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Treatment for Childhood-Onset Graves' Disease in Japan: Results of a Nationwide Questionnaire Survey of Pediatric Endocrinologists and Thyroidologists

Hirokazu Sato,[1,2] Shohei Harada,[3] Susumu Yokoya,[4,8] Toshiaki Tanaka,[5,8] Kohtaro Asayama,[6,8] Masatomo Mori,[7] and Nozomu Sasaki[2,8]

Objective and design: To determine the present condition of treatment of childhood-onset Graves' disease in Japan, a nationwide questionnaire survey was conducted among councilors of the Japanese Society for Pediatric Endocrinology and the Japan Thyroid Association. *Main outcome:* Responses were received from 125 individuals, and the rate of collection of questionnaires was 47%. Methimazole was selected for first-line initial antithyroid drug therapy by 92% of respondents. Antithyroid drugs tended to be given at larger initial doses and over longer periods of time to childhood-onset patients than to adult patients, and these tendencies were more pronounced for pediatric endocrinologists. Combination therapy with an antithyroid drug and thyroxine was used more frequently by pediatric endocrinologists. Thyroidologists had more experience with radioiodine therapy than pediatric endocrinologists. Opinions regarding preparation of guidelines for the initial dose of methimazole in childhood-onset Graves' disease were almost equally divided among the following: the dose of methimazole should be adjusted according to the severity of disease as in adult cases, methimazole should be started at a dose of 1 mg/kg per day in all patients, and the dose should be determined based on results of a randomized study. *Conclusions:* The present condition of treatment of childhood-onset Graves' disease in Japan was clarified.

Introduction

GRAVES' DISEASE is the most common cause of thyrotoxicosis in children and adolescents. There are three different methods currently available for the treatment of Graves' disease: use of antithyroid drugs, thyroidectomy, and radioiodine administration. Most practitioners consider antithyroid drugs first-line therapy for most young people with Graves' disease, as recommended in most medical textbooks (1). Methimazole (MMI) and propylthiouracil (PTU) are the antithyroid drugs used in the United States and Japan. MMI is used in most of Europe and Asia and carbimazole, a MMI analogue, is used in the United Kingdom and parts of the former British Commonwealth (2). Since most children with Graves' disease require relatively longer periods of antithyroid drug treatment than adult patients (1–3), choice of antithyroid drugs, initial dose and duration of treatment, and criteria for discontinuation of treatment are still controversial. The choice between drugs is presently a matter of personal preference.

To determine the present condition of treatment of Graves' disease in children and adolescents in Japan, a nationwide questionnaire survey was conducted among councilors of the Japanese Society for Pediatric Endocrinology and the Japan Thyroid Association under the leadership of the Committee on Pharmaceutical Affairs of the Japanese Society for Pediatric Endocrinology.

Materials and Methods

A questionnaire on treatment of Graves' disease in patients aged 15 years or younger was sent to 80 councilors of the

[1]Sunrise Children's Clinic, Funabashi, Japan.
[2]Department of Pediatrics, Saitama Medical University, Moroyama, Japan.
[3]Department of Health Policy, National Research Institute for Child Health and Development, Tokyo, Japan.
[4]Department of Pediatrics, Toranomon Hospital, Tokyo, Japan.
[5]Department of Laboratory Medicine, National Center for Child Health and Development, Tokyo, Japan.
[6]Kanagawa Health Service Association, Yokohama, Japan.
[7]Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Japan.
[8]Committee on Pharmaceutical Affairs, the Japanese Society for Pediatric Endocrinology.

Japanese Society for Pediatric Endocrinology, who were endocrinologists treating children and adolescents (group of pediatric endocrinologists: PE group) and 185 councilors of the Japan Thyroid Association who were thyroidologists primarily treating adults (group of thyroidologists: TH group). All councilors were physicians belonging to the Japan Endocrine Society, and a few were serving concurrently as councilors of both societies. The completed questionnaire was returned by mail.

