

BENIGN MULTINODULAR GOITER

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Key words: Benign multinodular goiter; diagnosis; treatment recommendations

Multinodular non-toxic goiter is the most prevalent thyroid pathology characterized by unilateral or bilateral thyroid growth with morphologically and/or functionally transformed follicles and euthyroidism. At thyroid sonography in unselected populations, 20 to 30 % incidence of thyroid nodules has been reported (1). Beside morphologic variability, lack of hyperstimulation in the majority of the multiplied follicles is the hallmark of the disorder. Most nodular goiters grow slowly and undergo different morphologic changes, encompassing diffuse hyperplastic enlargement in the early phase, development of large follicles loaded with abundant colloid and with increasing age, formation of functionally autonomous tissue. Annual growth potential of approximately 20 % can be assumed.

The pathogenesis of nodular goiter is multifactorial and probably differs from patient to patient. In contrast to the endemic goiter, iodine deficiency is not a primary causal factor. Environmental factors such as natural goitrogens, iodine intake, malnutrition, drugs, stress, pollution or infections, constitutional factors such as female gender and several genetic factors, i.e. circulating thyroid growth factors contribute to different degree to the development of nodular thyroid enlargement. Also controversially debated, thyroid-stimulating hormone (TSH) presumably has an important role in the maintenance of thyroid growth and goitrogenesis. The observation that TSH-suppressive treatment may cause a reduction of goiter volume underlines the role of TSH as goitrogen factor.

DIAGNOSIS

SYMPTOMS AND SIGNS

The clinical symptoms of nodular goiter rely on the type of thyroid enlargement. Simple hyperplasia of the thyroid gland without compromising of adjacent structures is frequently associated with feeling of tightening or bulk in the neck. Larger multinodular goiters can cause compression or deviation of the trachea and esophagus leading to dyspnea, stridor, choking sensation and dysphagia. Particularly in goiters with mediastinal or thoracic extension leading to narrowing of the thoracic inlet signs of airway obstruction, distension of jugular veins and development of venous collaterals on the chest can be present. As a result of intrathyroidal hemorrhage particularly in a large preexisting cystic nodule, acute pain due to local extension can occur. Hoarseness caused by alteration of the recurrent laryngeal nerve, very firm and fixed nodules or enlarged cervical lymph nodes may imply malignancy. Depending upon regional dietary supply of iodine, the incidence of clinically relevant carcinoma in unselected patients with multinodular goiter is 1 to 4 % (2, 3).

LABORATORY TESTS AND INVESTIGATIVE IMAGING

In recent reports concerning the management of patients with multinodular goiter it has been shown that serum TSH and a total and/or free T₄ (tetraiodo-L-thyronine) assay are the *in vitro* diagnostic procedures most frequently performed in the initial investigation of patients with multinodular goiter (4, 5, 6). Additionally, evaluation of antithyroid peroxidase (anti-TPO) antibodies is recommended in order to rule out autoimmunity or autoimmune thyroiditis. Under consideration of cost-benefit, TSH determination alone provides sufficient information for accurate assessment of thyroid function.

There are controversial recommendations about routine measurement of serum calcitonin in the diagnostic evaluation of thyroid goiter. While several European groups advocate routine implementation of calcitonin testing in order to detect medullary car-

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cinoma at earliest stage, American clinicians recommend to measure this tumor marker only in individuals with a family history of thyroid carcinoma (7).

Beside physical examination and biochemical testing, several imaging procedures can contribute to the diagnostic accuracy. During the last decade ultrasonography (US) became the imaging method with first priority. The advantages of US are evident: superior sensitivity, high accessibility, high cost-effectiveness, no ionizing irradiation, and the non-invasive nature (8). Evidence of sonographic findings such as dominant hypoechoic nodules, thick or irregular "halo sign", microcalcifications, or increased intranodular blood flow are suggestive for malignancy and should be subjected to fine-needle aspiration biopsy (FNAB). Scintigraphy provides information regarding functional status of the thyroid and may be helpful in the estimation of retrosternal gland extension or identification of ectopic thyroid tissue. For evaluation of the function, the method seems to be of limited value for nodules smaller than 15 mm in diameter. Increased malignancy rate of dominant hypofunctioning lesions implies liberal use of FNAB. Computed tomography (without iodinated contrast agents) and magnetic resonance imaging are useful methods in the pre-operative assessment of suspected large retrosternal or intrathoracic goiters in order to select appropriate technical strategy.

