Graves' disease.

The most likely hypothesis is that intrathyroidal lymphocytes affect the synthesis of TBII, TSAb, and IgE. We measured peripheral IFN-γ, a marker for Th-1 cells, after 18 months of treatment in patients with Graves' disease. Although three of four patients who had detected IFN-γ were without remission, no conclusion can be made. We also measured peripheral IL-4 concentrations at the time of remission and recurrence because it is a marker for Th-2 cells and stimulates IgE secretion (15, 16). Unfortunately, IL-4 was not detected at any time in any patients. Peripheral IL-6 and IL-10

concentrations were measured after 18 months of treatment, at remission, or at recurrence. These ILs were detected in the majority of patients, but no correlation was found among patients without remission, with remission, or with recurrence. Finally, we measured peripheral IL-13, which also is a marker for Th-2 cells and has modulating activities on many cell types, including stimulation of IgE secretion (2, 6). It is not possible to quantify the role of IL-13 in the autoimmune process of Graves' disease, because its measurement using patient's sera is impaired by poor sensitivity. It may be more important to measure intrathyroidal concentration of IL-13. However, the detection rate of IL-13 did provide qualitative information. For example, the rate of detectable IL-13 was higher 1) in patients who did not have than did have remission, 2) at the time of recurrence than at the time of remission, and 3) in patients with elevated than normal IgE concentration. Thus, the most plausible explanation is that IL-13 is secreted from Th-2 cells and has functions to stimulate B cells to secrete TBII, TSAb, and IgE. Additional studies are required to confirm this concept.

FIG. 1. The detection rate of serum IL-13 in patients with Graves' disease after MMI treatment (□, patients with elevated IgE; ■, patients with normal IgE). Statistical analysis was performed by χ^2 test with Yate's correction or Fisher's exact probability test. *, $P = 0.0012$, $\chi^2 = 9.261$ vs. groups I and III (2×3 contingency table).

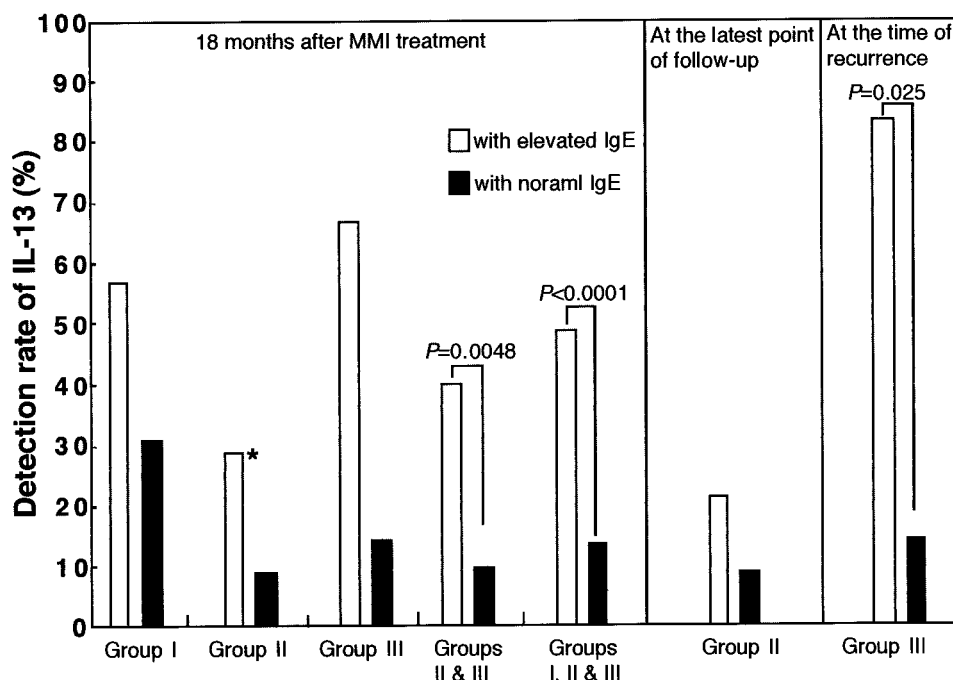


TABLE 4. Frequencies of allergic diseases in patients with Graves' disease and allergic diseases and AITD in their first-degree relatives

