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Thyrotoxic graves' disease with normal thyroidal technetium-99m pertechnetate uptake

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We saw 24 thyrotoxic Graves' patients with normal thyroidal uptake of technetium-99m pertechnetate (^{99m}Tc) out of 201 untreated thyrotoxic Graves' patients seen over 4 years. The clinical and laboratory findings for these patients were studied and analysed.

Thyroid uptake and scintigraphic examinations by means of ^{99m}Tc, TBII and TSab activity measurement clearly distinguished these patients from other thyrotoxic disorders (destruction-induced thyrotoxicosis and autonomously functioning thyroid lesions). Different from other disorders, these patients had not lower but normal thyroid uptake and also showed diffuse and discrete trapping into the enlarged glands.

These patients had significantly smaller goiters, a lower serum thyroid hormone level, and lower TBII and TSab activity, when compared with other high ^{99m}Tc uptake groups with Graves' disease, and their condition could be easily controlled with small amounts of antithyroid drugs.

Our study indicates that thyrotoxic Graves' disease with normal ^{99m}Tc uptake exists and ^{99m}Tc uptake study and TBII activity measurement is very useful for the diagnosis. The normal ^{99m}Tc uptake thyrotoxic Graves' patient might be early stage patients with general Graves' disease and their early discrimination from general Graves' patients is very advantageous for treatment and prognosis.

Key words: thyrotoxic graves' disease, normal thyroidal Technetium-99m pertechnetate uptake, TSab, TBII

INTRODUCTION

THYROTOXIC Graves' disease can be characterized as follows: 1) increased circulating thyroid hormone with suppressed TSH, 2) increased thyroid radioiodide (or radiopertechnetate) uptake which is non suppressible with T_3, and 3) detectable serum thyroid stimulating autoantibodies (TSab) and/or TSH-binding inhibitor immunoglobulins (TBII) in most of the cases but not necessarily in all. It is well known, however, that some patients with typical Graves' ophthalmopathy remain in a euthyroid or even hypothyroid state. The difference between these two conditions has not been well elucidated. Borderline cases between the above two conditions may exist, and indeed we are facing them daily with great varieties in clinical and laboratory findings in thyrotoxic Graves' patients.

Thyroid uptake and scintigrams are useful tools for evaluating thyroid states. We have been using technetium-99m pertechnetate (^{99m}Tc) uptake and scintigraphy routinely for studying our thyroid patients.

From 1984 to 1987 we performed 2,252 examinations, among them 246 untreated thyrotoxic patients were picked up through *in vitro* function test results,

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and 201 of them were diagnosed as having Graves' disease. Among them we observed 24 thyrotoxic Graves' patients with normal ^{99m}Tc uptake.

In order to determine the characteristic features of these 24 patients, their clinical and laboratory findings are retrospectively studied and analysed.

MATERIALS AND METHODS

Patients

The 246 untreated thyrotoxic patients who were studied by means of ^{99m}Tc uptake and scintigram included 201 patients with Graves' disease, 41 with destruction-induced thyrotoxicosis (DIT) and 4 with toxic autonomously functioning thyroid lesions (AFTL).[1] The 41 cases with DIT were further categorized as 25 with subacute thyroiditis and 16 with autoimmune thyroiditis (12 painless thyroiditis, 2 postpartum transient thyrotoxicosis and 2 acute exacerbation of Hashimoto's disease[2]).

None of the patients took medication, food or drink which interfered with ^{99m}Tc uptake at the time of their first visit.

Diagnosis of the diseases was made on the basis of clinical and laboratory findings. In 16 of the 24 Graves' patients with normal ^{99m}Tc uptake studied, non T_3 suppressibility of thyroid ^{99m}Tc uptake was confirmed. Nine of 16 patients had positive TBII and/or TSab activities. The remaining 8 patients who had not undertaken T_3 suppression test had positive TBII and/or TSab activities. Diagnosis of painless thyroiditis was confirmed by low ^{99m}Tc uptake and by the remission of thyrotoxicosis when no antithyroid drug treatment was given.

