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Results of Surgery for Toxic Multinodular Goiter

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Abstract

Purpose. We analyzed the clinical and histological features of patients operated on for toxic multinodular goiter (TMG) to determine the clinical profile and evaluate the surgical results.

Methods. We reviewed 672 patients who underwent surgery for multinodular goiter (MG), 112 (17%) of whom had hyperthyroidism, and analyzed the epidemiological, clinical, and surgical variables.

Results. The patients with TMG tended to be older than those with nontoxic MG, with a greater evolution time of the goiter and a higher rate of positive antithyroid antibodies. In the multivariate analysis, the only feature characteristic of TMG, as opposed to nontoxic MG, was the evolution time. Morbidity was 34%, representative of the fact that that most of the patients were seen before the establishment of our endocrine surgical unit. The hyperthyroid symptoms resolved in all patients, but 4 of 17 patients who underwent partial surgical resection showed signs of relapse within a follow-up period of 98 ± 71 months.

Conclusions. TMG is characterized by a long evolution time and is most effectively treated by total thyroidectomy, which achieves complete remission from symptoms, without relapse, and is necessary if there is associated carcinoma. However, the incidence of complications may be high if this procedure is not carried out by surgeons with experience in endocrine surgery.

Key words Multinodular goiter · Hyperthyroidism · Surgery · Morbidity · Relapse

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Introduction

Toxic multinodular goiter (TMG) is the final phase in the evolution of multinodular goiter (MG), and for this reason, its incidence increases with age and is closely related to geographical areas in which goiter is endemic.[1,2] Surgery is the treatment of choice because it achieves fast and permanent relief of symptoms.[3,4] Most studies have shown that hyperthyroidism produces the highest rate of complications, in the form of hypoparathyroidism (3.8%–14%) or recurrent lesions (4%–13%),[5–7] Moreover, it usually occurs in older patients, who often have high surgical risk, which is why alternative nonsurgical therapy is being sought.[8,9] Thus, treatment through ablation with radioiodine has been assessed in various studies, often achieving euthyroidism, although the incidence of relapse of hyperthyroidism is high (6%–64%) and radioiodine is not risk free, being associated with thyroid dysfunction and cancer,[10–14] Our objective was to analyze the clinical and histological features of patients treated surgically for TMG to establish a clinical profile and evaluate postoperative morbidity and mortality, remission of symptoms, and relapse of the goiter.

Patients and Methods

We retrospectively reviewed 672 patients diagnosed and treated in our hospital between 1970 and 1999. A subgroup of 112 (17%) patients with hyperthyroidism, defined by an increase in thyroid hormones to higher than normal values (T3 > 9.4 ng/dl, T4 > 62 ng/dl or T4 free > 7.3 ng/dl, and TSH < 0.0001 U/m) was selectively studied. The average age of the patients with TMG was 51 ± 14 years (22–28 years); most (91%) were women, and 26 (23%) patients lived in an area with a high incidence of goiter. Eleven (10%) patients had a family history of thyroid pathology, and one had received

cervical radiotherapy for skin hemangioma. In addition to hyperthyroidism, 22 (22%) also had symptoms of compression, such as dyspnea (n = 17), dysphagia (n = 9), and dysphonia (n = 5). On exploration, the goiter had an elastic consistency in 91 patients (81%), and an intrathoracic component in 45 (40%). The goiters were clinically graded as 0–I in 20 patients, (18%), II in 70 (62%), and III in 22 (20%). Chest radiography showed tracheal displacement or compression in 49 (43.8%) patients. A fine-needle aspiration biopsy was taken from the dominant nodule in 47 (42%) patients, revealing colloid histology in 40, follicular or Hurthle proliferation in 5, and evidence of malignancy in 2. Computed tomography was done for the eight patients with compression symptoms and chest X-ray findings of a large intrathoracic component. Scintigraphy was done in 79 (70.5%) patients, and laryngoscopy was done in 5 patients with preoperative dysphonia.

