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Multinodular Thyroid Disease

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Benign nodular thyroid disease constitutes a heterogeneous thyroid disorder which is highly prevalent in iodine deficient areas. On a general basis it is divided into solitary and multinodular thyroid disease.[1]

Multinodular goitre is the most prevalent thyroid pathological abnormality worldwide, although its geographical incidence varies greatly according to environmental iodization Most countries in central and southern Europe have endemic goitre areas with a prevalence of multinodular goitre (MG) of 3-6%. In United States, the annual incidence of nodular thyroid disease is 0.1% to 1.5% and the prevalence is 4-7%.[2] In older studies as in 1950's in Framingham, Massachusets 1% of persons in the age 30-59 yrs had a multinodular goitre. In Whickham in northeast England, palpable goitres were detected in 10% of adult women and 2% of adult men[3] Multinodular goitre refers to an enlargement of the thyroid with deformation of normal parenchymal structures by the presence of nodules. These nodules vary considerably in size, morphology and function. The development of nodular goitre is very likely a continuous process that starts with thyroid hyperplasia and simple goitre. The main epidemiological determinants are iodine deficiency, age, sex and duration of goitre in iodine deficient and also iodine sufficient areas.[1]

Thyroid nodules are discovered by palpation in 3-7% of the population. However on ultrasonography (US) it is noted in 20-76% and by autopsy in approximately 50%.[4] Increasing use of high resolution ultrasonography (HRUSG) over the last two decades has lead to an increasing prevalence of thyroid nodules in asymptomatic subjects. Moreover, 20-48% of patients with single palpable thyroid nodule are found to have additional nodules when investigated by HRUSG.[5] Prevalence increases linearly with age, exposure to ionizing radiation and iodine deficiency. Thyroid nodules are more common in women.[4]

In contrast to solitary nodular thyroid disease that has a more uniform clinical pathological and molecular picture, one finds a combination of hyperfunctional, hypofunctional or normally functioning lesions within the same thyroid gland.[3] The overall functional balance of these individual nodules determine whether patient has a euthyroid multinodular goitre (MNG) with normal TSH and free thyroid hormone levels or toxic multinodular goitre (TMNG). This can be overtly toxic with suppressed TSH and elevated free thyroid hormones or subclinical hyperthyroidism (low or suppressed TSH and normal free thyroid hormones). It is important to note that the functional status is not stationary and those who have had TMNG have been having a goitre of long standing

with euthyroidism. Moreover the status of TSH indicates that a critical level of thyroid autonomy has been reached.[3] The rate of progression from euthyroidism to thyrotoxicosis in patients with nodular goitres has not been studied extensively, but in two studies, the incidence of overt thyrotoxicosis was approximately 10% during 7-12 yrs of follow up.[3]

On functional grounds, nodules are classified as "cold", "normal" or "hot" depending upon whether they show decreased, normal or increased uptake on scintiscan. Approximately, 85% of all nodules are cold, 10% are normal and 5% are hot nodules.[1]

Non toxic goitre may be defined as a diffuse or nodular enlargement that is not associated with thyrotoxicosis and does not result from an autoimmune or inflammatory process. The term endemic goitre is used when prevalence in children 6-12 yrs of age within a population is more than 10%. Goitre is called sporadic when the prevalence is 10% or less.[3] The natural history of nontoxic goitre is characterized by gradual thyroid growth, nodule formation and development of functional autonomy.

Worldwide the most important environmental factor contributing to goitre is iodine deficiency. Since goitres also occur in individuals without iodine deficiency and not all individuals in an iodine deficient area develop a goitre, other suggested risk factors include cigarette smoking, infections, drugs and goitrogens.[6] The impact of smoking on thyroid disease could be due to increased thiocyanate levels which exert a competitive inhibitory effect on iodide uptake and organification.

Radiation is the other risk factor both for thyroid malignancy and nodular disease. An increased prevalence of nodular disease has been associated with exposure to radionuclear fallouts and therapeutic external radiation.[1]

Development of nodular disease is influenced by multiple environmental components interacting with constitutional parameters of gender and age. Multinodular goitre is probably a life long condition that has its inception in adolescence or at puberty.[7] In areas of iodine deficiency with a high prevalence of goitres, many prepubertal children have diffuse goitres although these may regress in early adolesence. In areas with a lower prevalence of goitre, goitrogenesis usually starts at an older age. With time, diffuse goitres tend not only to grow but also to become nodular.

Nodular disease is 5-15 times more frequent in females. At present it is believed to be a genetic susceptibility and/or a direct impact on steroid hormones. Estrogen has been shown to have a growth promoting effect in vitro in rat FRTL-5 cells and thyroid cancer cell lines[1] Also, 17 B estradiol has been shown to amplify growth factor induced signaling in normal thyroid and thyroid tumours. Use of oral contraceptives is associated with decrease in goitre but not nodules.