The questionnaire concerned the following: (i) laboratory examinations usually used at initial diagnosis; (ii) first-line medications and the dose of initial treatment, treatment for adverse drug reactions, and concomitant use of other drugs for severe symptoms; (iii) treatment for increased serum triiodothyronine (T3) concentration during maintenance antithyroid drug therapy, combination therapy with antithyroid drug and thyroxine (T4), frequency of hematological examinations, and situations in which physicians consider surgical treatment; (iv) criteria for and timing of discontinuation of treatment, (v) management at relapse and after discontinuation of treatment; (vi) experience with radioiodine therapy; and (vii) if doses of MMI should be determined for preparation of guidelines, and whether the initial dose should be changed depending on the severity of disease.

Data were evaluated primarily based on overall response rates. Differences between the PE group and TH group were determined by chi-square test for questions requiring a single answer. These data are shown in the tables, while the results for questions permitting multiple answers are shown in the text. Differences were considered significant at $p < 0.05$.

Results

The questionnaires were returned by 56 in the PE group and 71 in the TH group. The rate of collection of questionnaires was 47% overall. Two pediatricians in the TH group were excluded to avoid overlap. In total, results for 125 respondents were analyzed, including those for 56 pediatricians, 59 physicians, 6 surgeons, and 4 physicians in other departments. The mean duration of experience in treating patients with Graves' disease was 21.8 ± 6.9 years ($\pm$ standard deviation). The mean total number of patients treated previously was 32.8 ± 36.2, and the number of patients being treated at present was 10.0 ± 8.2.

Laboratory examinations usually used at diagnosis (Table 1)

Serum thyroid-stimulating hormone (TSH) levels were examined in almost all patients, and free thyroid hormones were usually tested. TSH binding inhibitory immunoglobulin (TBII) was measured in almost all patients as a test for thyroid antibodies. However, passive agglutination tests (anti-microsomal test and anti-thyroglobulin test) were still performed by approximately 30% of respondents. Laboratory examinations were more frequently performed by those in the PE group.

Initial treatment (Table 2)

All respondents selected use of antithyroid drugs as primary treatment for childhood-onset Graves' disease. As first-line antithyroid drugs, 92.0% of respondents used MMI and 8.0% PTU. MMI was selected by the entire TH group ($p < 0.001$). The reasons for and numbers of physicians selecting MMI were as follows: greater efficacy, 67 respondents; fewer adverse drug reactions, 25; less frequent administration, 23; lower prevalence of anti-neutrophil cytoplasmic antibodies (ANCA), 21; less bitter taste, 6; and familiarity with use, 2. The reasons for selection of PTU were suppression of peripheral conversion from T4 to T3: 4 respondents; fewer adverse drug reactions, 3; familiarity with use, 2; shorter half-life, 1; and possibility of use during pregnancy, 1.

Treatment with MMI was begun at 1 mg/kg or with PTU at 10 mg/kg by more than half of respondents. If the dose based on body weight exceeded the dose for adults (6 tablets per day, 30 mg of MMI, and 300 mg of PTU; 5 mg tablets of MMI and 50 mg tablets of PTU are now available in Japan), then 36.0% of respondents started treatment at doses exceeding the dose for adults. Antithyroid drugs were started at larger doses in the PE group ($p < 0.05$). Cardiovascular drugs were more frequently used in the TH group ($p < 0.01$).

Maintenance treatment (Table 3)

For patients who had serum TSH below the lower limit of detection, serum T4 within the normal range, increased serum T3, and positive results for TBII or thyroid-stimulating antibody (TSAb) during maintenance treatment, larger doses of antithyroid drugs were used in the TH group ($p < 0.05$).

TABLE 1. RESPONSES PROVIDED BY PEDIATRIC ENDOCRINOLOGISTS AND THYROIDOLOGISTS REGARDING LABORATORY EXAMINATIONS USUALLY USED AT INITIAL DIAGNOSIS OF CHILDHOOD-ONSET GRAVES' DISEASE[a]

TSH	100	TSH-releasing hormone test	14.3
Free T4	94.6	Free T3	87.5
Total T4	23.2	Total T3	19.6
TBII	94.6	TSAb	67.9
TPOAb	57.1	TGAb	55.4
Anti-microsomal test	32.1	Anti-thyroglobulin test	32.1
Gray-scale ultrasonography	64.3	Color Doppler ultrasonography	30.4
Scintigraphy	32.1	Radioiodine uptake	30.1

[a]Values are percentages. TSH = thyroid stimulating hormone; TBII = TSH binding inhibitory immunoglobulin; TSAb = thyroid stimulating antibody; TPOAb = anti-thyroid peroxidase antibody; TGAb = anti-thyrogloblin antibody.

