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Early Recurrence of Hyperthyroidism in Patients with Graves' Disease Treated by Subtotal Thyroidectomy

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Abstract. Prerequistes for surgical treatment of Graves' disease are that it can be done safely and that it is associated with a low incidence of recurrent hyperthyroidism. Early recurrence is especially undesirable. We studied 728 patients with Graves' disease treated by subtotal thyroidectomy using multivariate analysis in order to determine the factors related to early recurrence. The following factors were analyzed: age, sex, duration of medical treatment, weight of resected thyroid tissue, thyroid remnant size, preoperative level of thyroid-stimulating hormone (TSH) binding inhibitory immunoglobulin (TBII), and antimicrosomal hemagglutination antibody (MCHA). "Early recurrence" was defined as TSH suppression observed within the first year after surgery and continuing for at least 6 months. A total of 106 patients (14.6%) had early recurrence. Statistical analyses were performed by the chi-square test for univariate analysis and a logistic model for multivariate analysis. Significant factors were thyroid remnant size, MCHA, and TBII. These results indicated that TBII and MCHA are related to early recurrence of hyperthyroidism, and smaller remnant size is recommended for patients with a high MCHA titer or a high TBII level (or both) in order to avoid early recurrence.

Although surgical treatment for Graves' disease can induce rapid remission of hyperthyroidism compared with other therapies, the widespread use of radioiodine and antithyroid drug has resulted in a remarkable decrease in the number of surgical cases. However, as the incidence of delayed hypothyroidism after radioiodine therapy is unacceptably high, and the improvement of surgical technique has brought a low incidence of surgical complications, surgery can still be considered the treatment of choice in many patients with Graves' disease [1, 2]. Although many studies on the outcome of surgical treatment for Graves' disease have been published, and some factors have been reported to be related to postoperative thyroid function, definite factors (except thyroid remnant size) remain unknown [3–11]. If surgery can be justified as the treatment for Graves' disease, it is important not only that it can be done with a low incidence of surgical complications but also that the recurrence rate of hyperthyroidism is low. Especially, early recurrence is undesirable. We evaluated postoperative thyroid function in a large number of patients with Graves' disease treated by subtotal thyroidectomy and analyzed the risk factors related to early recurrence of hyperthyroidism.

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Patients and Methods

Patients

Between January 1988 and August 1990 a total of 819 patients underwent subtotal thyroidectomy for Graves' disease at Ito Hospital. Among them, 728 patients could be followed up regularly for at least 2 years after surgery, and they constituted the subjects of this study (follow-up rate 88.9%; range of follow-up 24–58 months; median follow-up 42.5 months). There were 147 males and 581 females, with mean age of 25.9 years (range 11–68). Elderly patients are generally treated with radioiodine in our hospital; therefore only 27 patients over age 40 were included as subjects. Bilateral subtotal thyroidectomy was employed for all patients. The mean weights of the thyroid remnant and resected thyroid tissue were 5.0 g and 65.4 g, respectively. Thyroid remnant on both sides were estimated by modeling the remnants to the resected segment. The segment was then weighed.

The reasons for surgery were (1) relapse of hyperthyroidism after several courses of medical treatment (34.9%); (2) large goiter size (31.1%); (3) patient's choice (22.4%); (4) adverse effects of antithyroid drug (6.0%); and (5) coexistence with tumor (5.6%). Preoperative medical treatments were as follows: (1) antithyroid drug (ATD) only, 66.2%; (2) ATD with β-blocker, 20.3%; (3) ATD with β-blocker and iodine, 7.4%; (4) β-blocker with iodine, 1.9%; (5) β-blocker with iodine and steroids, 2.5%; (6) iodine with steroids, 1.6%.