The thyroid enlargement in pregnancy has been related to iodine deficiency. In one German study the increased prevalence of multinodular goitre with parity was only observed in those women who had not taken iodine supplementation during an earlier pregnancy.[1]

Age : In a cross sectional study of patients with nontoxic goitre evidence for thyroid growth, nodular formation and development of functional autonomy with age was found. Thyroid volume was positively correlated with age and duration of goitre. Patient with MNG were older and had a large thyroid volume and significantly lower serum TSH concentration. In a borderline iodine deficient area, MNG was present in 23% of the studied population of 2656 Danish people aged 41-71 yrs and increased with age in women from 20-46% as well as in men.[1]

Thyroid Growth

The increased thyroid mass of a nontoxic goitre is mainly caused by excessive cell replication as demonstrated by the finding of a highly significant positive correlation between the total DNA content of nodular goitre and their weight. Histologically, the

newly generated cells appear to be mainly thyroid follicular cells and increase in interstitial tissue and colloid contribute little to the goitre growth.[3] Several growth stimulating factors (endocrine or paracrine) are thought to be of importance for the increased follicular cell replication.

Thyrotropin(TSH) is the main extra thyroidal growth stimulation factor and plays an important role in pathogenesis of iodine deficiency goitre.The first comprehensive theory about the development of multinodular goitre was proposed by David Marine and studied further by Selwyn Talyor.[7] He proposed that in response to iodine deficiency, the thyroid first goes through a period of hyperplasia as a consequence of the resulting TSH stimulation, but eventually, possibly because of iodine repletion or a decreased requirement for thyroid hormone, enters a resting phase characterized by colloid storage and the histologic picture of a colloid goitre. Marine believed that repetition of these two stages of cycle would eventually result in the formation of nontoxic multinodular goitre.

Since many patients with nontoxic goitre have normal serum TSH concentrations and that they grow despite administration of T4 in doses that reduce TSH below normal, it is suggested that other growth stimulating factors are involved in thyroid growth.

Growth factors such as insulin like growth factor–1,(IGF-1) epidermal growth factor (EGF) and fibroblast goitre factor (FGF) may be important for stimulation of thyroid growth.The expression of IGF-1 and FGF is increased in nodular goitres in humans.[3]

Expression of FGF-1 and 2 and FGF receptor-1 accompany thyroid hyperplasia and may play a role in the development of multinodular goitre.[7] Acromegalic subjects with elevated levels of serum growth hormone and IGF-1 and normal TSH levels have an increased prevalence of goitre.[6]

In vitro IG-1, EGF and FGI stimulate proliferation of thyroid follicular cells and in vivo, administration of FGF intravenously in rats resulted in an increased weight. In contrast, transforming growth factor (TGF) seems to inhibit thyroid growth. It acts as an autocrine growth inhibitor on follicular cells by inhibiting growth stimulating actions of TSH, IGF-1 and EGF. Tissue concentrations of TGF messenger RNA are lower in iodine deficient nontoxic goitres than in normal thyroid tissue.

Other factors promoting cell growth and differentiation identified in the last decade include cytokines, acetylcholine, norepinephrine, vasoactive intestinal peptide and substances of C-cell origin. It is however not known to what extent these compounds play a role in the genesis of multinodular goitre.[7]

In addition to and possibly modulated by extracellular stimulators of thyroid growth, some alterations in intracellular mechanisms related to the control of cell replication. (e.g. increased expression of protooncogenes such as the ras protooncogene) may contribute to the growth of non toxic goitres. Also, intrathyroidal depletion of iodine may stimulate follicular growth irrespective of the serum TSH concentration.[3]

Nodular Growth

Heterogeneity

In a normal thyroid gland, the growth potential and functional activity of individual cells within a single follicle varies. Immunohistochemical studies have demonstrated that only a small fraction of thyroid follicular cells contains the Na / iodine cotransporter.

Despite the heterogeneity in function between individual cells within normal follicles, the balance between thyroglobulin synthesis and endocytic activity in the follicle as a whole is finely tuned, so that the size of most follicles is similar. In contrast, the follicles of nontoxic goitre vary much more widely in both functions. Thus both iodine metabolism and growth rate of cells within newly formed follicles vary widely.[3] Large colloid rich follicles and small follicles co exist in most non toxic goitres.

It is assumed that during formation of non toxic goitre the stimulation of follicular cells by TSH or other thyroid growth stimulating factors is relatively weak. Hence only a small fraction of follicular cells namely those with a high growth potential, will enter the mitotic cycle and contribute to the formation of new follicles. These cells transfer their high growth potential to their daughter cells and the number of replicating cells increases progressively.

