Thyrotoxicosis and thyroiditis

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Abstract

Thyrotoxicosis is a common condition resulting from excess of circulating thyroid hormones in the blood. The most frequent cause of thyrotoxicosis is Graves' disease and the clinical features include goitre and eye disease. The treatment strategies of Graves' disease involve anti-thyroid drugs, radioiodine and thyroidectomy. Thyroiditis (inflammation of the thyroid) is caused by release of stored thyroid hormones and may also result in thyrotoxicosis. The aetiology, pathogenesis, diagnosis, investigation and management of conditions causing thyrotoxicosis and thyroiditis are reviewed in this article. Rare causes of thyrotoxicosis are highlighted.

Keywords Graves' disease; Hashimoto's thyrotoxicosis; thyroid disease; thyroidectomy; thyrotoxicosis

Definition

The terms thyrotoxicosis and hyperthyroidism should be distinguished. **Thyrotoxicosis** refers to the clinical syndrome of excess circulating thyroid hormones while **hyperthyroidism** is due to excess synthesis and/or secretion of thyroid hormones from the thyroid gland. Thyrotoxicosis is frequently a result of hyperthyroidism. Sometimes thyrotoxicosis may be due to conditions that are not associated with hyperthyroidism, such as thyroiditis, in which inflammation of the thyroid gland causes destruction of thyroid cells releasing stored thyroid hormones into the circulation without an increase in synthesis.

Aetiology

It is important to determine the cause of thyrotoxicosis to decide best treatment plan. Over 95% of cases are due to Graves' disease, toxic multinodular goitre and solitary toxic nodule (Table 1).

Causes of thyrotoxicosis

Thyrotoxicosis with hyperthyroidism		
Origin	Thyroid	Graves' disease
		Toxic multinodular goitre
		Solitary toxic nodule
		Iodine-induced hyperthyroidism
		TSH-induced hyperthyroidism (pituitary adenoma)
		Hydatidiform mole, choriocarcinoma
	Extra-thyroid	Metastatic follicular cell carcinoma
		Struma ovarii
Thyrotoxicosis without hyperthyroidism		
Thyroiditis	Acute	Acute suppurative thyroiditis
	Subacute	De Quervain's thyroiditis
		Postpartum/silent thyroiditis
	Chronic	Hashimoto's/atrophic thyroiditis
		Focal thyroiditis
		Juvenile thyroiditis
		Drug-induced thyroiditis
		Radiation-induced thyroiditis
Ingestion of thyroid hormones		Factitious/iatrogenic thyrotoxicosis, 'hamburger' thyrotoxicosis

Table 1

History

The clinical features of thyrotoxicosis are usually due to the systemic effects of excess circulating thyroid hormones with an increase in basal metabolic rate and sensitivity to catecholamines. These include anxiety, fatigue, irritability, heat intolerance, sweating, palpitations, dyspnoea, increased appetite, weight loss, diarrhoea and menstrual irregularity. It is important to remember that some may present with only a few of these effects, particularly those who are older or have mild disease. Features of the history, examination and investigations, outlined in this article, may reveal the underlying aetiology.

Examination

'Goitre' refers to a diffuse enlargement of the thyroid gland resulting in a swelling in the neck. It is common in thyrotoxicosis, particularly in Graves' disease and toxic multinodular disease. A small goitre may be palpable, but not necessarily visible. Larger goitres will usually be visible and if particularly vascular, may be associated with a bruit or thrill in Graves' disease. Eye signs may be present in thyrotoxicosis, due to sympathetic over-activity, and should be differentiated from the infiltrative ophthalmopathy of Graves' disease.

Investigations

Elevated serum free thyroxine (T4) or triiodothyronine (T3) confirms the diagnosis of thyrotoxicosis. Thyroid-stimulating hormone (TSH, also known as thyrotropin) levels are suppressed due to the negative feedback of T4 and T3 on the hypothalamo−pituitary−thyroid axis, except in thyrotoxicosis due to the rare TSH-secreting pituitary adenoma. Subclinical hyperthyroidism is defined as a normal T4/T3 level in the presence of a suppressed TSH. There is controversy as to whether subclinical hyperthyroidism should be treated or observed as only 5% eventually

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Please cite this article in press as: Ali O, et al., Thyrotoxicosis and thyroiditis, Surgery (2017), http://dx.doi.org/10.1016/j.mpsur.2017.06.014

develop overt hyperthyroidism and long-term effects of subclinical disease are uncommon.

Once the diagnosis of thyrotoxicosis is confirmed, a cause should be established. Thyroid autoantibody determination may be useful. TSH receptor antibodies (TRAb) are elevated in 90% of patients with Graves' disease and have a high specificity (99%) for this disease. Thyroid peroxidase antibodies (TPO-Ab, also known as anti-microsomal antibodies) are a sensitive marker of autoimmune thyroid disease and are frequently present in thyroiditis and Graves' disease.

Thyroid ultrasound is also a useful test in assessing vascularity of the gland; it is usually increased in Graves' disease and reduced in thyroiditis.

Thyroid scintigraphy (Figure 1) may be helpful to establish the diagnosis: using technetium 99m pertechnetate (Tc-99m) or radioactive iodine-123 (I-123). Thyroid scintigraphy demonstrates the functional state of the thyroid gland and shows diffuse and increased activity in Graves' disease, heterogeneous uptake in toxic multinodular goitre, a solitary focus of increased activity in solitary toxic nodule and reduced thyroid activity in thyroiditis, iodine-induced hyperthyroidism and factitious thyroiditis.[1]

Conditions causing thyrotoxicosis and hyperthyroidism

Graves' disease[2]

Definition: Graves' disease, named after Robert Graves, an Irish physician, is an autoimmune condition mediated by TRAb which stimulate the over production of thyroxine from the thyroid gland causing hyperthyroidism and thyrotoxicosis.