Evaluation of Thyroid Function

Postoperative examination of thyroid function was performed 1, 3, 6, 12, 18, and 24 months after surgery. Thyroid function tests used for the evaluation of preoperative and postoperative thyroid status were free triiodothyronine (FT_3), free thyroxine (FT_4), TSH, TSH inhibitory immunoglobulin (TBII), and antimicrosomal antibody. FT_3 and FT_4 were measured by the Amerlex-M FT3 and Amerlex-M FT4 kit (Amersham International, Buckinghamshire, U.K.), respectively. TSH was measured by the DELFIA TSH kit (Pharmacia Diagnostic AB, Sweden) and TBII by Smith's kit (Cosmic Co., UK). Antimicrosomal antibody was measured by

Table 1. Univariate analysis of recurrent hyperthyroidism.

		Thyroid function					
		Hyperthyroidism		Euthyroidism		Hypothyroidism	
	No.	No.	%	No.	%	No.	%
Age (years)							
−19	144	20	13.9	54	37.5	70	48.6
20–29	388	49	12.6	154	39.7	185	47.7
30–39	169	28	16.6	70	46.4	71	42.9
40+	27	8	29.6	8	29.6	11	40.7
Sex							
Male	147	26	17.7	34	23.1	87	59.2
Female	581	80	13.8	250	43.0	251	43.2
Duration of medical treatment (years)							
≤ 1	305	43	14.1	114	37.4	148	48.5
> 1, ≤ 3	193	19	9.9	86	44.8	30	36.6
> 3	230	44	19.1	84	36.5	102	44.3
Resected thyroid tissue (g)							
< 50	330	36	10.9*	142	43.0	152	46.1
≥ 50, < 100	287	45	15.7	112	39.0	130	45.3
≥ 100	111	25	22.5*	30	27.0	56	50.5
Thyroid remnant size (g)							
≤ 4	139	13	9.3*	46	33.1	30	57.6
> 4, ≤ 5	254	29	11.4	106	41.7	119	46.9
> 5, ≤ 6	231	38	16.5	94	40.7	98	42.4
> 6	104	26	25.0*	38	36.5	40	38.5
Antimicrosomal antibody (×)							
−100	137	6	4.4**	66	48.2	65	47.4
400–1640	212	51	14.3**	135	37.9	170	47.8
6,560–26,240	248	23	22.2**	43	41.3	38	36.5
104,960+	131	26	19.9**	40	41.3	65	49.6
TSH receptor antibody (%)							
≤ 20	217	19	8.8***	97	44.7	101	46.5
> 20, ≤ 40	211	26	12.3***	90	42.7	95	45.0
> 40, ≤ 60	171	30	17.5***	59	34.5	82	48.0
> 60	129	31	24.0**, ****	38	29.5	60	46.5

*$p < 0.005$; **$p < 0.0001$; ***$p < 0.01$; ****$p < 0.001$.

a hemagglutination assay (MCHA). The normal ranges are as follows: FT_3 3.8 to 8.4 pmol/L; FT_4 10.3 to 24.5 pmol/L; TSH 0.3 to 3.5 mU/L; TBII −10% to 10%.

Patients were divided into three groups according to their TSH level after surgery: (1) the patients with a suppressed TSH level observed within the first year and continuing for at least 6 months were the hyperthyroid group; (2) the patients with a normal TSH level at the first year examination were the euthyroid group; and (3) the patients with a elevated TSH level at the first year examination were the hypothyroid group. We used a sensitive TSH assay kit, so thyroid function could be evaluated by the serum TSH level alone. However, FT_3 and FT_4 were examined simultaneously to exclude any errors that arose in the measurement and any patients complicated by TSH-producing pituitary tumor, although there was none.

Statistical Analysis

The risk factors analyzed were as follows: age, sex, duration of medical treatment, weight of the resected thyroid tissue, weight of the thyroid remnant, preoperative titer of MCHA, and preoperative level of TBII. Statistical significance was analyzed by the chi-square test for univariate analysis and the logistic model with stepwise regression method for multivariate analysis (PHREG procedure, SAS).