The variables analyzed were age, sex, family history of thyroid pathology, history of cervical radiotherapy, residence in areas with a high incidence of goiter in Murcia, evolution time before surgery, presence of compressive symptoms, the intrathoracic component according to Eschapase's definition[15] (namely, a goiter located totally or partially in the mediastinum, the edge of which in operating position is at least 3 cm below the sternal manubrium), the consistency of the goiter on physical exploration, clinical grading of the goiter (grade 0, not seen or felt; grade I, felt but not seen; grade II, seen and felt; grade III, affecting neighboring structures), cervical-thoracic radiography changes such as tracheal diversion, upper mediastinal mass or tracheal compression, the presence of antithyroid or positive antimicrosomal antibodies, surgery before of after establishment of the endocrine surgical unit, the surgical technique used, the operation time, the weight of the extracted goiter, the presence of associated carcinoma, postoperative morbidity, and evolution time.

The following postoperative complications were evaluated:[16]

1. Hypoparathyroidism, defined by postoperative calcium levels <7.5 mg/dl, or <8.5 mg/dl if the patient showed signs of clinical hypocalcemia. Hypoparathyroidism was defined as permanent when calcium levels were <8.5 mg/dl 1 year after surgery;
2. Recurrent nerve lesions, diagnosed by changes in the tone, timbre, or intensity of the voice after surgery, or confirmation of vocal cord paralysis by laryngoscopy. Vocal cord paralysis was defined as permanent when it persisted for more than 12 months postoperatively;
3. Damage to the upper laryngeal nerve, defined by a normal voice with loss of tone and timbre after talking, and normal laryngoscopy;
4. Complications of the surgical wound;
5. Systematic complications.

Postoperative morbidity was also evaluated. The 560 patients with MG comprised the control group.

Statistical Analysis

The X-squared test complemented the analysis of residues, and the Fisher test and Student's t test were used if necessary. For determining and evaluating the multiple risks, a logistical regression analysis was done using the variables that were significant according to the bivariate analysis. Differences were considered significant at $P < 0.05$.

Results

The characteristics differentiating the patients with TMG from those with nontoxic MG were older age (51 versus 48 years of age; $P = 0.0249$), a high evolution time for the MG (112 months versus 85 months; $P = 0.0178$), and a higher rate of positive antithyroid antibodies (12% versus 1%; $P = 0.0036$) (Table 1). In the multivariate analysis, the only variable characteristic of TMG was a greater evolution time. [Regression coefficient(β) = 0.002, standard error = 0.0008, $P = 0.016$].

All of the patients underwent surgery: a total thyroidectomy in 95 (85%), a hemithyroidectomy in 7 (6%), a subtotal bilateral thyroidectomy in 6 (5%), the Dunhill technique in 3 (3%), and a subtotal hemithyroidectomy in 1 (1%). The most recent 45 patients were all treated by total thyroidectomy in our endocrine surgical unit. All thyroids were extracted through the cervical route, except in one patient who required a sternotomy to complete the thyroidectomy.

Postoperative complications developed in 38 (34%) patients: dysphonia in 20 (18%), which persisted permanently in 4 (3.6%); postoperative hypoparathyroidisms in 18 (16%), which persisted permanently in 4 (3.6%); cervical hemorrhage on the operating table in 3 (2.7%), resulting in a suffocating hematoma requiring drainage in 2; and wound infection in 1 (1%) (Table 2). There was no postoperative mortality. When the study period was divided into before and after the establishment of our endocrine surgical unit, most of the complications occurred in the former group, whereas only one permanent complication (hypoparathyroidism) occurred in the recent group.

