

Total thyroidectomy in Basedow-Graves' disease treatment: our experience

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SUMMARY: Total thyroidectomy in Basedow-Graves' disease treatment: our experience.

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In the present study the authors, after a short historical description of the Basedow-Graves' disease, describe their case-study gathered over the last five years. They mention the most widely accepted hypothesis re-

garding disease's etiology, strongly linked to autoimmune disorders, and the role that some viral agents (Cocksackie B and HTLV-II) may have in initiating autoantibody production and T cells activation in genetically predisposed individuals. Basic and clinical aspects of the diagnosis and disease treatment, highlighting the use of thyroidectomy, are addressed.

They conclude that total thyroidectomy represents today the treatment of choice, which, after appropriate preparation to reach the euthyroidism condition, can ensure a successful cure.

KEY WORDS: Basedow-Graves disease - Hyperthyroidism - Thyroidectomy.

Introduction

The disease entity characterized by the association of goiter and exophthalmos was observed in the nineteenth century by Robert James Graves (1796-1853) in Dublin and, at the same time, by Carl Adolph von Basedow (1799-1854) in Merseburg, Germany.

In particular, in 1835 Graves described on the London Medical and Surgical Journal, three women with "continuous and violent palpitations, eyes that were apparently enlarged and, in one of them, a heartbeat that could be heard even at a distance from the bed" (1).

In 1840, von Basedow described in detail the symptoms observed in 1832 on Mr. M.: "hot flashes, profuse sweating, in which he found relief by opening the dress on the chest to rain, wind and sleet, palpitations, exophthalmos, increased thyroid volume, weight loss and vomiting undigested food three to four times a day maintaining, however, a strong appetite. He was sleeping with

open eyes and the bulbs were absolutely healthy and had a completely full sight". von Basedow envisaged the hypertrophy of the orbital tissue as the cause of the exophthalmos (2). The same von Basedow subsequently defined the association of exophthalmos, palpitations of the heart, and goiter, as we know it today, as "the triad of Mersenburg", and in 1848 published the results of an autopsy of a patient who died of "goggle eye cachexia".

Case-study

Over the last five years, in 429 patients affected by thyroid disease, we have observed 57 cases (13.3%) of Graves' disease. Of these 44 (77.2%) were females and the remaining 13 (22.8%) were males. In addition, 26 cases (45.6%) were patients aged between 17 and 30 yr, 14 cases (24.6%) were between 31 and 40 yr, 11 cases (19.3%) between 41 and 50 yr, and 6 cases (10.5%) between 51 and 62 yr (Table 1). In 21 patients, a familiarity for thyroid disease was documented, and seven of them showed familiarity for Graves' disease. In all patients, the diagnosis of hyperthyroidism was done following an accurate morphological and functional evaluation of the thyroid gland. Consequently, all patients underwent medical treatment with anti-thyroid drugs, often associated with beta-blockers. This treatment, con-

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TABLE 1 - PATIENT'S PARAMETERS AND CLINICAL FEATURES.

Age range (yr)	17-30	31-40	41-50	51-62
Number of patients (percentage)	26 (45.6%)	14 (24.6%)	11 (19.3%)	6 (10.5%)
Gender				
Females 44 (77.2%)	24	13	4	3
Males 13 (22.8%)	2	1	7	3
Relapse, n				
1 (28.07%)	7	9	-	-
2 (19.29%)	-	2	8	1
3 (8.77%)	-	-	-	5
Nodularity				
1 lobe (71.9%)	32	9	-	-
2 lobes (28.1%)	3	5	6	2
Ophthalmopathy (84.21%)	21	13	9	5
Symptomatic goiter (19.29%)	-	-	7	4
Neoplastic degeneration (8.77%)	-	2	3	-

tinued for a time ranging from 4 to 24 months, allowed to reach the euthyroidism condition in all patients. However, as verified by medical examination and periodic hormonal assays, several of them had hyperthyroidism relapses. The latter occurred only once in 16 patients, 2 times in 11 patients and 3 times in 5 patients (Table 1).

In all patients, often at the first instrumental evaluation, the presence of nodules within the gland was observed. In particular, the nodules were present only in one lobe in 71.9% of cases (41 patients), and in both lobes in the remaining 28.1% of cases. Five patients showed the presence of nodules suspicious of malignancy, which was later confirmed by preoperative cytological examination and, following thyroidectomy, by histology. In 48 patients (84.2%), all relevant symptoms of Graves' disease were present, including an impressive exophthalmos. In 11 patients (19.29%), a massive increase in the gland volume was evident, in most cases limited to one lobe and with tendency of the gland to intrathoracic development. We performed total thyroidectomy only in euthyroid patients as follows: Kocher's cervicotomy, opening the median raphe of the prethyroid muscles and their divergence, ligation of vascular pedicles near the parenchyma, removal of the gland prior identification and respect of inferior laryngeal nerves and parathyroid, haemostasis and, after affixing the drainages, reconstruction of the various planes. In any case, the surgical procedure was preceded by treatment with Lugol's solution, which generally produced no increase in intra- and post-operative bleeding, limited to 130-200 ml. Only one patient, three hours after the end of surgery, showed significant bleeding and malfunction of the drainage under moderate