Results

Surgical Outcome

According to the above-mentioned criteria, there were 106 patients (14.6%) in the hyperthyroid group, 284 (39.0%) in the euthyroid group, and 338 (46.4%) in the hypothyroid group. Fifty-nine patients in the hyperthyroid group had latent hyperthyroidism, which means normal thyroid hormone with a suppressed TSH; they were followed without medication. The other 47 patients in the hyperthyroid group were treated with ATD (38 patients) and radioiodine (9 patients).

Surgical complications were as follows: temporary hypoparathyroidism, 71 patients (9.8%); permanent hypoparathyroidism, 3 patients (0.4%); temporary recurrent nerve palsy, 8 patients (1.1%); postoperative bleeding requiring reoperation, 10 patients (1.4%). None had permanent recurrent nerve palsy.

Risk Factor Analyses for Recurrent Hyperthyroidism

Results obtained by univariate analysis are shown in Table 1. Recurrent hyperthyroidism was seen more frequently in elderly patients than in young patients, but not significantly so. There was no significant difference in sex and duration of medical treatment. Statistically significant differences were observed in the weight of

Table 2. Logistic model findings of recurrent hyperthyroidism.

Factors	Odds ratio	95% Confidence interval
Thyroid remnant (g)		
≤ 4	1.000	
> 4, ≤ 5	1.439	1.281–1.615
> 5, ≤ 6	2.069	1.146–3.261
> 6	2.976	1.504–5.886
Antimicrosomal antibody (×)		
−100	1.000	
400–1640	1.526	1.360–1.714
6,560–26,240	2.326	1.475–3.673
104,960+	3.551	1.791–7.040
TSH receptor antibody (%)		
≤ 20	1.000	
> 20, ≤ 40	1.323	1.195–1.465
> 40, ≤ 60	1.750	1.173–2.611
> 60	2.315	1.270–4.220

the resected thyroid tissue, thyroid remnant size, preoperative titer of MCHA, and preoperative level of TBII. Concerning the resected thyroid tissue, the recurrence rate was significantly higher in patients with a large goiter than in those with a small goiter. However, the mean weight of the thyroid remnant in patients with resected thyroid tissue that weighed 50 g, 50 to 100 g, and more than 100 g were 4.6, 5.2, and 6.0 g, respectively, and this difference was significant ($p < 0.0001$, Kruskal-Wallis test). The interrelation between those factors may provide incorrect information, so their prognostic values were determined by multivariate analysis. The summary of the logistic model with stepwise regression method are shown in Table 2. Significant factors were thyroid remnant size, titer of MCHA and TBII level. There were significant correlations between the TBII level and the recurrence rate and between the MCHA titer and the recurrence rate (Fig. 1).

