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Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

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- What tests to use
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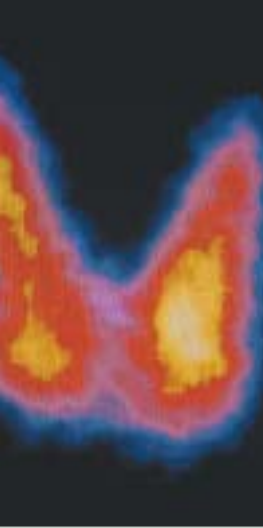
CURRENT
STRATEGIES FOR

THYROID FUNCTION TESTING

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Current strategies for THYROID FUNCTION TESTING

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at Alfred Hospital, Melbourne



Introduction

The presentations of thyrotoxicosis and hypothyroidism are so diverse (see table 1, next page) that it is difficult to rule out these conditions, or to make a conclusive diagnosis, until the abnormality is far advanced. With any of these presentations, a clinician should seek other features that support a diagnosis of thyroid dysfunction, and consider measurement of serum TSH, with an assay sufficiently sensitive to separate the suppressed TSH values of thyrotoxicosis from the lower limit of the normal reference interval.

This review summarises principles for the use of laboratory assays in the diagnosis and follow-up of thyroid disorders. Symptoms, physical signs and imaging techniques will not be considered, although results should always be interpreted in this broader context.

Apart from testing when thyroid dysfunction is suspected, or in groups with an increased risk of thyroid dysfunction (see table 2, next page), there are situations where routine testing is appropriate. First, neonatal screening for congenital hypothyroidism is widely established. Second, recommendations from the American College of Physicians suggest that thyroid dysfunction is sufficiently common in women older than 50 to justify routine testing at first presentation for medical care (case-finding). The majority of abnormal results in this group will identify subclinical rather than overt dysfunction (see below). Third, the finding of significant intellectual impairment in the offspring of women who were mildly hypothyroid early in pregnancy may justify routine testing of thyroid function as early as possible in pregnancy, or before conception.

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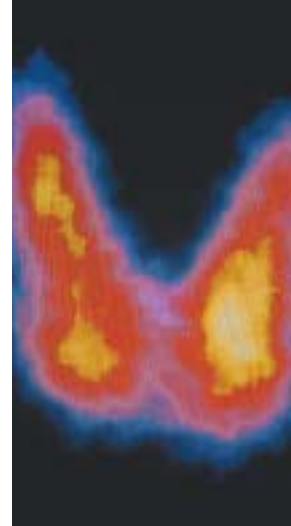
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Current laboratory techniques make the diagnosis and follow-up of thyroid disorders straightforward in most patients. However, in a small minority, problems due either to assay artifacts or atypical clinical presentations can lead to misdiagnosis, inappropriate treatment, or unnecessary further investigation. Such cases emphasise the importance of careful correlation between clinical and laboratory findings.

Terminology

The terms “subclinical” hypothyroidism or thyrotoxicosis are used when a persistent serum TSH abnormality is associated with serum-free T3 and T4 values that remain within the reference interval. The terminology “mild thyroid failure” rather than “subclinical hypothyroidism” is gaining support, based on studies that show tissue abnormalities before serum free T4 becomes clearly subnormal. There is increasing evidence that thyrotoxicosis and hypothyroidism can have important consequences before the full-blown laboratory findings appear (table 3, next page).

Prevalence of thyroid dysfunction

A study from an iodine-replete region in northern England showed a prevalence of 1.9-2.7% overt thyrotoxicosis and 1.4-1.9% overt hypothyroidism in women, with progressive increase with age. Estimates of subclinical hypothyroidism were 4-5-fold higher, with about 10% of women older than 50 showing an increase in serum TSH. Prevalence in males is generally about 10-fold lower. US studies and Australian data from the Busselton study suggest a similar prevalence.

Thyroid dysfunction is also common when younger women are tested post-partum. A Perth study found abnormal thyroid function in 11.5% of women tested six months after delivery, with TSH values higher than 4.8mU/L in 6%, of whom almost 90% had positive thyroid peroxidase antibody, indicating an autoimmune abnormality.

Accuracy and sensitivity of clinical assessment

To place laboratory testing in perspective, we need to know the sensitivity and accuracy of clinical assessment. Studies of patients evaluated in primary care show clinical acumen alone lacks sensitivity and specificity. In two Scandinavian studies of more than 3000 unselected patients who were assessed by both clinical and laboratory criteria, a thyroid disorder was not suspected by primary care physicians in more than 90% of those who tested positive, even when clinical features were apparent in retrospect.