The average weight of the removed thyroids was 107 ± 89 g. An associated carcinoma was found in eight (7%) patients: a papillary carcinoma in seven and a follicular carcinoma in one. Five of these carcinomas were microcarcinomas (Table 3). Capsular invasion was

Table 1. Variables associated with toxic multinodular goiter (bivariate analysis)

Variable	Toxic multinodular goiter $n = 112$	Nontoxic multinodular goiter $n = 560$	P value
Age (years ± SD)	51.3 ± 14.3	47.8 ± 15.1	0.025*
Sex			
Male ($n = 55$)	10 (9)	45 (8)	0.753
Female ($n = 617$)	102 (91)	515 (92)	
Family history of thyroid pathology			
No ($n = 623$)	101 (90)	522 (93)	0.259
Yes ($n = 49$)	11 (108)	38 (7)	
Endemic goiter in area of residence			
No ($n = 525$)	86 (77)	439 (78)	0.707
Yes ($n = 147$)	26 (23)	121 (22)	
Evolution time (months ± SD)	112 ± 122	85 ± 106	0.018*
Compression symptoms			
No ($n = 515$)	90 (80)	425 (76)	0.308
Yes ($n = 157$)	22 (20)	135 (24)	
Intrathoracic component of multinodular goiter			
No ($n = 425$)	67 (60)	358 (64)	0.411
Yes ($n = 247$)	45 (40)	202 (36)	
Consistency of goiter			
Hard ($n = 124$)	21 (19)	103 (18)	0.929
Elastic ($n = 548$)	91 (81)	457 (82)	
Clinical grading of goiter			
Grade 0–I ($n = 105$)	20 (18)	85 (15)	0.418
Grade II ($n = 410$)	70 (62)	340 (61)	
Grade III ($n = 157$)	22 (20)	135 (24)	
Alteration cervical-thoracic x-ray changes			
No ($n = 396$)	63 (56)	333 (60)	0.528
Yes ($n = 276$)	49 (44)	227 (40)	
Antithyroid antibodies[a]			
Negatives ($n = 136$)	15 (88.2)	121 (99.2)	0.004*
Positives ($n = 3$)	2 (11.8)	1 (0.8)	
Antimicrosomal antibodies[b]			
Negatives ($n = 102$)	16 (80)	86 (88)	0.356
Positives ($n = 16$)	4 (20)	12 (12)	

Values are no. of patients (%), except for Age and Evolution Time
* Statistically significant
[a] Only in 139 patients
[b] Only in 118 patients

Table 2. Postoperative complications in patients with toxic multinodular goiter

Variable	No. (%) treated in pre-endocrine surgery unit ($n = 67$)	No. (%) treated in endocrine surgery unit ($n = 45$)	Total no. (%) ($n = 112$)
Postoperative hypothyroidism	12 (18)	6 (13)	18 (16)
Postoperative recurrent nerve lesion	13 (19)	7 (16)	20 (18)
Permanent hypoparathyroidism	3 (4.5)	1 (2.2)	4 (3.6)
Permanent recurrent nerve lesion	4 (6)	0	4 (3.6)
Upper laryngeal nerve lesion	2 (3)	0	2 (1.8)
Cervical hemorrhage	3 (4.5)	0	3 (2.7)
Wound infection	1 (1.5)	0	1 (0.9)
Tracheotomy	0	0	0
Systemic complications	0	0	0
Mortality	0	0	0
Total complications	25 (37)	13 (29)	38 (34)

Table 3. Thyroid carcinomas associated with toxic multinodular goiter

Patient no.	Type of carcinoma	Size (cm)	No. of foci	Vascular involvement	Capsular involvement	Lymph node involvement	Evolution time (months)	Condition
1	Papillary	3	1	Yes	Yes	Yes	96	Free of illness
2	Papillary	1.1	1	—	—	—	126	Free of illness
3	Papillary	0.7	1	—	Yes	—	24	Free of illness
4	Papillary	0.5	1	—	—	—	50	Free of illness
5	Papillary	0.5	1	—-	—	—	36	Free of illness
6	Papillary	0.3	1	—	—	—	24	Free of illness
7	Papillary	0.5	1	—	—	—	12	Free of illness
8	Follicular	2[a]	7	—	Yes	—	80	Free of illness