Follicular cells with a high growth potential are not evenly distributed within the thyroid gland and after replication their daughter cells remain clustered. Therefore nontoxic goitres become increasingly nodular with time. There is evidence that rapidly replicating cells remain clustered during goitrogenesis as demonstrated by X-chromosome inactivation analysis that some macroscopic nodules within a nontoxic goitre are monoclonal. Despite their monoclonal nature, nodules may contain morphologically and functionally heterogeneous follicles.[2,6]

The growing thyroid gland also requires expansion of blood vessels. However the newly formed capillary network is often fragile and unable to supply the growing thyroid tissue adequately. This leads to areas of hemorrhagic necrosis within goitre. The necrotic areas are invaded by granulation tissue, ultimately resulting in fibrosis, scarring and even calcification. The resulting network of inelastic strands of connective tissue interferes with smooth growth of thyroid parenchyma and will further increase the formation of macroscopic nodules. Further the distended follicles may fuse to form colloid cysts which are characteristic of non toxic goitres.[3]

If a group of follicles generated in this way grows large enough, it may become visible as a hot or cold area on thyroid scintigraphy depending on the degree of activity of its iodine metabolism. The iodine metabolism of particular areas within a nontoxic goitre and their growth behaviors are not necessarily parallel. The areas of increased or decreased iodine uptake do not necessarily correspond to thyroid nodules detected by physical examination or ultrasonography.

Development of Functional Autonomy

Some normal thyroid follicular cells take up and organify iodine in the absence of TSH during goitrogenesis, the number of cells with functional autonomy increases especially when the cells have a replicating capacity.[3] The increase in the total mass of follicular cells with autonomous iodine metabolism during goitre growth would explain why a patient with nontoxic goitre can develop subclinical and later overt thyrotoxicosis.

The hypothesis that the development of thyroid autonomy is due to a gradual increase in the number of cells having relatively autonomous thyroid hormone synthesis is supported by the 27% prevalence of impaired TSH responses to TRH in patients with nodular goitre as opposed to such responses in only 1 of 15 patients with diffuse goitre.[7] The fact that it is possible to induce hyperthyroidism in some patients with multinodular goitres by administration of iodide suggests that certain nodules are autonomous but unable under normal iodine intake to concentrate sufficient iodide to cause hyperthyroidism.

Prevalence of thyroid autonomy correlates with increased thyroid nodularity and increases with age. Correction of iodine deficiency in a population results in a decrease of thyroid autonomy as demonstrated by the impressive 73% reduction in prevalence of TMNG only 15 yrs after doubling of iodine content of salt in Switzerland.[1]

Iodine deficiency as the sole factor responsible for goitre seems an oversimplification. The role of genetic factors is suggested by several lines of evidence such as

the clustering of goitres within families

the higher concordance rate for goitres in monozygotic than in dizygotic twins

the female/male ratio (1:1 in endemic vs 7:1 to 9:1 in sporadic goitres)

the persistence of goitres in areas where a widespread iodine prophylaxis program has been properly implemented.

Goitre should thus be regarded as a complex trait in which both genetic susceptibility and environmental factors probably contribute to the development of disease.[6]

Mutations

In recent years, activating mutations in TSH receptor have been found in hyperfunctioning nodules of TMNG. So far mutations in MNG have only been found in the TSH-receptor (TSHR) gene, and not in the Gs-alpha of TMNG. Different somatic mutations are found in exon 9 and 10 of the TSHR gene and the majority of mutations that are present in toxic adenomas are also found in toxic nodules of multinodular goitre. Sometimes, different toxic nodules in the same multinodular goitre harbor different mutations. An important fact is the finding of a germline mutation of codon 727 of the TSHR gene that is specially associated with MNTG.[7]

Three dominant MNG loci have been identified in familial MNG i.e. MNG 1, 2 and 3. In MNG 1 a major locus was identified on chromosome 14q by a genomic search on a single large Canadian family with 18 cases of nontoxic multinodular goitre.[6,7] In the analysis of an Italian three-generation pedigree with familial MNG 2, including 10 affected famales and 2 affected males, an X-linked autosomal dominant pattern of inheritance was hypothesized and confirmed. The locus maps to chromosomeXp 22 A third locus,MNG 3 for a dominant form of familial multinodular goitre was detected on 3q26.1-q26.3 in two independent Japanese families. This variant was characterized by congenital hypothyroidism.[7]

Multinodular goitre is considered a nonautoimmune thyroid disease and there have been findings to support these hypothesis. However, several immunological alterations have been found in patients with multinodular goitres such as HLA-DR antigen expression in thyrocytes, the presence of growth stimulating iimmunoglobulins, increase in dendritic cells and lymphocytes which suggest the possibility of autoimmune problems although these findings may be an epiphenomenon of other primary defects in immunoregulation.