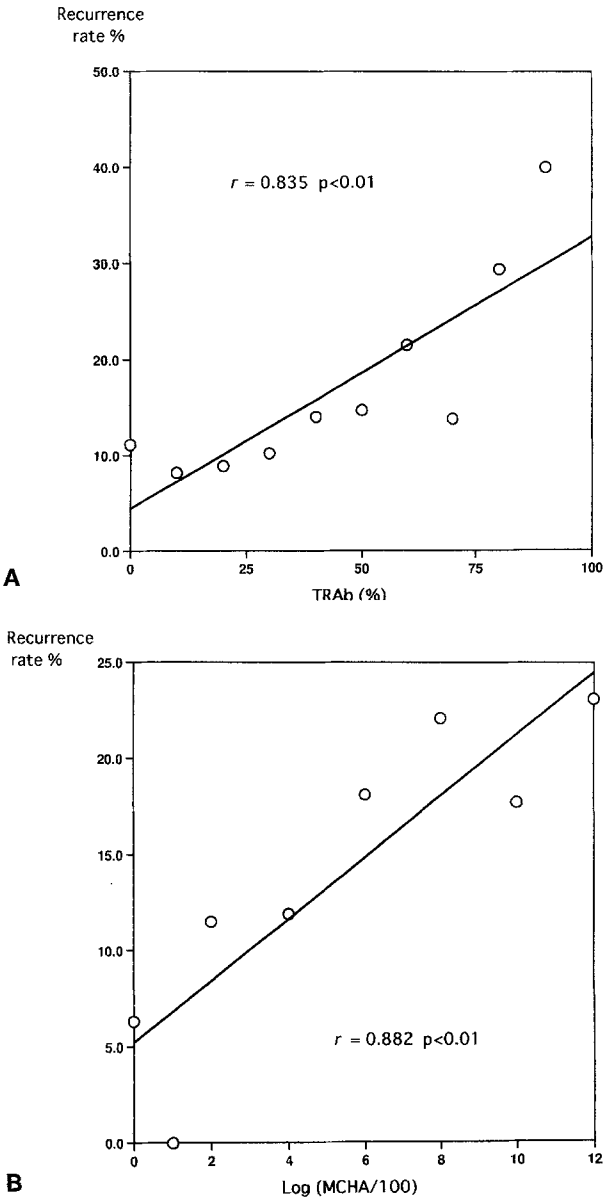

Fig. 1. Correlation between preoperative (**A**) TBII level or (**B**) MCHA titer and the recurrence rate. Significant correlations were observed between both TBII and the recurrence rate (Pearson's correlation coefficient = 0.835; $p < 0.01$) and between MCHA and the recurrence rate (Pearson's correlation coefficient = 0.882; $p < 0.01$).

Discussion

In recent years the number of physicians who choose thyroidectomy as the therapy of choice for Graves' disease has decreased [12–14]. Surgery can induce the remission of hyperthyroidism more rapidly than the other remedies. However, we have reported the long-term outcome of surgical treatment, and the results were not as good as those reported previously [3]. The improved sensitivity of the TSH assay kit has brought to make a correct diagnosis of subclinical thyroid dysfunction [15–18] and was thought to be main reason why so many patients were categorized as having recurrent hyperthyroidism. In this study, recurrent hyperthyroidism was observed in 14.6% of the patients evaluated by serum TSH alone. However, among these patients, 59 patients (55.7%) had latent hyperthyroidism, which means a normal thyroid hormone level with suppressed TSH. Latent hyperthyroidism can be diagnosed only when evaluated by the sensitive TSH assay kit. The conventional TSH radioimmunoassay would have categorized these patients as being euthyroid.

The main goal of surgery is to avoid recurrent hyperthyroidism, and so the remnant size should be extremely small because postoperative recurrent hyperthyroidism is more difficult to treat than permanent hypothyroidism. In our recent studies [3], 9.7% of patients had overt hyperthyroidism and 10.2% had overt hyperthyroidism after an 8-year follow-up; they had been treated for thyrotoxicosis or hypothyroidism. From this result, we do not consider near-total thyroidectomy an ideal treatment, as it induces permanent hypothyroidism in 80% of the patients who had been free of any treatment.

A prerequisite for surgical treatment of Graves' disease is that it can be done not only safely but also with a low incidence of recurrent hyperthyroidism. If the aim of surgery is not permanent hypothyroidism but a long-standing euthyroid state, an adequate thyroid remnant should be left in place. From this point of view, an early recurrence of hyperthyroidism is undesirable and should be avoided as much as possible. Although many reports about factors related to postoperative thyroid dysfunction have been

published [3–11, 19, 20], definite factors remain unknown except thyroid remnant size. Endocrine surgeons need to know which patients need to retain a small or a large thyroid remnant. If definite factors can be discovered, more ideal surgery can be performed.