Three recent surveys have shown that there is a substantial lack of consensus in approaches to the diagnosis and treatment of patients with multinodular goiters (4, 5, 6). The discrepancy exists not only between different countries but also between endocrinologists and surgeons (6). While in Europe and in North America all clinicians order TSH determination, free T_4 /index would be used only by 74.2 % of European and 54.3 % of North American clinicians. For 31.7 % of European clinicians but only for 3.6 % of those from North America, calcitonin assay is an essential part of biochemical evaluation. Ultrasound would be used by 84.2 % and only by 59.3 % of clinicians in Europe and in the United States, respectively. Altogether, North American physicians act much more restrictively as the Europeans do as regards diagnosis of the nodular goiter. Concerning the use of TSH, FNAB and ultrasonography, recommendations would be equal by endocrinologists and surgeons, however more endocrinologists than surgeons would employ antibody testing and scintigraphy and more surgeons than endocrinologists request CT or MRI.

TREATMENT

The available therapeutic options are therapy with thyroxine, radioiodine treatment, and surgery. The most striking indications for treatment are large goiters causing compression of vital neck structures or suspected malignancy. In an individual patient, intrathoracic goiter growth not accessible for accurate surveillance or cosmetic reasons may present the indication for treatment. Each treatment modality has its specific advantages and disadvantages.



Fig. 1. A 70-year-old patient with a long history of multinodular goiter. Significant local compression was the indication for surgical treatment.

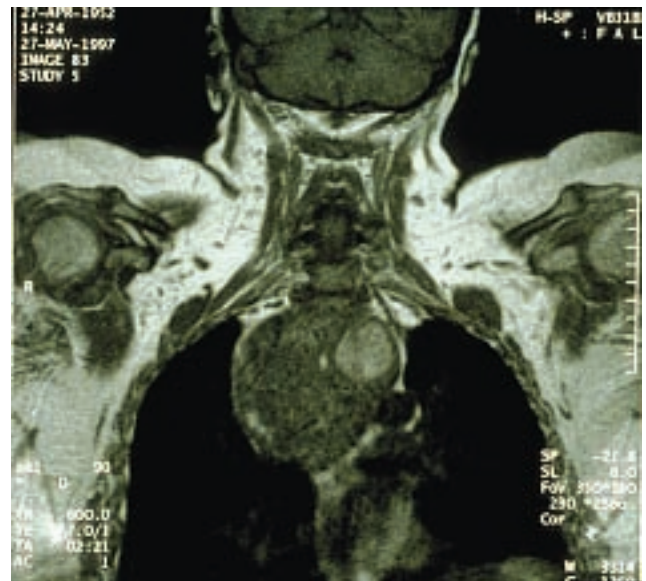


Fig. 2. T1-weighted MRI demonstrating a large recurrent intrathoracic goiter. The patient underwent previous subtotal thyroid resection for multinodular goiter. Ten years later dysphagia and stridor due to goiter recurrence occurred.

THYROXINE THERAPY

Treatment with thyroxine is easy to implement, however probably effective only in some patients with relatively small goiters. In the only randomized, placebo-controlled study in patients with small goiters (mean volume, 53 ml) a reduction of thyroid volume of more than 13 % was evident only in 58 % of the cases in the real arm and in 5 % of those in the placebo arm (9). Results of the studies showing positive effect of T_4 therapy in the presence of large goiters are not reliable since they include patients with insufficient dietary iodine intake or subclinical hypothyroidism. Particularly in elderly female patients with long-term suppressed serum TSH levels, cardiac side effects and decrease in bone mineral density

are well documented disadvantages of this therapeutic option.

RADIOIODINE THERAPY

Although several groups have reported on encouraging results of radioiodine treatment in non-toxic nodular goiters (10, 11), most clinicians restrict this therapy to hyperthyroid disorders. It has been shown that radiotherapy can lead to a mean reduction of thyroid volume (base line range, 73 to 269 ml) of 40 % after 1 year and up to 60 % after 5 years (11). Randomized studies on patients with large goiters, frequently harbouring a mixture of degenerated areas, colloid cysts and poorly functioning nodules do not exist, nevertheless one can presume that under this condition high doses of radioiodine and consequently in-hospital treatment are required. As side effects radiation-induced thyroiditis and autoimmune response are known. In up to 30 % of the patients treated permanent hypothyroidism and in approximately 10 % recurrent goiter will occur after mean follow-up ranging from 5 to 8 years. The life-time risk of cancer is probably negligible in patients over 65 years of age. Being aware of these limitations, in our experience ¹³¹I treatment can be recommended only in an individual patient with a small goiter or in elderly patients with markedly increased perioperative risk.