[a] Largest tumor focus

Table 4. Outcome of partial thyroid surgery for toxic multinodular goiter

Patient no.	Surgical technique	Evolution time (months)	Relapse	Relapse time (months)	Second surgery
1	Subtotal bilateral thyroidectomy	36	Yes	12	Yes
2	Subtotal bilateral thyroidectomy	144	Yes	132	Yes
3	Subtotal bilateral thyroidectomy	157	No	—	—
4	Subtotal bilateral thyroidectomy	166	No	—	—
5	Subtotal bilateral thyroidectomy	182	No	—	—
6	Subtotal bilateral thyroidectomy	228	No	—	—
7	Dunhill technique	146	No	—	—
8	Dunhill technique	161	No	—	—
9	Dunhill technique	250	No	—	—
10	Hemithyroidectomy	2[a]	—	—	Yes[a]
11	Hemithyroidectomy	12	No	—	—
12	Hemithyroidectomy	90	No	—	—
13	Hemithyroidectomy	116	No	—	—
14	Hemithyroidectomy	130	No	—	—
15	Hemithyroidectomy	134	Yes	120	—
16	Hemithyroidectomy	164	No	—	—
17	Subtotal hemithyroidectomy	228	Yes	36	Yes

[a] Underwent reoperation for papillary macrocarcinoma found on histological examination

observed in three patients, being vascular in one and in a lymph node in two. All cancers were unifocal, except for the follicular carcinoma, in which seven tumoral foci were detected. After a follow-up time of between 12 and 126 months, all the patients were asymptomatic and free of tumoral illness.

The average postoperative follow-up time was 98 ± 71 months. The symptoms of hyperthyroidism progressively resolved after treatment in all patients. However the remission was permanent only in those patients who underwent a total thyroidectomy. Of the 17 patients treated with partial resection, 4 (24%) suffered a relapsed of goiter and hyperthyroidism after 1, 3, 10, and 11 years respectively (Table 4). Four (3.6%) patients underwent reoperation, one, 2 months after the detection of a 3-cm papillary carcinoma by definitive histological study, and the other three months later, because of a relapse of goiter and hyperthyroidism (Table 4). The patient with papillary carcinoma underwent a jugular lymph-node dissection, and the other patients underwent completion of the thyroidectomy.

Discussion

The incidence of hyperthyroidism in our series of patients with MG was 17%, with a follow-up period of more than 9 years. These findings support those of other studies[17] indicating that hyperthyroidism occurs with an average evolution time of 7 years and an incidence of less than 20% (13%–16%). The main factor in the development of hyperthyroidism is time, with TMG being the final phase in its evolution, while nodules acquire autonomy.[1,2,18–20] According to our multivariate analysis, the most characteristic feature of TMG is its greater evolution time. The long preoperative evolution time explains why more than 40% of our patients with TMG had an associated intrathoracic component and a high incidence of compressive symptoms.

Hyperthyroidism is a known risk factor predisposing a patient to complications after thyroid surgery. Thus, in our series, the incidence of permanent complications was 7.1%, with recurring damage and permanent hyperthyroidism in 3.6%. A multicentric German study by Thomusch et al.[7] showed that hyperthyroidism is a risk factor in the development of surgical complications. They observed a higher incidence of hyperthyroidism, but not of recurrent nerve paralysis. We also observed a high incidence of cervical hemorrhage, which has been described by others and is attributable to the greater thyroid vascularization in these patients.[7] Despite hyperthyroidism being an important risk factor, most permanent damage occurred in the first part of this series before our endocrine surgical unit was opened and, thus, corresponded to the prespecialization phase and to the learning period in our hospital. Furthermore, after our endocrine surgical unit opened, we performed total thyroidectomy for all patients, whereas previously, more partial resections had been done. Only one case of permanent damage causing hyperparathyroidism occurred after our endocrine surgery unit opened, whereas four (6%) recurrent lesions and three (45%) cases of permanent hyperparathyroidism occurred prior to its opening, reinforcing the importance of specialization in endocrine surgery for patients at risk of hyperthyroidism, as has been stressed by various authors.[21]