In a study for the association between HLA and multinodular goitre performed on 90 patients of MG with a mean evolution time of goitre of more than 6 yrs who underwent surgery (pressure symptoms or progressive increase in size or on patient's request) vs 100 controls, a significant association was found between the lower incidence of HLA –Cw allele and the appearance of goitre (15.5% vs 8.3% respectively; $p = .001$; $RR = 0.49$). These results suggest that HLA-Cw 4 allele can act as a protector against the development of MG as it occurs less frequently in the population with MG and those with this allele develop smaller goitres with no intrathoracic component.[2]

Clinical Implications

The natural development of MG is characterized by progressive thyroid growth. It can owing to its anatomic location, expand to jeopardise neighboring structures and lead to different compression symptoms, some of which are potentially fatal. The most common are tracheal and esophageal compression, followed by recurrent and superior vena cava syndrome.

Most patients, however are asymptomatic with a mass discovered by a physician on routine neck palpation or by the patient during self-examination. Nearly 70% of cases of sporadic nontoxic goitre complain of neck discomfort; the remainder have cosmetic concerns or fear of malignancy. Diagnostic evaluation of nodular goitres begins with a detailed patient history and careful thyroid palpation. Many disorders benign and malignant can cause thyroid nodules as listed in Table 1.

An inquiry should be made about family history of benign or malignant thyroid disease. Thyroid cancer (medullary thyroid carcinoma [MTC] or papillary thyroid carcinoma [PTC], multiple endocrine neoplasia type 2, familial polyposis coli,

Table 1 : Common causes of thyroid nodules

Benign
Colloid nodule
Hashimoto thyroiditis
Simple or hemorrhagic cyst
Follicular adenoma
Subacute thyroiditis
Malignant
Primary
Follicular cell-derived carcinoma:
PTC, follicular thyroid carcinoma, anaplastic thyroid carcinoma
C-cell-derived carcinoma:
MTC
Thyroid lymphoma
Secondary
Metastatic carcinoma

Cowdens disease and Gardener's syndrome are rare disorders but have to be considered. History of exposure to radiation in childhood to the head, face and neck should be especially asked for (Table 2).

Multinodular goitre with compression symptoms has a clinical profile different from that of goitre without these symptoms. Many of the symptoms of large multinodular goitre are chiefly due to the presence of an enlarging mass in the neck and its impingement upon the adjacent structures. There may be dysphagia, cough, and hoarseness. Paralysis of a recurrent laryngeal nerve may occur when the nerve is stretched taut across the surface of an expanding goitre, but this event is very unusual. When unilateral vocal cord paralysis is demonstrated, the presumptive diagnosis is cancer. Pressure on the superior sympathetic ganglions and nerves may produce a Horner's syndrome.

In a retrospective study of 157 patients of MG with compression symptoms who underwent surgery multinodular goitre was characterized by a series of distinguishing features from 512 cases of MG with no compressive symptoms: they were older (mean age 56 vs 46 $p < .001$); longer evolution time (mean128 vs 78 mths) and

Table 2 : Increased risk of malignancy in thyroid nodule

- History of childhood head/neck irradiation
- Family history of PTC, MTC, or multiple endocrine neoplasia type 2 (MEN2)
- Age < 20 or > 70 years
- Male sex
- Enlarging nodule
- Abnormal cervical adenopathy
- Fixed nodule
- Vocal cord paralysis

higher frequency of intrathoracic component; chest radiography showing tracheal displacement. Airway compression was the commonest and serious problem. Esophageal compression can occur and is more often reported when the extension is posterior. In this study the incidence of recurrent symptoms was high.[8] Uncommon compression symptoms included superior vena cava syndrome and Horner's syndrome. The surgical treatment of MG with compression symptoms has a higher rate of sternotomy and morbidity.

As the gland grows it characteristically enlarges the neck, but frequently the growth occurs in a downward direction, producing a substernal goitre. A history sometimes given by an older patient that a goitre once present in the neck has disappeared may mean that it has fallen down into the upper mediastinum, where its upper limit can be felt by careful deep palpation. Hemorrhage into this goitre can produce acute tracheal obstruction. Sometimes substernal goitres are attached only by a fibrous band to the goitre in the neck and extend downward to the arch of the aorta. They have even been observed as deep in the mediastinum as the diaphragm.

A significant proportion of patients with nodular thyroid glands develop thyrotoxicosis, and this is directly related to the duration of the goitre. Typically, the thyrotoxicosis comes about so insidiously that the patient is often unaware of the symptoms. Emotional lability, heightened neuromuscular activity, increased metabolic rate, cardiac irritability and tachycardia, and increased

Table 3 : Thyroid ultrasonographic examination

Not indicated
• As screening test in general population
• In patient who has low risk for thyroid cancer and normal thyroid on palpation
Indicated
• In a patient who has a palpable nodule
• In a patient who has history of neck irradiation
• In a patient who has a family history of MTC, MEN2, or PTC
• If unexplained cervical adenopathy is present

motility of the intestine are seen, as in Graves' disease, but infiltrative ophthalmopathy is absent.