Histological diagnosis was also performed on 16 of the 25 subacute thyroiditis patients and on all 4 toxic AFTL patients. Of the 4 toxic AFTL, there were 2 cases with follicular adenoma and 2 with papillary adenocarcinoma.[3]

^{99m}Tc uptake and scintigram

Thyroid uptake and scintigram were studied 30 minutes after intravenous administration of 74 MBq (2 mCi) of ^{99m}Tc sodium pertechnetate with an Ohio Nuclear Sigma 410 gamma camera equipped with a converging collimator as previously reported.[4] The normal range of ^{99m}Tc uptake was from 0.4% to 2.5%.

For the T_3 suppression test, ^{99m}Tc uptake was assessed after the administration of L-T_3 (75 μg a day for 7 days). T_3 suppressibility was considered positive if the uptake after T_3 was less than 50% of the initial value and less than 1%.

Measurement of thyroid weight

Thyroid weight was calculated from a thyroid scintigram according to the method of Allen-Goodwin.[5]

Measurement of serum thyroid hormones and TSH

Serum thyroid hormones (T_3, T_4 and FT_4) were determined with commercially available kits. Serum TSH was measured with a highly sensitive TSH RIA[6] or RIA-gnost hTSH IRMA kit (Hoechist Co. Japan).

Measurement of antithyroid autoantibodies

1) TBII activity

Serum TBII activity was measured with a commercially available TRAb kit (R.S.R. Ltd. UK). The normal range was -10% to $+10\%$.

2) TSab activity

TSab activity in serum immunoglobulin preparation was assayed by measuring cAMP production of FRTL-5 thyroid cells as an index of the stimulator as previously reported.[7] The normal range was 55.0–145.0%.

3) Anti-Tg and anti-M

Antibodies to thyroglobulin (anti-Tg) and thyroid microsomes (anti-M) were assayed with commercially available kits (Fujizoki Inc, Tokyo). Antibody titer over 1 to 100 dilution was taken as positive.

All data were analysed for statistical significance by Student's t-test and χ^2 test.

RESULTS

Table 1 shows the sex and age distributions of patients in each untreated Graves' disease group classified according to the range of ^{99m}Tc uptake. Twenty-four patients (12%) had ^{99m}Tc uptake less than 2.5%. None of them had a previous history of any thyroid diseases.

The mean age of group A was 44 years, which was significantly higher than that of groups E and F, and the number of males in group A tended to be higher than in groups E and F. However, there was

Table 1 Data of groups of patients with Graves' disease classified according to ranges of ^{99m}Tc uptakes

Group	Ranges of ^{99m}Tc uptakes (%)	No. of patients	Sex (F/M)	Age Mean±SD (Year)
A	≦2.5	24	16/8	44±12*
B	2.6–5.0	27	15/12	48±12
C	5.1–10.0	64	48/16	41±15
D	10.1–15.0	33	23/10	38±17
E	15.1–20.0	24	20/4	32±14
F	20.1≦	29	24/5	33±16

*Significant difference ($p<0.01$) from group E and F

no significant difference between the mean age and sex ratio in group A and groups B-D.

Figure 1 shows the distribution of ^{99m}Tc uptake values in group A, DIT and toxic AFTL. All patients in group A had diffuse ^{99m}Tc trapping. None of them had uptake values less than 0.4%, and the average uptake was 1.8±0.5%, whereas all DIT patients but one with subacute thyroiditis had uptake values less than 0.4%. In the recovering phase a month after onset this patient was mildly thyrotoxic and had an uptake value of 0.5%, but histological examination showed typical subacute thyroiditis.

No thyroid image was obtained in 28 DIT patients, and there was only partial visualization of the thyroid in six others. Thyrotoxicosis spontaneously disappeared in several weeks (mean; 4 weeks) in all 12 patients with painless thyroiditis and four of these patients needed replacement therapy with thyroid hormones for hypothyroidism following thyrotoxicosis. All 4 toxic AFTL patients had a hot nodule, and 3 of them had normal uptake; one case had a value below 0.4%.

Mean serum T_3 and T_4 concentrations and T_3/T_4 ratios in group A were 2.52±0.49 ng/m*l*, 17.1±3.39 μg/d*l* and 15.1±2.57 ng/μg, respectively, and 2.68±1.11 ng/m*l*, 17.8±4.25 μg/d*l* and 14.3±3.47 ng/μg for DIT. There were no significant differences between the mean concentrations of serum T_3, T_4 and T_3/T_4 ratios in groups A and DIT. Serum TSH was undetectable in most patients in both these groups. Anti-Tg or/Anti-M was detected in 81% of group A, in 80% of all Graves' patients, in 50% of autoimmune thyroiditis, and in only 5% with subacute thyroiditis.