The TSH receptor antibody has been noted as an immunologic marker, or an essential cause, of Graves' disease and has been reported to be useful for diagnosing and monitoring the clinical course of the disease. Antimicrosomal antibody is also an immunologic marker that is reported to be related to postoperative thyroid dysfunction [3, 21]. The microsomal antigen is now known to be thyroid peroxidase [22], and the antimicrosomal antibody probably participates in the pathogenesis of autoimmune thyroid disease by binding to the cell surface, causing damage [23]. We have shown that the TSH receptor antibody level and the antimicrosomal antibody titer are related to postoperative recurrent hyperthyroidism. However, concerning the TSH receptor antibody level, some reports (including our previous study) have noted that the preoperative TSH receptor antibody level could not predict the long-term outcome of surgically treated patients with Graves' disease [3, 5, 19, 20]. The difference between these studies and ours was that we restricted our examination to patients with recurrent hyperthyroidism that was seen only within the first year after surgery. Previously, we had reported [3] that the recurrence appeared frequently both within the first year after surgery and after a 5-year period had elapsed. We think that early recurrence and late recurrence are due to different factors. It is thought that the early phase after surgery is markedly affected by the preoperative condition of the disease, the preoperative TSH receptor antibody level, and the antimicrosomal antibody titer. On the other hand, late recurrence seems to develop after remission has been acquired. Thus preoperative factors, except thyroid remnants, do not affect late recurrences. We think that this is why definite factors predicting long-term surgical outcome of patients with Graves' disease remain unknown. We conclude that in order to avoid the early recurrence, a thyroid remnant size smaller than 4 g is recommended for patients with high levels of preoperative TBII or MCHA.

Résumé

Le traitement chirurgical de la Maladie de Basedow se doit d'être non seulement sûr mais doit aussi éviter un taux excessif de récidive d'hyperthyroïdie. La récidive précoce est particulièrement fâcheuse. Nous avons étudié 728 patients atteints de Maladie de Basedow, traités par thyroïdectomie subtotale, en analyse multifactorielle, de façon à détecter les facteurs éventuels de récidive précoce. On a analysé les facteurs suivants: âge, sexe, durée du traitement médical, le poids del la pièce réséquée, la taille du moignon restant, les niveaux préopératoires de TSH binding inhibitory immunoglobuline (TBII) et des anticorps antimicrosomial hemagglutination (MCHA). On a utilisé le test Chi2 en analyse monofactorielle et, par modèle logistique, pour l'analyse mulitfactorielle. La récidive précoce a été définie par l'existence d'une suppression de la TSH observée pendant la première année après la chirurgie et durant au moins 6 mois. Cent six patients (14.67%) ont eu une récidive précoce. Les facteurs significatifs étaient la taille du moignon, le MCHA et l TBII. Ces résultats indiquent que TBII et MCHA sont des facteurs de récidive précoce. Chez le patient ayant des taux élevés de TBII et MCHA, il vaut mieux réduire d'avantage la taille du moignon pour éviter les risques de récidive précoce.

Resumen

Un prerrequisito para el tratamiento quirúrgico de la enfermedad de Graves es que pueda ser realizado no sólo con seguridad sino también con una baja incidencia de hipertiroidismo recurrente. La recurrencia temprana es especialmente indeseable. Hemos estudiado 728 pacientes con enfermedad de Graves tratados mediante tiroidectomía subtotal utilizando análisis multivariable con miras a identificar los factores que se relacionan con recurrencia temprana. Los siguientes factores fueron analizados: edad, sexo, duración del tratmiento médico, peso del tejido tiroideo resecado, tamaño del remanente tiroideo, nivel sérico preoperatorio de inmunoglobulina inhibidora de la ligadura de TSH (TBII) y de anticuerpo antimicrosomal de hemaglutinación MCHA). Se definió la "recurrencia temprana" como la supresión de TSH que ocurre en el curso del primer año luego de la cirugía y que se continúa por lo menos por 6 meses. Ciento seis pacientes, 14.6%, presentaron recurrencia temprana. El análisis estadístico demostró que el remanente de tiroides, el MCHA y la TBII fueron los factores de significación. Estos resultados indican que la TBII y el MCHA están relacionados con el fenómeno de la recurrencia temprana del hipertiroidismo y por ello se recomienda, para evitar tal recurrencia, un remanente tiroideo menor en los pacientes con MCHA elevada y/o nivel elevado de TBII.