TABLE 2. RESPONSES PROVIDED BY PEDIATRIC ENDOCRINOLOGISTS AND THYROIDOLOGISTS REGARDING INITIAL TREATMENT OF CHILDHOOD-ONSET GRAVES' DISEASE

	Pediatric endocrinologists	*Thyroidologists*	*Total*[a]
First-line antithyroid drugs			
MMI***	46	69	115 (92.0)
PTU***	10	0	10 (8.0)
Initial doses of antithyroid drugs			
MMI at 1 mg/kg or PTU at 10 mg/kg*	38	28	66 (52.8)
MMI at 0.5 mg/kg or PTU at 5 mg/kg*	4	16	20 (16.0)
At intermediate doses based on the case*	9	11	20 (16.0)
Initial doses, if the dose based on body weight exceeded the dose for adults (6 tablets/day)[b]			
6 tablets/day*	22	38	60 (48.0)
9 tablets/day*	13	13	26 (20.8)
12 tablets/day*	13	3	16 (12.8)
Adhered to doses obtained from conversion based on body weight*	1	2	3 (2.4)
Cardiovascular drugs			
Rarely use**	27	15	42 (33.6)
Use as needed**	19	29	48 (38.4)
Often concomitantly use**	10	24	34 (27.2)
If minor adverse reactions occurred			
Observation for period of time[c]	34	33	67 (53.6)
Immediate change of the antithyroid drug[c]	18	21	39 (31.2)
Selection of surgical treatment as first-line treatment[c]	2	4	6 (4.8)
Use of iodide			
Experience[c]	23	20	43 (34.4)
No experience[c]	33	38	71 (56.8)

*$p < 0.05$ (chi-square test).
**$p < 0.01$ (chi-square test).
***$p < 0.001$ (chi-square test).
[a]Percentages of all respondents in parentheses.
[b]30 mg of MMI and 300 mg of PTU; 5 mg tablet of MMI and 50 mg tablet of PTU are available in Japan.
[c]Not significant.

Combined treatment with an antithyroid drug and T4 was more frequently used in the PE group ($p < 0.05$). Concomitant use of T4 was considered for persistent elevation of TBII or TSAb by 27.2% of respondents, for large goiter by 24.8%, high T3 to T4 ratio by 12.9%, TSH remaining below the lower limit of detection by 9.6%, and dose of antithyroid drug decreased to a certain number of tablets (1–4 tablets) by 8.0%. Other reasons included large fluctuation in serum T4 or T3 levels, increased TSH with normal T4 and T3 levels, and appearance of symptoms of hypothyroidism.

After patients had achieved normal thyroid function, hematological examination was performed 3 or 4 times a year by 80.0% of respondents.

Thyroidectomy was considered at the occurrence of adverse drug reactions by 75.2% of respondents, large goiter by 62.4%, frequent relapse by 44.0%, persistent increase in TRAb or TSAb by 16.8%, severe proptosis by 13.6%, persistent increase in T3 by 12.0%, completion of puberty by 10.4%, and TSH remaining below the lower limit of detection by 4.8%.

Criteria for and timing of discontinuation of treatment (Table 4)

Antithyroid drugs tended to be given over longer periods of time to patients with positive TBII in the PE group ($p < 0.005$). For patients with persistently positive, though not high TBII, 6.4% of respondents discontinued antithyroid drugs after 2 years, and 3.2% after 3 years. The T3 suppression test was performed at discontinuation of antithyroid drugs by 11.2% of respondents, and 19.2% used TSAb as a marker for discontinuation of drug treatment.

Management at relapse and after discontinuation of treatment (Table 4)

At relapse, 97.6% of respondents restarted antithyroid drugs, 5 (0.4%) considered thyroidectomy, and 3 in the TH group (0.1%) considered radioiodine. As maintenance doses after restart of antithyroid drugs, larger doses of antithyroid drugs were used in the PE group ($p < 0.05$).