SURGERY

Most patients with multinodular goiter are candidates for surgical treatment. Bilateral thyroid resection is considered as a strategy of choice, however the extent of the resection is currently under controversial debate. The recommendations vary between organ preserving meticulous selective resection of entire pathologic tissue tailored to the situation found at surgery, ipsilateral lobectomy and contralateral subtotal resection, bilateral subtotal resection, near total thyroidectomy, and routine use of total thyroidectomy. Irrespective of the extent of the resection, virtually all goiters can be removed through a standard collar Kocher's incision. Only in a single patient with a large mediastinal or intrathoracic goiter sternotomy or lateral thoracotomy may be necessary.

Subtotal thyroid resection based on the morphologic changes within the thyroid gland still presents the standard treatment strategy for nodular goiter in several units (12, 13). The procedure, however, is burdened by a recurrence rate of 10 to 30 % and the necessity of reoperation which in general is associated with 3- to 10-fold increase in postoperative complications (14, 15). In 1990, Delbridge et al reported that in their center the peak incidence of secondary thyroidectomy for recurrent nodular goiter was registered 13 years after the peak incidence of subtotal thyroid resection for nodular goiter (14). The data forced the group to change their policy toward more radical approach in terms of total thyroidectomy. A decade later, the rate of secondary thyroid resections decreased in the same unit significantly. Based on

their observation, the Australian group recommended to consider total thyroidectomy as a preferred surgical approach for nodular goiter. Other centers increasingly became supporters of this opinion, especially as it became evident that total thyroidectomy can achieve the same low morbidity rate as subtotal resection (16, 17, 18). In addition, proponents of total thyroidectomy argue for routine total removal of the thyroid gland to avoid completion thyroidectomy in case of incidentally detected thyroid carcinoma (19).

Complication rates associated with thyroid resection depend upon the extent and nature of the underlying disease, the technique performed, the experience of the surgeon, and hospital operative volume. Beside meticulous operative technique under consideration of routine identification of recurrent laryngeal nerve and at least one parathyroid gland, numerous innovative technical tools such as bipolar coagulation forceps, magnifying glasses and monitoring of the laryngeal nerve have been introduced into endocrine surgery during the recent few years in order to achieve low morbidity rates. In experienced hands, the overall permanent surgical morbidity should nowadays amount to 1 % or less. A prospective multicenter study from Germany on 7266 patients undergoing thyroid surgery for benign goiter in units with different number of annual thyroid procedures revealed patient gender, recurrent goiter, extent of resection, hospital operative volume and recurrent laryngeal nerve identification to be factors that influence operative outcome (20). In a multivariate analysis routine identification of the recurrent laryngeal nerve was determined as the most significant risk factor irrespectively of the extent of the thyroid resection.

Recently it has been shown that minimally invasive surgery is feasible also in treatment of thyroid disorders. Compared with open cervicotomy, better cosmetic results and postoperative course should be the advantages of the procedure. Since the mean thyroid volume was only 16.1 ml (range, 5–38 ml) in one of the largest series published on this topic so far (21), presumably only a very small group of patients could be suitable candidates for this approach.

There is substantial disagreement among clinicians on treatment recommendations for optimal management of multinodular goiter. When a hypothetical 42-year old female patient with bilateral goiter (volume 50–80 g) and moderate local neck discomfort would be presented to a clinician, 65 % of the endocrinologists and 67 % of the surgeons would recommend no treatment, 22 % and 2 % of endocrinologists and surgeons, respectively would recommend therapy with thyroxine, 3 % of endocrinologists and no surgeons would support an indication for radioiodine treatment, and 10 % of endocrinologists and 31 % of surgeons would suggest thyroid resection. Of the surgeons, the vast majority would perform total thyroidectomy (6). Similar variations exist between different countries. While clinicians in Italy, France and Germany would favour thyroxine treatment, radioiodine therapy would be recommended in Denmark, and observation only in the United Kingdom. In

North America 36 % of the physicians would advocate no treatment and 57 % would recommend T₄ therapy.

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Received: November 9, 2004