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Invited Commentary

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The number of patients submitted to surgical treatment of hyperthyroidism has during the last decades been significantly reduced in many countries, especially in the United States, partly because of the use of radioiodine in young patients. Even if the use of radioiodine is justified with certainty in higher ages and (of course) where contraindications for surgery are present, surgery is—as these authors state—a good treatment for hyperthyroidism with many advantages compared to radioiodine: specifically, it offers a rapid, usually definite cure, and with an accurate technique, the majority of the patients can in fact be made euthyroid without any treatment. Long-term follow-up usually is not needed except in risk-groups for postoperative dysfunction, which have to be identified at the time of treatment.

Surgery has been referred to as an expensive, time-consuming treatment compared to radioiodine, but within the above-mentioned considerations, this is not true. Repeated treatment with radioiodine (which is often needed) and/or life-long follow-up also is expensive and time-consuming. It also has to be borne in mind that the big wave of enthusiasm to treat young patients (even children) with radio-iodine has lasted only a little more than a decade, and very little is known about the real long-term consequences of this change in policy.

One prerequisite for surgical treatment is that it can be done with minimal morbidity. The present authors should be congratulated for the excellent results of no single case of persistent recurrent laryngeal nerve injury in 728 patients and only 0.4% persistent hypoparathyroidism. Even if these findings are not unique for specialized centers, they are among the best published to date. They confirm the already well-known high quality of surgical technique among endocrine surgeons in Japan. They also confirm that thyroid surgery can be performed safely when it is done as it should be done, which means in departments with sufficient interest, experience, and frequency.

Another pre-requisite for surgical treatment should be to avoid, or at least minimize, recurrent disease. It is easy to do this through total or "near-total" thyroidectomy, leaving only 1–2 grams of thyroid tissue. On the other hand, all patients will need thyroxin supplementation, and one advantage compared to radioiodine is lost. However, it has been shown that the incidence of recurrence can be brought down to less than 2% even if sufficient thyroid tissue is left to reduce the need of thyroxin supplementation to less than 50%. This requires a proper adjustment of the remnant size and the identification of patients at risk for recurrence (where a more radical operation followed by supplementation should be the method of choice).

With regard to the first requirement, these authors have not been very successful, and an early recurrence rate of 14.8% is not acceptable. This high incidence is astonishing with regard to the fact that the remnant size generally was less than 10% of the original weight to the gland. In our own series, leaving a remnant size of about 25% of the original weight resulted in a recurrence rate of less than 2%. In our series, however, the total weight of the gland was generally smaller, often 20 grams or less. This illustrates the epidemiologic differences between different populations, which makes comparison and transfer of conclusions between different series so difficult. Furthermore, within a small country like Sweden, there are such differences between populations that arguments about a standardized policy often are fruitless. The recommendation must be to base your policy on carefully registered results from your own population. These authors apparently have to leave smaller remnants, and, based on our own experience, I think the authors should be able to do so without a dramatic increase in the incidence of hypothyroldism. We look forward with great interest to seeing this.

With regard to identification of patients at risk, the authors have made an important point in showing a significant correlation between recurrence and preoperative titres of MCHA and preoperative levels of TBII. In many other series, such correlations have been difficult to confirm. In identified risk-groups for recurrence the recommended approach should be (as the authors state) a more radical removal of thyroid tissue plus thyroxine supplementation.

In summary, the authors have given a very valuable contribution to the knowledge in this field and should not be discouraged by the high incidence of early recurrence. This contributes to the understanding that there are differences in population, and with a slight adjustment of the technique the authors should achieve results supporting the important role of surgery in the treatment of this disease.

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