	Groups I, II, and III		Group I		Group II		Group III	
	Elevated IgE	Normal IgE	Elevated IgE	Normal IgE	Elevated IgE	Normal IgE	Elevated IgE	Normal IgE
Patients with Graves' disease								
Atopy	9.8% (4/41)	3.1% (2/65)	9.5% (2/21)	7.7% (1/13)	7.1% (1/14)	2.2% (1/45)	16.7% (1/6)	0% (0/7)
Allergic rhinitis	29.3% (12/41)	4.6% (3/65)	23.8% (5/21)	0% (0/13)	35.7% (5/14)	4.4% (2/45)	33.3% (2/6)	14.3% (1/7)
Asthma	9.8% (4/41)	0% (0/65)	9.5% (2/21)	7.7% (1/13)	7.1% (1/14)	0% (0/45)	16.7% (1/6)	0% (0/7)
Either of above	41.5% (17/41)	7.7% (5/65)	9.5% (7/21)	7.7% (1/13)	42.9% (6/14)	6.6% (3/45)	66.7% (4/6)	14.3% (1/7)
<i>P</i> ^a	0.0017		0.1164		0.0037		0.1026	
First-degree relatives								
Atopy	12.3% (5/41)	3.1% (2/65)	9.5% (2/21)	15.4% (2/13)	14.3% (2/14)	0% (0/45)	16.7% (1/6)	0% (0/7)
Allergic rhinitis	41.5% (17/41)	1.6% (1/65)	38.1% (8/21)	0% (0/13)	42.9% (6/14)	2.2% (1/45)	50.0% (3/6)	0% (0/7)
Asthma	29.3% (12/41)	0% (0/65)	33.3% (7/21)	0% (0/13)	7.1% (1/14)	0% (0/45)	66.7% (4/6)	0% (0/7)
Either of above	70.7% (29/41)	4.6% (3/65)	76.2% (16/21)	15.4% (2/13)	50% (7/14)	2.2% (1/45)	100% (6/6)	0% (0/7)
<i>P</i> ^a	<0.0001		0.0011		<0.0001		0.0436	
Graves'	4.9% (2/41)	1.6% (1/65)	4.8% (1/21)	0% (0/13)	0% (0/14)	2.2% (1/45)	16.7% (1/6)	0% (0/7)
Hashimoto	9.8% (4/41)	6.2% (4/65)	14.3% (3/21)	7.7% (1/13)	14.2% (2/14)	6.7% (3/45)	0% (0/6)	0% (0/7)
Either of above	14.6% (6/41)	6.2% (4/65)	14.3% (3/21)	7.7% (1/13)	14.2% (2/14)	6.7% (3/45)	16.7% (1/6)	0% (0/7)
<i>P</i> ^a	0.1802		>0.9999		0.5833		0.4615	

Data are reported as percentage (n). Group I, Without remission during 18-month treatment; Group II, without recurrence during 26- to 48-month follow-up; Group III, with recurrence during 26- to 48-month follow-up.

^a χ^2 test or Fisher's exact probability test between patients with and without elevated IgE in each group.

An elevation in IgE concentration is thought to be linked with hereditary abnormalities (17, 18). Human IL-4 operates through the IL-4 receptor (IL4R), thereby modulating IgE production and Th-2 inflammatory reaction (19). As is the case with IL-4, IL-13 operates through the IL-13R to stimulate IgE production and Th-2 inflammatory reactions. Moreover, IL-13R and IL4R share a common component in IL4R α (2, 6) that is crucial for IL-4 (or IL-13) binding and signal transduction. Gain-in-function mutations in IL4R α have been reported to be associated with atopy or asthma patients with elevated IgE concentrations (20, 21). These might be present in Graves' patients with elevated IgE, even if peripheral IL-13 or IL-4 were within normal range or not detected. Additional experiments are required to analyze gain-in-function mutations in IL4R α in the patients with Graves' disease.

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