Certain features are much more prominent than in Graves' disease, perhaps because the disease usually appears first in the fifth through seventh decades Congestive heart failure occurs, and is often resistant to the usual therapeutic measures. Recurrent or permanent atrial fibrillation, or recurrent episodes of atrial tachycardia may dominate the picture. In fact, thyrotoxicosis should be carefully excluded in any goiterous adult with congestive heart failure or tachyarrhythmia. Occasionally muscle weakness is so severe that the patient is unable to climb stairs, or even to walk, when few other symptoms or signs of the disease have become manifest.

The clinical importance of thyroid nodules, besides the infrequent local compressive symptoms or thyroid dysfunction, is primarily the possibility of thyroid cancer, which occurs in about 5% of all thyroid nodules regardless of their size. Because of the high prevalence of nodular thyroid disease, it is not economically feasible or clinically necessary to perform a complete structural and functional assessment for all or even most thyroid nodules. Therefore, it is essential to develop and follow a systematic, cost-effective strategy for diagnosis and treatment of thyroid nodules and to avoid unnecessary, potentially harmful surgery.

Roentgenographic examination is useful in defining the extent of tracheal deviation and compression is frequently seen but rarely is functionally significant.

It is recommended that all patients who have a nodular thyroid, with a palpable solitary nodule or a multinodular goitre (MNG), be evaluated by ultrasonography (Table 3). Newly diagnosed thyroid nodules should be evaluated primarily to rule out thyroid malignancy. Sonographic examination should be ordered for all patients who have a history of familial thyroid cancer, multiple endocrine neoplasia type-2, or childhood head/neck irradiation, even if the thyroid appears normal by palpation (Table 3). The finding of adenopathy suspicious for malignancy in the anterior or lateral neck compartments warrants US examination of the lymph nodes and thyroid because of the risk of nodal metastasis from an otherwise unrecognized papillary microcarcinoma.

Thyroid micronodules that are not clinically apparent (14%-24% of those with a diameter > 10 mm) are detected by US in about half (27%-72%) of the women evaluated.[4] The prevalence of cancer ranges from 5.4% to 7.7% in studies regarding the cytologic evalution of nonpalpable thyroid lesions and seems to be similar to that reported for palpable lesions (5.0%-6.5%).

Although no single US characteristic can unequivocally distinguish benign and malignant nodules several features have been studied to predict malignancy. Nodule size is not predictive of malignancy. The risk of cancer is not significantly higher for solitary nodules than for glands with several nodules.The specificity for US features for diagnosing cancer varies from 85-95% for microcalcifications and 83-85% for an irregular or indistinct nodule margin.[4]

Color Doppler US evaluates nodule vascularity. The assumption is that hypervascularity with chaotic arrangement of blood vessel favors malignancy whereas peripheral flow indicates a benign nodule (specificity of about 81%).

Complex thyroid nodules have solid and cystic components, often with a dominant cystic part and are frequently benign. These lesions are common, frequently smaller than 3-4 cms in diameter and

Table 4 : Indications for ultarasonography fine-needle aspiration

• Palpation-guided FNA nondiagnostic
• Complex (solid/cystic) nodule
• Palpable small nodule (< 1.5 cm)
• Impalpable incidenteloma
• normal cervical nodes
• Nodule with suspicious US features

asymptomatic. Cytology is necessary to document morphology because some PTCs(Papillary thyroid carcinomas) are cystic.

MRI and CT are not recommended for routine use but are of value to assess size, substernal extension and positional relationsihip of the goitre to surrounding structures. Contrast media containing iodine should be used with caution because it decreases subsequent iodine I131 uptake.

Positron emission tomography with fluorodeoxyglucose may add functional information to anatomic visualization provided by US. The high cost of these procedures makes them impractical for routine clinical assessment of thyroid nodules.

Fine needle aspiration biopsy

Thyroid FNA biopsy is the most accurate test for determining malignancy and is an integral part of thyroid nodule evaluation. In glands with multiple nodules, selection for cytology(FNAC) should be based on US features rather than on size or clinically "dominant" nodules (Table 4). A marked hypoechogenicity of a solid lesion on USG of a nodule may suggest malignancy and warrants FNAC from that site.

FNAC results are categorized as diagnostic (satisfactory) or adequate if it contains no less than six groups of well-preserved thyroid epithelial cells consisting of at least 10 cells in each group. Nondiagnostic or unsatisfactory smears with an inadequate number of cells result from acellular cystic fluid, bloody smears, or poor techniques in preparing slides. The most common benign diagnosis is "colloid nodule," which may come from a normal thyroid gland, a benign nodule, an MNG, or a macrofollicular adenoma.

