Endocrinology

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Diagnosis and treatment of thyroid nodules and goitre

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Thyroid nodules and goitre are common, population screening in the UK indicating an 8.6% prevalence of palpable enlargement of the thyroid. The frequency of thyroid enlargement increases with age and is more common in women than in men. Nodular thyroid disease is even more common than population screening studies suggest; nodules are found in 50% of thyroid glands examined post-mortem, and high resolution ultrasound scans reveal a similarly high prevalence of nodules, most of which are not detectable clinically.

Thyroid cancer is rare, accounting for less than 0.5% of new malignancies diagnosed in England and Wales each year. The challenge facing the clinician is to identify the tiny proportion of patients with goitre or nodular thyroid disease who harbour malignancy and require definitive surgical treatment.

Assessment of thyroid size and other clinical features

Thyroid enlargement may be associated with obstruction of the upper airways or other structures within the mediastinum. Symptoms of choking, breathlessness and noisy breathing may indicate upper airways obstruction, although obstruction may be present in the absence of such symptoms. Radiological assessment of thyroid size is not indicated routinely, but in symptomatic patients plain X-ray of the thoracic inlet may reveal both deviation and narrowing of the trachea. Computed tomography scanning or magnetic resonance imaging provides more detailed and accurate information. Functional obstruction of the upper airways can be investigated by measurement of a respiratory flow loop (Fig 1). If available, it is the investigation of choice; it is quick and easy to perform, and provides a specific and sensitive means of detecting extrathoracic airways obstruction and differentiation from intrathoracic airways disease.

Physical findings such as hoarseness of the voice, fixation of the thyroid to local structures and lymphadenopathy are uncommon but nearly always indicative of malignant pathology. Obstructive symptoms and signs may, however, result from a large benign multinodular goitre, while a simple thyroid cyst may lead to rapid thyroid enlargement. Thyroid enlargement in a male should always be treated with suspicion. Although less common in males overall, a greater proportion of goitres and nodules are due to neoplastic disease. Risk factors for the development of malignancy include

Figure 1. Respiratory flow loop examination in a patient with goitre before and after thyroidectomy. Marked truncation of the inspiratory and expiratory limbs is observed in the pre-operative picture.
previous external irradiation to the neck and a family history of thyroid cancer, especially medullary cancer which is familial in 20–25% of cases.

Biochemical assessment

Free thyroxine and thyroid-stimulating hormone

Measurement of serum concentrations of free thyroxine (T4) and thyroid-stimulating hormone (TSH) is essential to identify patients with hyper- or hypothyroidism:
- Overt thyroid dysfunction effectively rules out a diagnosis of thyroid malignancy, and treatment for hyper- or hypothyroidism often results in goitre shrinkage.
- Suppression of serum TSH in the absence of a rise in free T4 or free triiodothyronine is a frequent finding in otherwise euthyroid patients with goitre or nodule(s) and does not indicate the need for specific antithyroid treatment.

Thyroid antibodies

Measurement of thyroid antibodies (thyroglobulin and microsomal or thyroid peroxidase) may indicate an underlying diagnosis of autoimmune thyroid disease, but the presence of antibodies does not obviate the need for a pathological diagnosis.

Serum thyroglobulin

Measurement of serum thyroglobulin is an accurate tumour marker in patients who have had definitive treatment for differentiated thyroid cancer. It is unhelpful in the investigation of subjects at presentation because elevated values are found in benign diseases of the thyroid.

Serum calcitonin

Measurement of serum calcitonin is a valuable diagnostic marker in medullary thyroid cancer and should be performed in those with a family history of medullary cancer or multiple endocrine neoplasia syndrome type 2. Its role in the screening of unselected patients presenting with thyroid enlargement is unproven.

Imaging of the thyroid

Radionuclide scanning

$^{99m}$Tc$^m$-pertechnetate is the radionuclide most frequently employed in thyroid imaging. Pertechnetate ions are trapped by the thyroid in the same way as iodine but are not organified, in contrast to the more expensive isotope $^{123}$I which is both trapped and organified. Although thyroid malignancies do not concentrate isotopes and thus appear ‘cold’, less than 20% of ‘cold’ lesions represent thyroid cancers, the remainder being due to simple colloid lesions, haemorrhage, cysts or inflammatory lesions such as Hashimoto’s thyroiditis.