Table 2 shows the clinical data for patients in each group of Graves' disease. Exophthalmos was observed in 25% of group A patients, which was less than in the other groups except group C. The initial mean dose of Methimazole (MMI) administered to group A patients was 21±11 mg/day, which was significantly lower than that of the other groups.

Figure 2 shows the calculated thyroid weight of patients in each Graves' disease group. The mean weight of group A patients was 39.7±10.6 g, which was significantly lower than that of group C-F.

Table 3 shows thyroid functions of patients in each Graves' disease group. All mean thyroid hormone levels of group A patients were lower than those of the other groups. Particularly, T_3 values and the

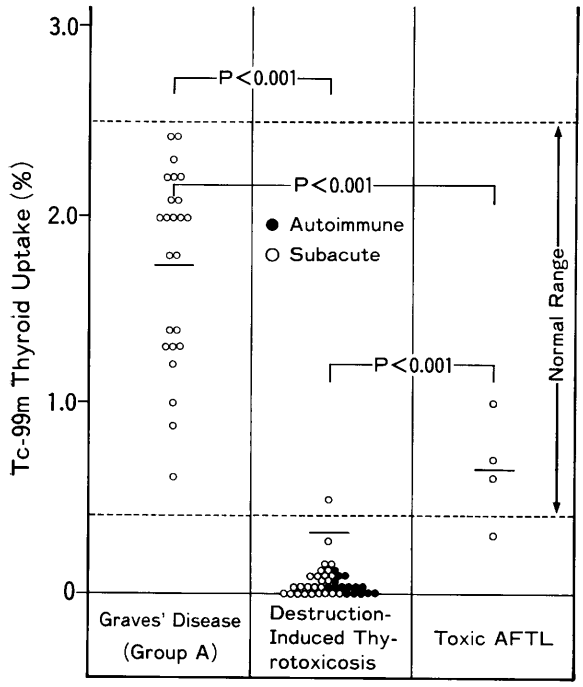

Fig. 1 Distribution of ^{99m}Tc uptake values in 24 patients in group A, 41 patients with destruction-induced thyrotoxicosis (DIT) and 4 patients with toxic AFTL.

Table 2 Clinical data of patients in each group of Graves' disease

Group	Goiter (soft/firm)	Exophthalmos (%)	Initial dose of MMI Mean±SD (mg/day)
A	19/5	6/24 (25%)	21±11*
B	19/8	9/27 (33%)	29±13
C	43/21	16/64 (25%)	31±12
D	19/14	12/33 (36%)	36±11
E	18/6	14/24 (58%)	37±7
F	26/3	13/29 (45%)	38±14

*Significant difference ($p<0.05$, $p<0.001$) from other group

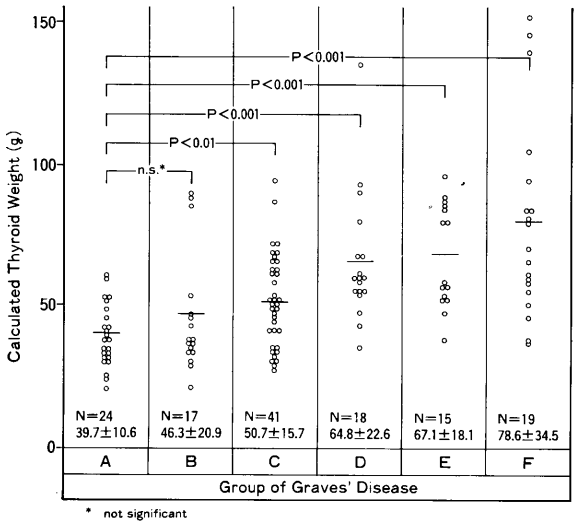

Fig. 2 Calculated thyroid weight of patients in each Graves' disease group.