Epidemiology: Graves' disease is four times more common in women and the incidence in Europe is approximately 20 per 100,000 person years. It typically affects young women aged 20–40 years, but may occur at any age.

Pathogenesis: environmental and genetic factors play a role. Stress, cigarette smoking, radiation, iodine and antibodies to *Yersinia enterocolitica* cross-reacting with TSH receptors are probable triggers for autoimmune thyroid disease. There is an association with the expression of genes including TSH receptor, major histocompatibility complex HLA-DR3 allele, cytotoxic T-lymphocyte associated protein-4 (CTLA-4), and Fc receptor-like 3 (FcRL3). There is an 80% concordance between identical twins, and patients with Graves' disease are more likely to have other autoimmune conditions. Unregulated production of thyroid hormones results from the action of TRAb. Autoantibodies to other thyroid antigens, such as thyroperoxidase (TPO) and thyroglobulin (Tg) are frequently present (Figures 2, 3).

Pathology: this is characterized by infiltration of the thyroid with inflammatory cells, hyperplasia and hypertrophy of thyroid follicles and resulting goitre formation. The variable presence of stimulatory and destructive thyroid autoantibodies may explain the diverse course of Graves' disease. Extra-thyroidal manifestations are thought to be due to immune cross-reactivity with cells expressing TSH receptors in the retro-orbital and connective tissue resulting in inflammatory cell infiltration, oedema and fibrosis.

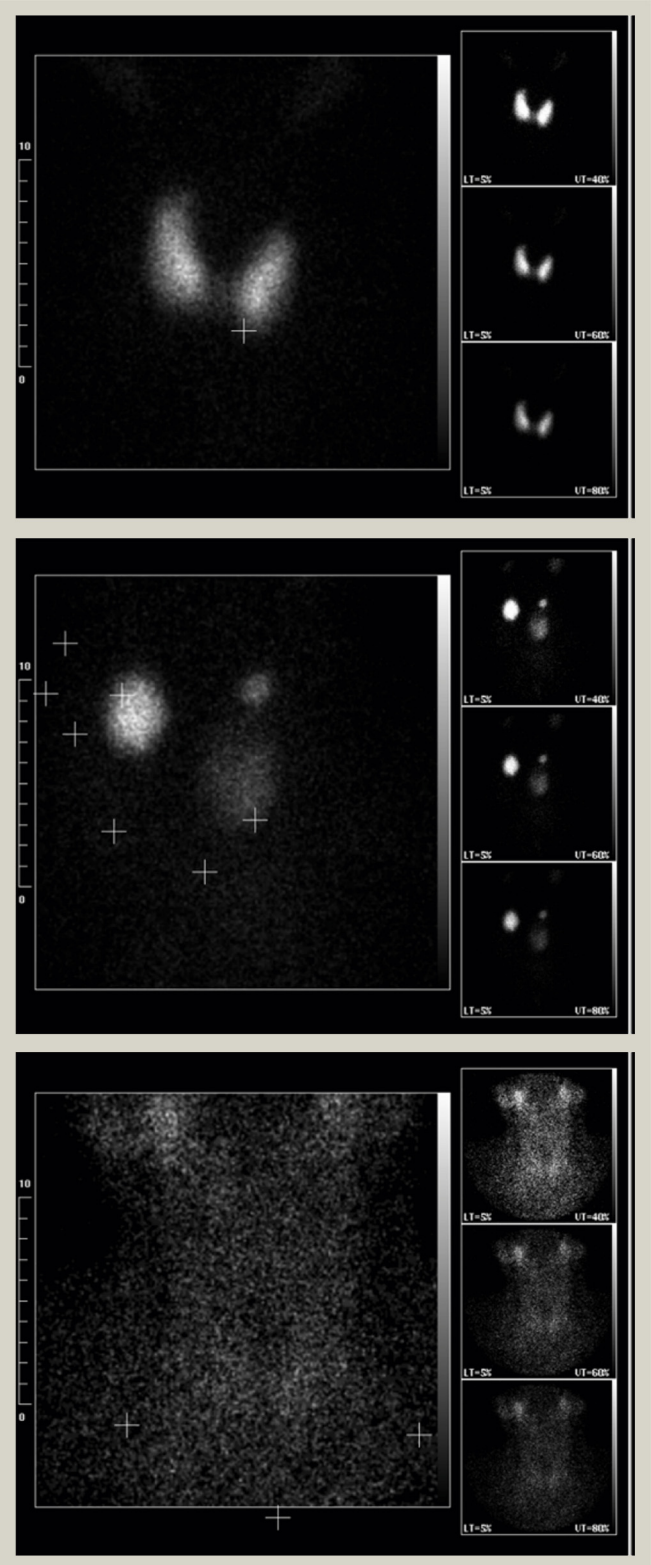

Figure 1 Thyroid scintigrams showing Graves' disease (top), toxic multinodular goitre (middle) and thyroiditis (bottom).

Presentation: Graves' disease commonly presents with a diffuse goitre (Figure 4) and symptoms of thyrotoxicosis (see above). In elderly patients, fewer symptoms are apparent.

Ophthalmopathy is a hallmark of Graves' disease. Occurring in up to 30% of patients, it may result in exophthalmos,

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