Radionuclide scanning is thus poorly specific (and sensitive) in the diagnosis of thyroid malignancy, as illustrated by a meta-analysis of 22 studies including a total of 5,000 patients with nodular thyroid disease who underwent surgery. Of the lesions removed, 84% were ‘cold’, 10.5% ‘warm’ and 5.5% ‘hot’, with malignancy found to be present in 16%, 9% and 4% of ‘cold’, ‘warm’ and ‘hot’ nodules, respectively. Thus, most ‘cold’ lesions are benign, and the presence of a ‘warm’ or ‘hot’ nodule does not exclude malignancy. As a result of these findings, many centres have now abandoned the routine use of thyroid scintigraphy.

Ultrasonography

Lesions in the thyroid as small as 1 mm in diameter can be detected by high-resolution ultrasonography, which is thus much more sensitive than palpation. Furthermore, many nodules thought clinically to be solitary on palpation are shown on scanning to be multiple. Data on the incidence of malignancy in multinodular goitre and solitary nodules relate to clinically defined lesions, so it is unclear whether the presence of multiple nodules detected ultrasonographically reduces the likelihood of malignancy associated with nodules considered ‘solitary’ on palpation. In general, the pathological significance of small impalpable lesions on ultrasound is unknown.

Ultrasonic scanning accurately differentiates solid from cystic lesions. Purely cystic lesions with a thin wall are generally innocuous, but most cysts

Key Points

- Thyroid nodules and goitre are very common. Thyroid cancer is rare. The challenge is to spot the few patients who need surgery among the many who don’t
- All patients with thyroid enlargement need biochemical assessment for hyper- and hypothyroidism
- Obstructive symptoms (eg from tracheal compression) call for intervention. A respiratory flow loop is a sensitive and specific test for upper airway obstruction
- In detection of thyroid cancer radionuclide and ultrasound scanning are not sufficiently specific for routine use
- The first line investigation of thyroid enlargement is fine needle aspiration cytology. If cytology is suspicious or diagnostic of neoplasia the lesion should be excised
- Radio-iodine therapy is increasingly used to good effect for benign thyroid enlargement, especially when surgery is contraindicated
contain at least some solid tissue and therefore potentially neoplastic tissue. There are no specific sonographic criteria for the diagnosis of thyroid malignancy. This was highlighted by a meta-analysis of data from 1,000 subjects undergoing surgery, 80% of whom were classified pre-operatively as having solid or mixed solid/cystic lesions and 20% with cystic lesions. Although solid or mixed cystic lesions harboured most malignancies, 6% were found in cystic nodules, presumably reflecting cystic degeneration in thyroid tumours. Ultrasonography does not have a role in the routine investigation of thyroid enlargement because of its poor specificity.

**Fine needle aspiration cytology**

Fine needle aspiration cytology represents the first-line choice in the investigation of patients presenting with thyroid enlargement. The technique requires a 22-27 gauge needle and a 10 ml or 20 ml syringe. The needle is inserted, without local anaesthetic, into the lesion (Fig 2). Suction is applied and maintained while the needle is agitated within the lesion. Suction is then released, and the needle removed before preparation of smears of aspirated material for cytological examination. Several passes through the same lesion are generally tolerated; the presence of more than one nodule or diffuse thyroid enlargement determines the need for aspiration at several sites. Thyroid malignancy cannot be
excluded in subjects with clinically multinodular goitre, so such patients and those with diffuse goitre should be investigated in the same manner as those with clinically solitary nodules. The technique of fine needle aspiration cytology is safe and inexpensive, although dependent upon the skills of the local cytopathologist.

Findings after aspiration can be classified as non-diagnostic (which require repeat aspiration), benign, suspicious (or intermediate) or frankly malignant (Figs 3 and 4). The last two groups should be referred for surgical excision and definitive treatment. Those with benign cytological findings may be observed, unless other factors such as upper airways obstruction determine the need for treatment. A cytological report suggesting the presence of a follicular lesion should prompt surgery because follicular adenomas cannot be distinguished from carcinomas on cytological grounds alone.

Analysis of outcome in large series of patients investigated using this method has generally revealed specificities and sensitivities for the diagnosis of thyroid cancer of greater than 90%\(^2,7,8\). Published rates of false negative findings vary from 1.5–6%, such cases usually representing sampling error. To minimise such errors in diagnosis, it is important to repeat fine needle aspiration in those who report further thyroid enlargement or any other suspicious clinical features, as well as in males, those at extremes of age, and any patient with a history of radiation exposure. It is clear that the use of fine needle aspiration cytology leads to more specific selection of patients for surgery than any other test. It has also halved the number of patients operated for thyroid enlargement and doubled the frequency of diagnosis of thyroid cancer in those offered surgery\(^6\). The technique may also be of therapeutic benefit, simple aspiration of cyst fluid leading to resolution of cysts in up to 50% of cases. Ultrasound guided aspiration of recurrent cysts and instillation of ethanol has also been reported to be successful in reducing cyst size\(^6\).