The symptoms caused by MG resolved progressively after surgery in all patients. However, this remission was permanent only in those who underwent total thyroidectomy. Four (24%) of the patients who underwent partial resection have suffered relapse of goiter and hyperthyroidism. This indicates that the incidence of recurrence of hyperthyroidism is related directly to the size of the remnant thyroid tissue, explaining the variation in the incidence of relapse of between 5% and 30%. On the other hand, the size of the remnant thyroid tissue is inversely related to the development of hyperthyroidism. Thus, the lower the rate of relapse, the higher the rate of hyperthyroidism.[6,22–24] According to Mittendorf and McHenry,[3] subtotal thyroidectomy is not appropriate for treating TMG because if the remnant is large, hyperthyroidism can result, necessitating more treatment or even surgical intervention with its consequent risk, whereas if the remnant is small, hypothyroidism will persist. Therefore, subtotal thyroidectomy has no advantage over total thyroidectomy, as it still results in the need for thyroxine supplementation.[24] We recommend total thyroidectomy for the treatment of TMG. Mittendorf and McHenry[3] also suggest the Dunhill technique as a good alternative. Only three of our patients were treated by the Dunhill technique, but none have experienced relapse, after 146, 161, and 250 months, respectively; it is impossible, however, to draw conclusions about this technique based on the results of only three patients.

Many authors have claimed that hyperthyroidism protects against thyroid cancer or that the incidence of malignancy is lower in patients with TMG than in those with nontoxic MG. In our series, thyroid cancer was found in 7% of patients with TMG, and three of these were macrocarcinomas. Furthermore, one was multifocal, there was capsular affectation in three patients, and one had vascular and lymph-node invasion. Mittendorf and McHenry[3] and others have noted that the incidence of malignancy with TMG is not as low as previously thought, and that macrocarcinomas with capsular, vascular, or lymphatic invasion are often found.[25–27]

In conclusion, TMG is characterized by a long evolution time, and therefore often results in an intrathoracic component associated with symptoms of compression. Total thyroidectomy is the treatment of choice because it achieves complete relief of symptoms, without relapse, especially considering that 7% of our patients were found to have associated carcinomas. However, the incidence of complications is higher than that in patients with nontoxic goiter if the operation is not performed by surgeons with experience in endocrine surgery.

References

1. Siegel RD, Lee SL. Toxic nodular goiter. Toxic adenoma and toxic multinodular goiter. Endocrinol Metab Clin North Am 1998;27:151–68.
2. Van Soestbergen MJM, Van der Vijver JCM, Graafland AD. Recurrence of hyperthyroidism in multinodular goiter after long-term drug therapy: a comparison with Grave's disease. J Endocrinol Invest 1992;15:797–800.
3. Mittendorf EA, McHenry CR. Thyroidectomy for selected patients with thyrotoxicosis. Arch Otolaryngol Head Neck Surg 2001;127:61–5.