Table 3 Thyroid functions of patients in each group of Graves' disease

Group	T_3 Mean±SD (ng/m*l*)	T_4 Mean±SD (μg/d*l*)	T_3/T_4 Mean±SD (ng/μg)	FT_4 Mean±SD (ng/d*l*)
A	2.52±0.49*	17.1±3.4	15.1±2.6**	3.96±1.19
B	3.20±0.89	18.5±3.5	17.7±3.8	4.75±1.97
C	3.61±1.34	19.1±4.0	18.3±4.8	5.36±1.81
D	4.31±1.43	20.6±3.4	19.3±4.2	6.79±2.77
E	5.53±1.94	22.5±2.6	18.1±6.3	7.40±2.00
F	5.12±1.96	21.3±4.0	19.6±4.2	6.90±6.90

* Significant difference ($p<0.01$) from other group
** Significant difference ($p<0.01$) from group B, C, D and F

Table 4 Comparison of percent positive of antithyroid antibodies in each group of Graves' disease

Group	Percent positive			
	Anti-Tg	Anti-M	TBII	TSab
A	29% (6/21)	81% (17/21)	52% (12/23)*	71% (10/14)
B	36% (8/22)	68% (15/22)	73% (11/15)	100% (11/11)
C	37% (21/57)	79% (45/57)	93% (41/44)	100% (11/11)
D	21% (6/29)	76% (22/29)	96% (27/28)	100% (14/14)
E	32% (6/19)	74% (14/19)	100% (19/19)	100% (10/10)
F	30% (6/20)	90% (18/20)	100% (23/23)	100% (13/13)

* Significant difference ($p<0.01$, $p<0.001$) from group C~F

Table 5 Comparison of mean TBII and TSab activities in each group of Graves' disease

Group	TBII		p*	TSab		p*
	N	Mean±SD (%)		N	Mean±SD (%)	
A	23	17±19		14	495±559	
B	15	34±25	0.05	11	1,054±800	0.05
C	44	38±21	0.001	11	1,841±2,296	0.05
D	28	47±25	0.001	14	2,869±3,028	0.01
E	19	50±24	0.001	10	2,746±2,820	0.01
F	23	62±21	0.001	13	2,029±1,636	0.01

p*: p value between group A and each other group

T_3/T_4 ratio in group A were significantly lower than those in the other groups. Serum TSH was undetectable in most of the patients and no difference among groups was observed.

Table 4 demonstrates the comparison of percent positive of various antithyroid autoantibodies in each Graves' disease group. There was no significant difference in the percent of anti-Tg, anti-M and TSab activity among the groups. However, the percent positive of TBII activity in group A patients was 52%, which was significantly lower than that in groups C-F.

There were no significant differences in mean antibody titers for anti-Tg and anti-M among the groups. Table 5 shows the comparison of mean activities of TBII and TSab in each Graves'disease group. Mean TBII and TSab activity in group A were significantly lower than those in the all high-uptake groups.

There were significant positive correlations ($n=73$, $r=0.44$, $p<0.001$) between TBII and TSab activity in all of the groups. Seventy-nine percent (11/14) of group A had positive TBII and/or TSab although neither TBII nor TSab activity was detected in 3 other patients. The correlation among ^{99m}Tc uptake, thyroid weight, TBII and TSab activity in all Graves' patients was statistically analysed. ^{99m}Tc uptake correlated with thyroid weight ($n=134$, $r=0.58$, $p<0.001$). There was a much higher correlation between TBII with ^{99m}Tc uptake ($n=152$, $r=0.47$, $p<0.001$) or/thyroid weight ($n=115$, $r=0.31$, $p<0.001$) than TSab with ^{99m}Tc uptake ($n=73$,

Table 6 Comparison between the period of treatment required for becoming euthyroid and the maintenance dose (5 mg/day) of MMI in each group of Graves' disease who are treated with MMI for more than one year

Group	N	Age Mean±SD (Year)	The period required for	
			Euthyroid Mean±SD (weeks)	Maintenance MMI Mean±SD (weeks)
A	16	44±14	7±5	18±16*
B	18	50±10	6±2	26±22
C	42	41±14	7±4	27±22
D	15	36±17	11±5	33±27
E	9	27±10	9±5	39±20
F	9	32±13	8±4	40±21

*Significant difference ($p<0.05$, $p<0.005$) from group D~F

$r=0.26$, $p<0.05$) or TSab with thyroid weight ($n=73$, $r=0.22$, n.s.).

