

Toxic multinodular goitre. Personal case histories and literature review

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SUMMARY: Toxic multinodular goitre. Personal case histories and literature review.

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The authors reviewed their own case histories of surgical thyreo-

pathy over the last 20 years in order to establish how many multinodular goitre (MNG) patients developed hyperthyroidism during the follow-up period. In agreement with the findings reported in literature, the authors observed that 220 out of 1117 patients with MNG developed hyperthyroidism caused by the appearance of hyperfunctioning nodules after 6-18 years from the initial diagnosis of MNG.

KEY WORDS: Multinodular goitre - Hyperthyroidism - Surgery.

Introduction

Multinodular goitre (MNG) is the most common thyroid disease in the world, with more than 300 million people estimated to be affected (1-4). Its incidence is strictly correlated with the availability of iodine being higher in iodine deficient geographical areas with respect to iodine sufficient areas and in areas where dietary iodine supplementation is in use. MNG is the result of aberrant growth of thyroid follicular cells following chronic TSH stimulation, which, via hyperplasia, leads to the nodular degeneration of thyroid tissue. Within a MNG the development of hyperfunctioning nodules, in the absence of an autoimmune stimulus as is the case with diffuse toxic goitre (Graves' disease), determines the clinical picture of toxic MNG (TMNG). In the present study, we have reviewed the records of patients with thyreopathy referred to our Clinic (General and Gastrointestinal Surgical Unit - "G. Martino" University Hospital of Messina, Italy) for

surgery over the last 20 years, all of whom came from areas (Sicilia and Calabria regions) of endemic goitre, in order to evaluate how many MNG patients during the follow-up period developed hyperthyroidism following the formation of autonomously hyperfunctioning thyroid nodules, and to assess their anatomo-clinical behaviour.

Case records

Between 1992 and 2012, 1826 patients with thyreopathy were referred to our clinic for surgery. Of these, 1653 (90.5%) had benign and 173 (9.5%) malignant pathologies (Tables 1 and 2). There were 1117 (67.6%) cases of multinodular goitre, 97 (8.7%) of which were recurring. Over a period of 6-18 years, 220 (19.7%) patients developed hyperthyroidism as a result of nodular autonomization. The presence of one, two, three or more functionally autonomous nodules was observed in 27 (13.3%), 151 (74.4%), 16 (7.9%) and 9 (4.4%) cases, respectively. In the majority of cases the hyperfunctioning nodules were confined to the same thyroid lobe. Ninety-one percent of patients were female with an average age of 73 yr (range 61-87 yr). Twenty-three percent of patients came to us following the sudden onset of hyperthyroid symptoms and were unaware that they had MNG; 67% of the remaining patients had known for some time that they had MNG. In 13% of patients TSH suppression was accompanied by hyperthyroidism with thyroid hormone values at the high limit of the normal range. In the patients who knew they had MNG, the onset of hyperthyroidism was triggered by the development of hyperfunctioning nodules 9-18 yr after diagnosis, with average onset at 12 yr. The administration of thyroid hormones for suppressive purposes seems not to have played a significant role in the development of functionally autonomous areas.

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TABLE 1 - BENIGN THYREOPATHIES TREATED IN THE PERIOD 1992-2012.

Multinodular goitre	851
Toxic multinodular goitre	220
Recurring multinodular goitre	97
Adenomatose goitre	291
Follicular adenoma	86
Oncocitary adenoma	32
Diffuse toxic goitre (Basedow)	34
Toxic adenoma (Plummer)	33
Hashimoto's thyroiditis	6
Lignaeus thyroiditis	3
TOTAL	1653

Observations

The pathogenesis of TMNG, which includes a broad spectrum of anatomo-clinical entities ranging from isolated to multiple hyperfunctioning nodules, remains a matter of debate (1-3). In our patients 91% of hyperfunctioning nodules were multiple, with the majority of patients showing two hyperfunctioning nodules. Along with Graves' disease, TMNG is the main cause of hyperthyroidism, with the difference that diffuse toxic goitre is most commonly found in iodine sufficient areas. In fact, in iodine insufficient areas 48% of hyperthyroid patients have TMNG, 10% toxic adenoma and 40% diffuse toxic goitre (4). Of our MNG patients, 19.7% had developed TMNG (220 out of 1117 cases).

The functionally autonomous areas synthesize and secrete thyroid hormones independently and aimlessly, thus suppressing TSH secretion; as a result, the remaining thyroid tissue becomes functionally quiescent. Areas of autonomous tissue and areas of inactive tissue thus come to coexist within the same thyroid (5). The functional autonomy acquired by one or more nodules is correlated with goitre "age", nodule size and patient age (+60 yr) mainly in female patients. Fifteen years are usually thought to be necessary for TMNG to develop. Our records show the disease to be most prevalent in female patients with an average age of 73 yr. The onset of hyperthyroidism occurred on average 12 yr after diagnosis and ranged from a minimum of 9 to a maximum of 18 yr.