Table 5 : Ways to minimize false-negative results

• Follow-up cytologically benign nodules
• Aspirate multiple nodule sites
• Aspirate multiple nodule sites in MNG
• Submit cyst fluid for examination
• Review slides with experienced cytopathologist

Overall, 70% of FNA specimens are benign, 5% malignant, 10% suspicious, and 15% unsatisfactory. The final FNA report is critical in dictating whether the patient's management should be medical or surgical. FNA has improved patient selection for thyroidectomy, such that cancer yield at surgery has increased from 15% before the use of FNA to 50% with FNA use. The sensitivity and specificity of FNA in experienced hands are excellent. A major concern with FNA is the possibility of a false-negative result (i.e., a missed malignancy). Although the false-negative rate ranges from 1% to 11%, it is less than 2% in most clinics with adequate FNA experience. Table 5 illustrates some suggestions for minimizing false-negative results.

FNAC causes only mild temporary pain and occasionally a minor hematoma. No seedling of tumor cells in the neck track have been reported. It is a safe, useful and cost effective procedure . Rebiopsy is suggested only on a enlarging nodule, a recurrent cyst or a nodule showing no response to suppressive therapy (Table 5).

An important recent advance is the demonstration that thyroglobulin can be measured in lymph nodes or nodular aspirates and is useful in thyroid cancer practice. To measure Tg, the needle is rinsed with 1 ml of normal saline solution immediately after FNA biopsy and Tg is measured by immunoradiometric or chemiluminescence assays. Several molecular markers and assays have shown promise in clarifying suspicious FNA results.

Serum Tg concentration correlates with iodine intake and the size of the thyroid gland rather than with nature and function of the nodule. Since Tg measurements do not influence management,

measurement of Tg is seldom used in nodule diagnosis.[4]

Measurement of serum TSH is the most useful test in the initial evaluation of thyroid nodules. Third generation TSH assays, with detection limits of about 0.001 mIU/ml should be used in clinical practice. The measurement of free thyroid hormones and thyroid peroxidase antibodies (TPO Ab) should be the second diagnostic step. Occasionally, a nodular goitre may represent Hashimoto's thyroiditis.

Serum calcitonin is a good marker for C-cell disease and correlates well with tumor burden. It should be measured in patients who have a family history of MTC, MEN 2 or pheochromocytoma or when FNA suggest MTC. Normal levels are less than 10pg/ml.

Radioisotope scanning

Thyroid scintigraphy can be performed with 99m TcO4 or123 I, although the latter is preferred. Thyroid scanning is the only technique that allows for assessment of thyroid nodular function and detects areas of autonomy. Based on the uptake, nodules are classified as hyperfunctioning "hot" or hypofunctioning "cold". Hot nodules are seldom, if ever malignant, whereas the reported cancer risk is 5-15% in cold nodules. The diagnostic specificity is decreased in small lesions (< 1 cm) which may not be identified on scanning.

The role of scintigraphy in the diagnostic work-up of thyroid nodules is generally limited to.

a. a single nodule with suppressed TSH, in which case no FNA is necessary
b. a large toxic or nontoxic MNG, especially with substernal extension
c. when searching for ectopic thyroid tissue,such as struma ovari, sublingual thyroid

Management

If the enlargement of the gland is moderate, there are no symptoms and serum TSH is normal, therapy is not required. If there are symptoms due to pressure, if patient is disturbed by appearance of the goitre, if there is growth of one nodule, or possible toxicity develops, diagnostic measures and treatment are necessary.

Thyroxine therapy may be effective in reducing the thyroid volume in patients with diffuse nontoxic goitres, as measured by ultrasonography. Nonrandomized studies suggest that it is also effective in some patients with multinodular goitres.

Only two randomized trials on the effect of T4 therapy in patients with nontoxic goitre using objective thyroid volume measurements have been reported. In placebo controlled double– blind randomized trial in patients with relatively small nontoxic multinodular goitres, thyroid volume, as measured by ultrasonography, decreased substantially in 58% of the T4 treated patients, as compared with 5% of those given in placebo; the mean decrease in thyroid volume in patients who responded was 25% after 9 months of T4 treatment. Goitre size returned to baseline within 9 months after discontinuation of therapy, demonstrating that maintenance of volume reduction requires long term T4 treatment. In a more recent study, a significant decrease in goitre size was observed in 43% of patients after 2 years of T4 therapy. In nonresponders, a mean increase in thyroid volume of 16% was found.

Attempts to reduce multinodular goitre by administrating large suppressive doses of thyroid hormone are usually little or not effective and carry the risk of inducing thyrotoxicosis if autonomy of thyroid function is already present. Although this form of treatment is still being used, it is dangerous for the elderly. .