forced suction. This led us to review the thyroid bed, where, however, there was no evidence of any hemorrhagic source, and to relocate another drainage after removal of some blood clots. The drainages were always removed within 48 hours after surgery, and patients were discharged in the third day or, for 13 cases in which a slight decrease in calcium serum levels was noticed and promptly corrected, in the fourth day. We did not observe major clinical signs related to laryngeal nerve injury. Only in 7 cases we observed a paralysis of one vocal cord with slight narrowing of the breathing space, which resolved, with total functional reintegration, within a couple of months. Substitution therapy with L-thyroxine was started in escalating doses, and modulated according to FT₃, FT₄ and TSH serum levels. The ophthalmopathy present in 48 of our patients showed a clear regression in 81.3% of them (39 cases) and the remaining 18.7% (9 cases) showed a significant improvement.

All thyroids removed, of variable weight comprised between 78 and 250 g, were subjected to histological examination, which documented the presence of parenchyma with micro-medium follicles with irregular margins, pseudopapillary focal hyperplasia and interstitial lymphocytic infiltrates. These histo-pathological findings agreed, in cases where it had been previously performed, with the results of cytology, showing medium-high cell density, thyrocytes with moderate nuclear asymmetry and occasional regressive phenomena in single cells or cell-aggregates. The background included fibrous bands and abundant fluid colloid.

In five patients for which pre-operative cytological evaluation reported the presence of cells suspicious of ma-

lignancy, the histological examination confirmed the diagnosis of papillary thyroid carcinomas.

Discussion

The etiology of what in Europe is commonly called Basedow disease remained unknown until 1958, when McKenzie proved the presence in patient's blood of a long-acting thyroid stimulator (LATS), thus laying the hypothesis that it was an autoimmune disorder (3). Later, in 1965, Adams proposed the idea that the LATS was an antibody against a thyroid gland component, strengthening the beliefs, still accepted in our days, on the autoimmune pathophysiology of the Basedow-Graves' disease (4).

Like for other autoimmune diseases, it is not yet clear what causes the production of immunoglobulins directed against normal components of the organism. One etiopathogenetic hypothesis involves the Cocksackie B virus and the HTLV-II (human T-lymphotropic virus type II) that would act as a trigger for autoantibody production and T lymphocytes activation in individuals carrying mutations in the alleles HLA 6q21.3, CTLA4 2q33 and TSHr 14q31 (5, 6).

The Basedow-Graves' disease, most common in women, is held responsible for 60-80% of all cases of hyperthyroidism (7). The most common symptoms complained by patients are nervousness, palpitations, heat intolerance, increased sweating, easy fatigue and weight loss (8). In accordance with the clinical picture, patients show increased thyroid volume associated with tachycardia, tremors, hot skin and exophthalmos. Sometimes, especially in patients over age 50, atrial fibrillation may occur. From the anatomic-pathological point of view, the thyroid, beside increased volume, shows congestion and increased consistency. Usually there are no nodules, even if most patients affected by autoimmune thyroid disease reach the surgeon after prolonged periods of treatment with thyrostatic drugs that may determine the appearance of nodules because of parenchymal hyperstimulation due to reactive TSH increase.

The diagnosis of Basedow-Graves' disease stems from the combination of abnormalities in biochemical analysis, such as decreased TSH in concomitance with increased FT₄ and FT₃ serum levels and extra-thyroid manifestations of Graves' disease, such as dermopathy and ophthalmopathy. The thyroid scan may be useful, showing a high radioiodine uptake that reflects the increased accumulation and organification of iodine. In addition, the determination of autoantibodies against the TSH receptor may help the diagnosis of Graves' disease, although its usefulness is controversial (9).

For the treatment of hyperthyroidism caused by this disease, several therapeutical options are available, in-

cluding administration of thyrostatic drugs, radioactive iodine or surgical removal of the gland. Medical therapy, which is the treatment of choice for the European schools of endocrinology, is based on the use of two drugs: methimazole and propyl-thiouracil. Both inhibit iodine organification and coupling of the iodothyronine residues, thus hampering thyroid hormone synthesis. Furthermore, the propyl-thiouracil inhibits the conversion of T₄ to T₃. Nevertheless, both drugs appear to be equivalent in terms of efficacy (10, 11). For the majority of patients the euthyroidism condition is achieved after 6 weeks of treatment, and for almost all patients after 3 months. However, the therapy must be continued for a longer period (1-2 yr) in order to obtain a long-term remission. Despite that, a recurrence of symptoms may occur, and predictors of non-remission include male gender, massive goiter, severe hyperthyroidism with elevated T₄ and T₃ serum levels, and previous disease relapse(s) (12, 13).