In 1924 David Marine was the first to suspect that iodine deficiency might stimulate the pituitary gland to produce more TSH in order to allow the thyroid to maintain adequate hormone production levels (6).

Many studies subsequently demonstrated that a diffuse (hyperplastic) toxic goitre undergoing continuous TSH stimulation can evolve towards nodular degeneration with one or two nodules later becoming functionally autonomous and causing thyrotoxicosis. The pathogenesis un-

TABLE 2 - MALIGNANT THYREOPATHIES TREATED IN THE PERIOD 1992-2012.

	No. of cases	%
Differentiated carcinoma	154	79.8
Medullary carcinoma	12	7.8
Anaplastic carcinoma	5	3.3
Lymphoma	1	0.1
TOTAL	173	100

derlying nodule's autonomization in MNG patients has also been demonstrated to be the result of multiple causal mechanisms, ranging from chronic TSH stimulation to autocrine and paracrine factors, contributing to the development of active cells that are capable of replication and functional autonomy.

In normal thyroid cells proliferation and functional differentiation are controlled by cAMP cascade. Therefore, the fact that hyperthyroidism is associated with TSH-independent toxic nodule growth suggests an anomalous activation of the cAMP regulatory cascade to play a part in their genesis (7, 8). Other primary and secondary causal mechanisms that may have key roles in the autonomization of thyroid nodules are nevertheless acknowledged. Primary factors include:

- A. Genetic heterogeneity of follicular cells: thyrocytes are known to be of polyclonal origin and thus have different potentialities, different TSH-responsiveness, and variable ability to synthesize thyroid hormones, capture iodine and produce thyroglobulin.
- B. Capacity to mutate following cell replication: in the course of replication thyroid cells can mutate to forms not present in the mother cell, endowed with greater TSH-sensitivity and growth capacity.
- C. Functional and anatomical abnormalities during the growth phase: disorderly and heterogeneous growth is at the root of the nodular degeneration of goitres.

Secondary thyroid stimulating factors include:

- A. Increased TSH.
- B. Iodine deficits resulting from insufficient dietary intake or its altered metabolism have been demonstrated to stimulate TSH secretion.
- C. Estrogens that reduce the renal reabsorption of iodine are responsible for the higher incidence of goitre in women. A diet rich in goitrogenic substances such as thiocyanates can affect iodine insufficiency.

Numerous hereditary congenital defects have been found to affect thyroid hormonogenesis, which explains why goitre runs in families. These defects include anomalies in iodide transport, thyroperoxidase, iodotyrosine coupling and thyroid deiodinases, and in the synthesis of hydroproteins other than thyroglobulin. Recent studies have shown that many other factors can determine the onset of goitre, such as the epidermoidal

growth factor, the insulin-like growth factor and the fibroblast growth factor (9-13). Researchers have placed much emphasis on the identification of possible gene mutations. Activating mutations in the gene for the alpha polypeptide chain of the heterotrimeric protein G, involved in the cAMP cascade, have been observed in toxic adenomas (7, 8). The first TSH receptor (TSHR) mutation was documented in the third intracellular loop in residues homologous with those identified in the β_1 adrenergic receptor. Subsequently, 45 TSHR-activating mutations were described in hyperfunctioning adenomas (14, 15). TSHR mutations have been also described in some thyroid carcinomas, especially those associated with hyperthyroidism (16, 17). Nevertheless, despite encouraging studies acknowledging TSHR mutations to play a key part in the genesis of nodule autonomization, we are still far from having clarified their precise role. The frequency of TSHR mutations in hyperfunctioning nodules is not a constant, and varies considerably, from 8 to 82%, with the lowest incidence reported in Japan. There thus exist a considerable number of cases in which

no genetic mutation of TSHR is associated with toxic nodules (18-23). Whatever the actual pathogenesis of TMNG may be, there is no doubt that thyrotoxicosis manifests when the thyroid has at its disposal sufficient iodine to induce hormonogenesis. This condition occurs above all in iodine deficient areas when dietary iodine supplementation campaigns are activated, or when diagnostic contrast media or amiodarone are administered, as these can cause iodine overload when taken with incongruous doses of synthetic thyroid hormones.

Conclusion

The results of our experience, which broadly confirm those reported in literature and those of the many studies that have led to the discovery of TSHR-activating mutations, allow us to state that our findings constitute just one important step towards a partial understanding of the true nature of the actual mechanisms that regulate the formation of hyperfunctioning thyroid nodules.

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