A follow-up study was performed in all 201 patients with Graves' disease. All of them had been treated with MMI initially. MMI was switched to propylthiouracil (PTU) in 17 of them. Five patients had ^{131}I treatment and 12 patients had surgical treatment. One hundred and nine patients with Graves' disease followed up for more than a year could be controlled on a maintenance dose (5 mg/day) of MMI.

Table 6 shows a comparison between the period of treatment required to become euthyroid and the maintenance dose of MMI therapy in each group of these 109 Graves' patients. The former mean period for group A was 7 weeks and shorter than groups D and E, but was not different from groups B, C, and F. However, the latter mean period was 18 weeks and significantly shorter than the other high ^{99m}Tc uptake groups. Remission was observed in 4/16 (25%) of group A, 2/18 (11%), 5/42 (12%), 2/15 (13%), 0% and 2/9 (22%), for each group, respectively.

DISCUSSION

The present paper demonstrated that there is a group of thyrotoxic Graves' patients with normal thyroid ^{99m}Tc uptake. These patients were clearly differentiated from other thyrotoxic disorders by thyroid uptake and scintigraphic studies with ^{99m}Tc pertechnetate. Furthermore, these patients had significantly less prominent clinical and laboratory findings than other thyrotoxic Graves' patients with increased ^{99m}Tc uptake. They had a smaller goiter, lower serum T_3/T_4 ratio, infrequent association of exophthalmos, and lower TBII detectability.

To our knowledge, no such group of thyrotoxic Graves' patients had ever been well documented. One of the reasons may be that radioiodine (^{123}I or ^{131}I) has been used widely in thyroid uptake studies and this can be easily affected by dietary iodide intake and various iodide-containing medications. Further, 24 hour uptake of radioiodide not only indicates thyroidal uptake but also reflects the thyroidal iodine organification rate.[8] The latter may vary greatly among thyrotoxic Graves' patients. On the other hand, ^{99m}Tc uptake simply indicates the absolute thyroidal trapping with much less influence from body iodide content.

It is known that there are Graves' patients with typical ophthalmopathy but lacking thyrotoxicosis.[9-12] In some of these patients, however, abnormal thyroid states which are nonsuppressible by the T_3 in thyroidal uptake, blunted TRH response, suppressed serum TSH and detectable TSab or TBII[13-16] is not seen so frequently. The goiter is much smaller and thyroidal ^{99m}Tc uptake remains within the normal range.[17]

The present group of A patients appear to be located between euthyroid Graves' and thyrotoxic Graves' patients with increased thyroid uptake. The thyroid uptake shows the glandular ability to accumulate iodide, an essential material in producing thyroid hormone. The normal uptake value in group A patients may be closely related with their lower serum thyroid hormone concentration.

Their thyroid uptake, however, was not suppressed by T_3 administration, indicating that their thyroid functions are not regulated by TSH but by other factors such as TBII and/or TSab. Indeed, not all but most of the patients had positive TBII or TSab, even though detectability and titers were significantly lower than those with increased uptake.

In this regard, we observed a significant correlation among thyroid ^{99m}Tc pertechnetate uptake, thyroid weight and TBII. TSab, however, did not correlate so closely with these thyroid states. Kasagi et al reported a rather high incidence of detectable TSab in patients with euthyroid Graves' disease.[14,16] The clinical significance of TSab, which is measured with cultured thyroid cells under non-physiological, low salt conditions,[18] remains undetermined.

The group A patients had a lower T_3/T_4 ratio than other patients with increased uptake. Amino et al[19] reported that the serum T_3/T_4 ratio is a simple and helpful index for the differentiation of DIT from Graves' thyrotoxicosis. However, the serum T_3/T_4 ratio was not helpful in differentiating DIT from Graves' disease with normal ^{99m}Tc uptake in the present study.

Less severe clinical manifestations as well as a lower serum thyroid hormone concentration led us to prescribe smaller amounts of MMI initially. The follow-up study of the patients revealed a much more favorable clinical course and remission compared with other Graves' patients.

From these observations we conclude that a ^{99m}Tc pertechnetate uptake study and TBII measurement are very useful tests to subclassify thyrotoxic Graves' patients, and those showing normal uptake might be in the initial stage of the disease.

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