**Thyroxine suppression of thyroid nodules**

T4 treatment has been administered to patients with thyroid enlargement with the aim of reducing thyroid size or preventing thyroid growth. The findings from different series vary considerably, but generally the response to treatment is disappointing\(^4,11\). Most series indicate that solitary nodules respond no better to T4 than to placebo, although reduction in size is observed more frequently in those with multinodular or diffuse goitre. It is also unresolved whether T4 should be administered to prevent goitre re-growth after surgery for benign disease. The efficacy of T4 is probably related to the degree of suppression of circulating TSH. Fears regarding risks of osteoporosis and atrial fibrillation in patients given TSH-suppressive doses of T4 are relative contraindications to T4 therapy, especially in elderly subjects.

**Radioiodine treatment of benign thyroid enlargement**

Benign goitre is now a recognised and licensed indication for radioiodine therapy. Recent reports indicate that radioiodine, administered in doses similar to those used in hyperthyroidism, is effective in euthyroid goitre, reducing goitre size by approximately 40% in nearly all treated cases within 12 months of treatment\(^12\). Concerns that radioiodine treatment may lead to thyroid enlargement and worsening of airways obstruction in the short term have proved groundless, so radioiodine has a particular role in those with large multinodular lesions in whom surgery is contraindicated. Hypothyroidism may ensue, as may the development of Graves' hyperthyroidism, which surprisingly has been described in 5% of cases\(^13\).

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**Calcium homeostasis and disorders of the calcium-sensing receptor**

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Overview of calcium homeostasis.

In health, the serum ionised calcium concentration (Ca\(^{2+}\)) is tightly regulated within the range 1.1–1.4 mmol/l by the actions of the major calcitropic hormones, parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D\(_3\) (1,25(OH\(_2\))D\(_3\)). Any decrease in the extracellular calcium ion concentration leads to an increase in the rate of release from the parathyroid chief cells of PTH, which acts via the PTH receptor to increase the distal renal tubular reabsorption of calcium within minutes. PTH secretion also enhances the activity of osteoclasts and other bone cells, causing calcium release from the skeleton within 1–2 hours. More prolonged PTH release stimulates 1\(\alpha\)-hydroxylase activity in the proximal tubular cells which leads to 1,25(OH\(_2\))D\(_3\) production. The latter has long-term effects, regulating both intestinal calcium absorption and skeletal calcium turnover over days to weeks. All these mechanisms act to produce an increase in the serum Ca\(^{2+}\), correcting it towards the baseline value, then completing the 'feedback loop' by inhibiting PTH release. The increased 1,25(OH\(_2\))D\(_3\) levels also directly inhibit transcription of the PTH gene.

Role of the calcium-sensing receptor

The calcium-sensing receptor (CaR) is a G protein-coupled receptor which allows the parathyroid chief cells, the renal tubular epithelial cells and the thyroidal C cells, to respond to changes in the extracellular calcium concentration. The ability of the CaR to sense the serum Ca\(^{2+}\) is essential for the appropriate regulation of PTH secretion by the parathyroids. Calcitonin secretion and renal tubular calcium reabsorption are also directly regulated by the action of Ca\(^{2+}\) on the CaR. The CaR gene is located on chromosome 3q13–q21 and encodes a 1,078 amino acid protein with a large extracellular domain and seven transmembrane domains. The CaR is expressed in many tissues, including brain, lung, ileum, pituitary and testis, as well as parathyroid, kidney and thyroid C cells. Three uncommon human disorders are due to abnormalities of the CaR gene:

- familial benign hypocalciuric hypercalcaemia (FBHH)
- neonatal severe hyperparathyroidism (NSHPT)
- autosomal dominant hypocalcaemia with hypercalciuria (ADHH)

**Familial benign hypocalciuric hypercalcaemia**

FBHH is an autosomal dominant disorder characterised by lifelong and generally asymptomatic hypercalcaemia. It can be difficult to distinguish this condition from primary hyperparathyroidism (PHP) and FBHH is the diagnosis in about 10% of subjects who have successful parathyroid exploration. The hypercalcaemia is manifest as early as the first week of life in affected subjects, but may vary in severity from borderline elevation of ionised calcium alone to marked hypercalcaemia (total serum calcium ≤3.5 mmol/l). Borderline hypermagnesaemia (0.95–1.10 mmol/l) is also found in over half the cases. Serum phosphate values are normal or slightly reduced. Urinary calcium excretion is generally in the low normal to reduced range, with 75% of patients having 24-hour calcium excretion less than 2.5 mmol and 95% with values less