TABLE 3. RESPONSES PROVIDED BY PEDIATRIC ENDOCRINOLOGISTS AND THYROIDOLOGISTS REGARDING MAINTENANCE TREATMENT OF CHILDHOOD-ONSET GRAVES' DISEASE

	Pediatric endocrinologists	*Thyroidologists*	*Total*[a]
For patients with serum TSH below the lower limit of detection, normal serum T4, increased serum T3, and positive results for TBII or TSAb[b]			
Observation with the same dose of antithyroid drug*	24	17	41 (32.8)
Increase the dose of antithyroid drug*	13	29	42 (33.6)
Increase the dose with antithyroid drug with addition of T4*	10	15	25 (20.0)
Combined treatment with an antithyroid drug and T4			
Rarely use*	8	15	23 (18.4)
Use based on the individual case*	33	48	81 (64.8)
Use in almost all cases*	14	4	18 (14.4)
Hematological examination after patients had achieved normal thyroid function			
Every month[c]	2	1	3 (2.4)
Every 2 months[c]	0	2	2 (1.6)
4 times/year[c]	31	24	55 (44.0)
3 times/year[c]	23	22	45 (36.0)
2 times/year[c]	3	9	12 (9.6)

*$p < 0.05$ (chi-square test).
[a]Percentages of all respondents in parentheses.
[b]TSH = thyroid-stimulating hormone; T4 = thyroxine; T3 = triiodothyronine; TBII = TSH binding inhibitory immunoglobulin; TSAb = thyroid-stimulating antibody.
[c]Not significant.

TABLE 4. RESPONSES PROVIDED BY PEDIATRIC ENDOCRINOLOGISTS AND THYROIDOLOGISTS REGARDING TIMING OF DISCONTINUATION OF TREATMENT, MANAGEMENT AT RELAPSE, AND EXPERIENCE WITH RADIOIODINE THERAPY OF CHILDHOOD-ONSET GRAVES' DISEASE

	Pediatric endocrinologists	*Thyroidologists*	*Total*[a]
Discontinuation of antithyroid drugs in patients with initial negative TBII[b]			
After 1 year[c]	7	13	20 (16.0%)
After 2 years[c]	26	27	53 (42.4%)
Discontinuation of antithyroid drugs in patients with positive TBII			
6 months after patients are found to be negative for TBII**	4	18	22 (17.6%)
1 year after patients are found to be negative for TBII**	22	22	44 (35.2%)
2 years after patients are found to be negative for TBII**	18	8	26 (20.8%)
Initial dose of antithyroid drugs at recurrence			
Initial dose at onset[c]	32	39	71 (56.8%)
Previous maintenance dose[c]	7	2	9 (7.2%)
Intermediate dose[c]	16	18	34 (27.2%)
Maintenance dose after restart of antithyroid drugs			
Previous maintenance dose*	36	50	86 (68.8%)
Larger dose than previous maintenance dose*	10	3	13 (10.4%)
Larger dose with T4*	5	3	8 (6.4%)
Radioiodine therapy			
Experience***	5	27	32 (25.6%)
No experience***	51	41	92 (73.6%)

*$p < 0.05$ (chi-square test).
**$p < 0.005$ (chi-square test).
***$p < 0.001$ (chi-square test).
[a]Percentages of all respondents in parentheses.
[b]TBII = TSH binding inhibitory immunoglobulin.
[c]Not significant.

Including pediatricians who requested that other physicians follow patients, 64.8% of respondents followed patients until they were adults. On the other hand, 5.6% stopped following patients 1 year after discontinuation of treatment, 12.8% after 2 years, 11.2% after 3 years, and 5.6% after 5 years.

Experience with radioiodine therapy (Table 4)

Respondents in the TH group had more frequent experience with radioiodine therapy than those in the PE group ($p < 0.001$).

Opinions regarding preparation of guidelines for initial treatment with MMI

Opinions from 69 respondents were classified as follows. MMI should be started at 1 mg/kg per day in all patients (21; 30.4%). MMI should be started at 0.5 mg/kg per day in patients with pretreatment serum free T4 of less than 6 ng/dL (mild disease) and at 1 mg/kg per day in patients with that of 6 ng/dL or higher (severe disease) (20; 29.0%). Initial dose of MMI should be changed by the severity of disease, although pretreatment serum free T4 level distinguished the severity of disease should be decreased less than 6 ng/dL (5; 7.2%). In these respondents, four replied 4 ng/dL as adequate pretreatment serum free T4 level distinguished the severity of disease, and one replied 2.5 ng/dL. The dose should be determined based on results of a randomized study (23; 33.3%).