After surgical removal of nodular goitre, it seems theoretically sound to give the patient minimally replacement or suppressive doses of thyroid hormone to suppress TSH production and prevent regeneration of the goitre. However this form of therapy is controversial. Although in one report no recurrences were found during thyroid hormone administration,

in more recent studies others found no difference between untreated and patients treated with thyroid hormone after operation. In one of these studies carried out over 9 years, no effect of T4 treatment after thyroidectomy was seen in 104 patients operated for nontoxic goitre (the recurrence rate was 9.5% with treatment compared with 11.3% in untreated patients). If re-growth occurs, early ablative treatment with 131 I should be considered.

There is no place for administration of iodide in sporadic multinodular goitre. It generally has little or no beneficial therapeutic effect, and in an occasional patient may be followed by rise in plasma hormone concentration and symptoms of thyrotoxicosis. This condition is the 'Jodbasedow' phenomenon, and is dependent on autonomy of function of some elements of the goitre. Its occurrence is not confined to regions of iodine deficiency and is seen on occasion wherever iodide is administered to patients with well established multinodular goitre. This should be remembered when elderly patients are subjected to CT, MRI and administered radiographic contrast media.

Management

Clinical management of thyroid nodules is influenced by the combined results of TSH measurement. FNA biopsy, and US and depends primary on cytologic diagnosis.[4]

Fine-needle aspiration-positive nodule

If cytologic results are positive for primary thyroid malignancy, surgery is almost always needed. Cancer due to metastasis requires further investigations aimed at finding the primary lesion, which often precludes thyroid surgery. If preoperative FNA results suggest PTC, a near-total or total thyroidectomy is preferred.

Fine-needle aspiration-negative nodule

Administration of T4 with TSH suppression is aimed at shrinking nodule size, arresting further nodule growth and preventing the appearance of new nodules.

The use of T4 should be avoided for large thyroid nodules or long-standing goitres, particularly if the TSH value is less than 0.5 mIU/ml; in postmenopausal women or persons older than 60 years; and in patients who have osteoporosis, cardiovascular disease, or systemic illnesses. T4 treatment induces a clinically significant volume reduction only in a minority of patients and parameters of such a response are not known.

Fine-needle aspiration-suspicious nodules

Overall, about 20% of indeterminate specimens are malignant, but cancer risk varies from 15% for "follicular neoplasm" to 60% for "atypical PTC" specimens. It is generally agreed that cytologically suspicious lesions are to be surgically excised.

Fine-needle aspiration-nondiagnostic nodule

Despite experienced centres, repeat biopsy and US-FNA, a residual 5% of nodules remain nondiagnostic, which creates a management dilemma for the clinician. Nondiagnostic, large ($>$ 3-4 cm), recurrent cysts or solid nodules should be treated surgically.

Therapeutic techniques

Surgery

Surgical options include lobectomy plus isthmectomy for a benigh nodule, less than total thyroidectomy for MNG and near-total or total thyroidectomy for malignant disease. Frozen section should be performed at the time of surgery to help guide surgical decision making but may be of limited use in distinguishing benign from malignant follicular lesions.

Radioiodine

Toxic nodular goitres are usually more radioresistant than toxic diffuse goitres and higher I doses (30-100 mCi) may be needed for successful treatment. The aim of radioiodine treatment is the ablation of thyroid autonomy, restoration of normal thyroid function and reduction of thyroid mass. Although rare (occurring in $<$ 1% of patient), immunogenic hyperthyroidism may occur due to induction of

TSH receptor autoantibodies after I treatment of toxic nodular goitre. I therapy can be repeated after 6 months if thyrotoxicosis is not cured, as documented by persistent low TSH levels. It is not the treatment of choice if compressive symptoms are present, in larger nodules requiring high doses of I (which may be resistant to treatment or if an immediate resolution of hyperthyroidism is medically indicated.

Recombinant human thyroid-stimulating hormone

The administration of small doses (0.1 - 0.3mg) of recombinant human TSH (rhTSH) to patients who have low-uptake MNG increases I uptake by more than 4-fold in 24 to 72 hours. This allows for delivery of sufficient radiation to the thyroid to cause a decrease in size and amelioration of compressive symptoms within 2 months. As in patients who have high-uptake MNG, the average decrease in goitre size is 40% and 60% by the end of the first and second years, respectively.

Nonsurgical minimally invasive procedures

Percutaneous ethanol injection (PEI) is a US-guided, mini-invasive procedure that has been used for the nonsurgical management of some thyroid nodules.

Thyroid cysts : PEI is an effective alternative to surgery in the treatment of complex nodules with a dominant fluid component. Aspiration of thyroid cysts decreases the volume, but recurrences are common, and surgery is often required to remove large, relapsing lesions. Prospective randomized studies have shown that PEI is significantly superior to aspiration alone in reducing nodule volume. A reduction of greater than 50% of the baseline size is obtained in nearly 90% of cases treated with PEI.

Cold Solid Nodules : A clinically significant decrease in nodule size after PEI has been reported in patients who have been having, solitary, solid nodules that are cold on scintigraphy.