Radioactive iodine, used for the first time in 1940 by Hertz and Roberts at the Massachusetts General Hospital for the treatment of hyperthyroidism, may represent, in some patients, a safe and effective therapeutic approach characterized, however, by a long period of latency before the benefits can be appreciated (14). Of course, pregnancy and lactation are absolute contraindications to the use of radioactive iodine.

Despite the effectiveness of medical and radioiodine therapies, surgical treatment retains a clearly defined role, and also in the United States, where in the past was reserved to few selected cases, is recovering interest (15-19). On the other hand, surgery is a viable alternative to other therapeutical approaches only if it can guarantee the required functional results along with a minimum risk of complications (20). Today thyroidectomy can be considered a relatively safe procedure recommended in presence of large goiters causing compressive and/or painful symptoms.

The occurrence of a palpable nodule in patients with Basedow-Graves' disease is often associated with an increased incidence of cancer (21, 22). For this reason, and in view of the greater aggressiveness of thyroid cancer in these patients, reported by several authors, the surgical option should be seriously considered, especially in case of pre-operative cytological analysis suggestive of malignancy (23). In addition, a previous history of irradiation in the head-neck area constitutes an indication to surgical treatment, as a significant increase of cancer incidence in these patients has been demonstrated. In addition, for some endocrinologists the surgical treatment should be preferred in younger patients, compared to the older ones (24). This because of the lower rates of cure or remission of symptoms in patients younger than 40 yr, treated either with thyrostatic drugs or with radioactive iodine. This is particularly true for very young patients,

such as teenagers, in whom the medical treatment fails in about 80% of cases. This may also apply to male patients affected by Graves' disease, which show a lower rate of remission after radioactive iodine or medical therapy compared to the female population (47% vs 74 %) (25).

Also with regard to pregnancy, surgery is the best option for women who want a child and do not want to wait. In fact, it is worth to mention that after drug treatment, because of the high rate of relapse in the first few months, or after radioiodine exposure, potentially harmful for the fetus, it is essential to wait at least six months. Similarly, an ongoing pregnancy poses additional problems. In this condition, in fact, there is an absolute contraindication to radioactive iodine, while thyroidectomy should be taken into consideration only in those women where the hyperthyroidism is not well controlled by the use of the medical therapy. In such conditions, the optimum period for thyroidectomy is after the first trimester of pregnancy to prevent the theoretical risk of miscarriage during the first trimester (26). Traditionally, breastfeeding of women under medical therapy with thyrostatic drugs has always been discouraged, although some recent studies claim that it is completely safe (27). In addition, treatment with radioactive iodine can cause problems as iodine may be secreted in breast milk up to 8 weeks after the last administration. Therefore, also in lactating patients surgery appears to be the best option, allowing them to continue breastfeeding.

In the past, the presence of exophthalmos was considered a contraindication to thyroidectomy because it was thought to worsen following surgery. However, in 1988 Blichert-Toft paved the way for a new vision demonstrating an improvement of the exophthalmos in all patients after total thyroidectomy (28). Similar observations were later reported by Razack in 1997 and by Borrelli in 2000 (29, 30).

Finally, it should be included among the indications for surgery patient's will who, after appropriate and detailed information and by virtue of their personal needs, can exercise a legitimate choice (31, 32). In particular, for some patients surgery may be preferred since it can guarantee brilliant results in shorter times, with

respect to medical and radio-metabolic treatments for which much longer periods are required. Others patients are inclined to ask surgical intervention because they are reluctant to radioactive iodine treatment due to their fear of radiation exposure.

Whatever the indication, it is imperative to achieve a euthyroid condition before surgery. This can be accomplished with a proper pre-operative preparation of the patients through medical therapy. Importantly, beta-blockers are frequently co-administered to control tachycardia, tremor and anxiety, and to avert any post-operative thyrotoxic crisis.

Some authors, in order to decrease the vascularization of the gland and to facilitate its removal, have proposed the administration of Lugol's solution in the week before surgery.

Conclusions

Around the world, despite the effectiveness of medical and radioactive iodine treatments, surgery is playing an increasing and important role in the therapy of Basedow-Graves' disease.

At present total thyroidectomy, in spite of a minimum risk of complications related to this type of surgery, represents a valid alternative to other therapeutical approaches and capable of providing the required functional results in a very short time.

Since the objective of the surgical treatment of the Basedow-Graves' disease is resolution of the hyperthyroidism condition, it becomes clear that a total thyroidectomy, involving a programmed hypothyroidism easily correctable with oral synthetic thyroid hormone, is to be preferred to a partial removal of the gland. The latter, indeed, although leading to the restoration of euthyroidism, has an unpredictable evolution in the medium-long term.

Total thyroidectomy, like the subtotal one, is a safe surgical procedure if done by expert hands, that in addition to ensure the absence of recurrences, has also a positive effect on the autoimmune processes responsible for the disease.

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