Discussion

Graves' disease is rare in children and adolescents, with these age groups comprising 5% or less of all patients (4), and is often treated for many years. In Japan, most pediatric and adolescent patients are treated by specialists such as pediatric endocrinologists and thyroidologists. As this survey was conducted among councilors in the two academic societies specializing in this field and the rate of collection of questionnaires was nearly 50%, the results of this study appear to reflect the present condition of treatment of childhood-onset Graves' disease in Japan.

Over 90% of the respondents selected MMI as a first-line antithyroid drug. Clinical research on children with this disease has been extremely rare compared with that on adults, and in fact results of studies in adult patients have been used as references for the treatment of children (5,6). MMI has advantages over PTU in requiring only once- or twice-daily administration (7) and exhibiting more rapid improvement of serum concentrations of T4 and T3 (7–10). The side effects of MMI are dose related, whereas those of PTU are less clearly related to dose (2). This may favor the use of low-dose MMI rather than PTU. The reasons for selection of MMI, rather than PTU, in this survey were similar to these. ANCA-positive nephritis and vasculitis has been reported, especially in Asian patients treated with PTU (11), and a high prevalence of ANCA positivity in childhood-onset Graves' disease treated with PTU has also been reported (12). It is thus considered safer to avoid using PTU in Japan. PTU remains the treatment of choice during pregnancy, because congenital anomalies, particularly aplasia cutis, have been reported with MMI (6,13).

A wide range of initial doses of MMI (0.5–1.0 mg/kg per day) to treat childhood-onset Graves' disease has been described in many references and textbooks (1). No randomized studies in children have compared period to normalization of thyroid function or incidence of adverse drug reactions with differences in initial doses. In one randomized trial in adults, 85% of patients had normal levels of T4 and T3 after 6 weeks of treatment with 10 mg of MMI, compared with 92% of patients who received 40 mg daily (14). However, many respondents used MMI at somewhat larger doses in this survey. Some of the respondents indicated that all pediatric patients should start treatment at 1 mg/kg per day, since Graves' disease is often resistant to treatment. Others commented that MMI should be started at smaller doses in patients with mild Graves' disease, since adverse drug reactions are dose dependent. The decision regarding the initial dose of MMI is a matter of personal preference. Indeed, opinions regarding preparation of guidelines for initial treatment with MMI in this survey were nearly equally divided.

Combined treatment with an antithyroid drug and T4 was more often used by pediatric endocrinologists than by thyroidologists. The frequent use by pediatric endocrinologists is probably due to their treatment of younger patients. Combined treatment does not decrease the relapse rate (15), but avoids the development of hypothyroidism in a growing child and enables less frequent monitoring (4,16).

Many retrospective studies in adults have found that patients with more severe hyperthyroidism, large goiter, a high T3 to T4 ratio in serum, and higher baseline levels of TBII or TSAb are less likely to enter remission after treatment (17–19). However, a prospective study of more than 300 adults patients with Graves' disease was unable to identify any clinical or biochemical marker that predicted remission or relapse after 12 months of antithyroid drug therapy (18). The criteria for and timing of discontinuation of antithyroid drugs varied in this survey.

There is now an increasing tendency to advocate radioiodine as a choice of treatment in children who achieve a high rate of remission. Long-term follow-up data that have been published suggest that radioiodine treatment in older children and adolescents is safe and effective (3,16,20). Some respondents in this survey had experience with treatment with radioiodine. Thyroidologists had more frequent experience with it than pediatric endocrinologists. The differences in frequency between the two groups were probably due to experience with radioiodine therapy in adult patients by thyroidologists and treatment of younger patients by pediatric endocrinologists. A long-term study of larger populations is needed to determine the true incidence of thyroid neoplasia and other side effects in children treated with radioiodine.

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Address reprint requests to:
Hirokazu Sato
Sunrise Children's Clinic
Nakayama Medical Square 1F
4-22-10 Motonakayama
Funabashi
Chiba 273-0035
Japan

E-mail: hschiba@aol.com