Laser thermal ablation : PLA is a minimally invasive procedure that is proposed as an alternative to surgery for thyroid nodules causing local symptoms or cosmetic concern. With guidance and after local anesthesia, a 21-gauge needle is carefully inserted into the thyroid mass, and a thin optical fiber is advanced into the needle sheath. The fiber tips are seen as hyper echoic spots and the area to be treated appears as an echogenic area enlarging over time on US.

Adverse effects of PLA include burning cervical pain, which decreases rapidly as the energy is turned off. Localized pain can be treated with oral analgesics. Other problems, such as permanent dysphonia, skin burning, or damage to neck structures, have not been observed. PLA is an outpatient procedure that lasts about 30 minutes, and patients can be dismissed shortly after the treatment.

Radiofrequency ablation : RF is under evaluation as a nonsurgical therapeutics modality for the ablation of benign and malignant thyroid lesions.

Summary

Multinodular thyroid disease is perhaps the commonest of all thyroid disorders in clinical practice worldwide. It is highly prevalent in iodine deficient areas and possibly has its inception in adolescence or puberty. Nodules larger than 1 cm may be detected by palpation. Genetic heterogeneity of normal follicular cells and acquisition of new inheritable qualities of replicating cells are the primary factors for nodular disease.

The goitre may well give rise to local discomfort and may, in case of large goitres, cause mechanical obstruction of the upper airway. Goitres have an annual growth potential of up to 20%, which can complicate treatment, if it is delayed, more often then requiring surgery. Progressive autonomous function of thyroid nodules can cause overt thyrotoxicosis in 5–10% of multinodular goitre patients within a 5-yr period. Even more frequently, patients develop subclinical thyrotoxicosis with its potential for osteoporosis and atrial fibrillation. Finally,

Table 6 : Indication for repeat biopsy

- Follow-up of benign nodule
- Enlarging nodule
- Recurrent cyst
- Nodule > 4 cm
- Initial FNA nondiagnostic
- No nodule shrinkage after T4 therapy

Table 7 : Thyroxine-suppressive therapy for benign nodules

Not recommended:

- As routine treatment
- If TSH < 0.5 mlU/mL
- In large nodule or MNG
- For postmenopausal women
- In patients with cardiac disease

Table 8 : I therapy for nodular thyroid

- An effective alternative to surgery for patients with high-risk or previous thyroidectomy
- Can be effective in toxic and nontoxic MNG
- Risk of malignancy in residual thyroid tissue unknown

Contraindicated in pregnancy and lactation

Table 9 : Management of Nodules

Thyrotoxic hot nodules	Lobectomy,or Iodine131 therapy or sclerotherapy
Mainly cystic	Aspirate for diagnosis and therapy
	Reaspirate as needed, T 4 therapy, Resection
Other nodules	Aspiration cytology --- probable cancer--Operate
	Inadequate specimen --- reaspirate
	Suspicious or hypercellular ---Operate
	Benign ---- Follow up with/without T4 therapy
	And periodic examination

Table 10 : Advantages and disadvantages of the treatment options in nontoxic multinodular goitre

	Advantages	Disadvantages
Surgery	Significant goitre reduction	Inpatient
	Rapid decompression of trachea	High cost
	Prompt relief of symptoms	Surgical risk
	Definite histological diagnosis	Vocal cord paralysis: ~1%
		Hypoparathyroidism: ~1%
		Risk of hypothyroidism dependent of resection
		Risk of recurrence dependent of resection
^{131}I	Most often outpatient	Limitation of administrated radioactivity
	If outpatient: low cost	Restricted proximity to other persons
	Few subjective side effects	Contraceptives needed in fertile women
	Goitre reduction: 50% within 1 yr	Gradual reduction of the goitre
	Improves inspiratory capacity in long term	Decreasing effect with increasing size
	Can be repeated successfully	Small risk of acute goitre enlargement
		Risk of thyroiditis: 3%
		Risk of transition into Graves' disease: 5%
		1 yr risk of hypothyroidism: 15–20%
		Long-term cancer risk unknown
L-T_4	Outpatient	Low efficacy
	Low cost	Lifelong treatment
	May prevent new nodule formation	Adverse effects (bone, heart)
		Not feasible when TSH is suppressed

thyroid cancer is present in approximately 5% of multinodular goitre patients, which is comparable to the risk in solitary thyroid nodules.

Management of multinodular goitre patients by clinicians is not uniform. Differences in the availability and cost of the various biochemical tests as well as the accessibility of the imaging methods and treatment options without a doubt play a significant role in this setting. After serum TSH measurement, USG and FNAB is the diagnostic test most often employed. Usefulness of FNAB to exclude thyroid malignancy no doubt depends on

the cytopathological expertise available. Routine measurement of calcitonin is not recommended.

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