4. Werga Kjellman P, Zedenius J, Tallstedt L, Traisk F, Lundell G, Wallin G. Surgical treatment of hyperthyroidism: a ten year experience. Thyroid 2001;11:187–92.
5. Wagner HE, Seiler CA. Recurrent laryngeal nerve palsy after thyroid gland surgery. Br J Surg 1994;81:226–8.
6. Mishra A, Agarwal A, Agarwal G, Mishra SK. Total thyroidecotmy for benign thyroid disorders in an endemic region. World J Surg 2001;25:307–10.
7. Thomusch O, Machens A, Sekulla C, Ukkat J, Bippert H, Gastinger I, et al. Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. World J Surg 2000;24:1335–41.
8. Albero R, Berdun MA, Playan J, Acha J, Casamayor L, Sanz A. Does goiter constitute basically a surgical process? (in Spanish with English abstract). An Med Intern 1993:10:438–42.
9. Franklyn JA. The management of hyperthyroidism. N Engl J Med 1994;330:1731–8.
10. Hurley DL, Gharib H. Evaluation and management of multinodular goiter. Otolaryngol Clin North Am 1996;29:527–40.
11. Jensen MD, Gharib H, Naessens JM, van Heerden JA, Mayberry WE. Treatment of toxic multinodular goiter (Plummer's disease): surgery or radioiodine?. World J Surg 1986;10:673–80.
12. Bahmad AM, Ahmad M, Young ET. Objective estimates of the probability of developing hypothyroidism following radioactive iodine treatment of thyrotoxicosis. Eur J Endocrinol 2002;146: 767–75.
13. Pauwels EK, Smit JW, Slats A, Bourguignon M, Overbeek F. Health effects of therapeutic use of I131 in hyperthyroidism. Q J Nucl Med 2000;44:333–9.
14. Angusti T, Codegone A, Pellerito R, Favero A. Thyroid cancer prevalence after radioiodine treatment of hyperthyroidism. J Nucl Med 2000;41:1006–9.
15. Dahan M, Gaillard J, Eschapase H. Surgical treatment of goiters with intrathoracic development. In: Delarue NC, Eschapase H, editors. Thoracic surgery: frontiers and uncommon neoplasms. International trends in general thoracic surgery. St Louis: Mosby; 1989. p. 5.
16. Reeve T, Thompson NW. Complications of thyroid surgery: how to avoid them, how to manage them, and observations on their possible effect on the whole patient. World J Surg 2000; 24:971–5.
17. Elte JW, Bussemaker JK, Haak A. The natural history of euthyroid multinodular goitre. Postgrad Med J 1990;66:186–90.
18. Brownlie BE, Wells JE. The epidemiology of thyrotoxicosis in New Zealand: incidence and geographical distribution in North Canterbury, 1983–1985. Clin Endocrinol (Oxf) 1990;33: 249–59.
19. Katlic MR, Grillo HM, Wang CA. Substernal goiter. Analysis of 80 patients from Massachusetts General Hospital. Am J Surg 1985;149:283–7.
20. Berglund J, Ericsson UB, Hallengren B. Increased incidence of thyrotoxicosis in Malmo during the years 1988–1990 as compared to the years 1970–1974. J Intern Med 1996;239:57–62.
21. Sosa JA, Bowman HM, Tielsch JM, Powe NR, Gordon TA, Udelsman R. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. Ann Surg 1998; 228;320–30.
22. Menegaux F, Turpin G, Dahman M, Leenhardt L, Chadarevian R, Aurengo A, et al. Secondary thyroidectomy in patients with prior thyroid surgery for benign disease: a study of 203 cases. Surgery 1999;125:479–83.
23. Martos JM, Pérez M, del Valle López A, Naranjo JR, Pérez MI, Sousa JM, et al. Postoperative hypoparathyroidism (in Spanish with English abstract). Cir Esp 1998;63:25–9.
24. Tweedle D, Colling A, Schardt W, Green EM, Evered DC, Dickinson PH. Hypothyroidism following partial thyroidectomy for thyrotoxicosis and its relationship to thyroid remnant size. Br J Surg 1977;64;445–8.
25. Vaiana R, Cappelli C, Perini P, Pinelli D, Camoni G, Fargaglia R, et al. Hyperthyroidism and concurrent thyroid cancer. Tumori 1999:85:247–52.
26. Piñero A, Rodríguez JM, Sola J, Soria T, Riquelme J, Illana J, et al. Thyroid cancer in hyperthyroidism: not such an uncommon association (in Spanish with English abstract). Cir Esp 2000;67: 331–3.
27. Kasuga Y, Sugenoya A, Kobayashi S, Masuda H, Iida F. The outcome of patients with thyroid carcinoma and Graves' disease. Surg Today 1993;23:9–12.