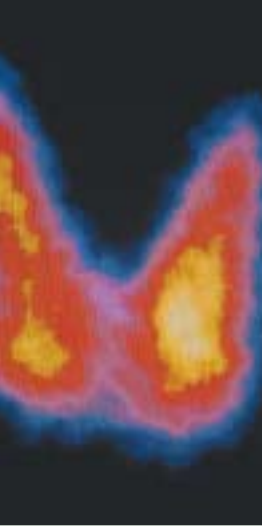
There are dissenting opinions on the relative value of clinical and laboratory clues to abnormal thyroid function. Some express the view that the clinical criteria are being sidelined,

Table 1: Diverse clinical presentations of thyrotoxicosis and hypothyroidism

Thyrotoxicosis	Hypothyroidism	Common to both
Heart failure	Anaemia	Classical presentations
Arrhythmia	Constipation	
Eye disease	Depression	Goitre
Anxiety state	Dementia	Post-partum
Weight loss	Myalgia	Menstrual disturbance
Diarrhoea	Nerve entrapment	
Apathetic hyperthyroidism	Hyperlipidaemia	Neonatal
Myopathy	Hypoventilation	Incidental finding
Periodic paralysis	Galactorrhoea	
Dermopathy	Infertility	
Itch	Puberty, precocious or delayed	
Thyroid storm	Delayed growth	
	Coma, hypothermia	

Table 2: Groups at increased risk of thyroid dysfunction

<p>General</p> <ul style="list-style-type: none"> ■ Positive family history ■ Previous post-partum thyroid dysfunction ■ Positive peroxidase antibody ■ Previous thyroid disease or surgery ■ Women over 55 ■ Origin from areas of endemic iodine deficiency ■ Very low birthweight premature infants <p>Associated diseases</p> <ul style="list-style-type: none"> ■ Diabetes ■ Any autoimmune disease ■ Other endocrine deficiencies ■ Down syndrome ■ Turner syndrome ■ Thalassaemia major 	<ul style="list-style-type: none"> ■ Pituitary or hypothalamic abnormality ■ Severe head injury ■ Recent Cushing's syndrome <p>Therapy</p> <ul style="list-style-type: none"> ■ Pituitary surgery or irradiation ■ Head and neck irradiation ■ Radical laryngeal/pharyngeal surgery ■ Treatment of growth hormone deficiency ■ Cytotoxic therapy ■ Lithium ■ Amiodarone ■ Exposure to iodine excess, eg, contrast agents ■ Interferon α, interferon β, Interleukin 2
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while biochemical assessments are lacking in specificity. This point is generally made by considering TSH and free T4 measurements individually, rather than in the trophic hormone-target gland relationship that is the cornerstone of endocrine diagnosis (see below). In fact, it may be no more valid to consider thyroid dysfunction only when typical symptoms or signs appear than to wait for the thirst and polyuria before considering the possibility of diabetes.

Measurement of serum TSH

Secretion of TSH from the anterior pituitary is regulated by negative feedback from the serum free thyroid hormone concentrations. The serum TSH response to changes in serum free T4 is logarithmic; a twofold change in free T4 induces inverse 10-100-fold changes in TSH. This amplified negative feedback, as the serum T4 increases or decreases, explains why serum TSH can fall outside the reference interval long before there is a diagnostic change in serum free T4.

Typical values for the lower reference limit for TSH are 0.3-0.5mU/L, with upper limits of 4-5mU/L, but the mean and median values are in the range 1-1.5mU/L because of the logarithmic distribution. Serum TSH can now be precisely measured to at least 0.03mU/L, so that the lowest concentrations in normal subjects are clearly distinguishable from those found in thyrotoxicosis. Terminology for subnormal serum TSH values needs comment. Values associated with thyrotoxicosis, either overt or subclinical, are typically suppressed (ie, <0.03mU/L) and need to be distinguished from subnormal-detectable values in the range 0.1-0.4mU/L that do not indicate thyrotoxicosis. Subnormal-detectable values are common in patients with goitre, only a few of whom develop thyrotoxicosis, unless exposed to iodine excess. Notably, serum TSH may be subnormal during many illnesses, without this indicating any persistent abnormality of thyroid function.

The TSH-T4 relationship

Whatever strategy is used for first-line testing, a sensitive serum TSH assay and an estimate of serum free T4 are both necessary for definitive assessment of thyroid status. As shown in figure 1, the common types of thyroid dysfunction can be identified in a single sample from characteristic diagonal deviations in the normal T4-TSH relationship. The figure at right shows primary hypothyroidism due to target gland failure (high serum TSH, low free T4: A), failure of TSH secretion (both low: B), autonomous or abnormally stimulated target gland function (high free T4, suppressed TSH: C), and primary excess of TSH, or thyroid hormone resistance (both high: D). Abnormal results that fall outside these areas suggest another factor has disturbed the TSH free T4 relationship. (The links between components of other feedback systems can also be applied to the investigation of hypogonadism, glucocorticoid and mineralocorticoid abnormalities, hypoglycaemia, insulin resistance, hypercalcaemia, etc.)

Key assumptions (table 4) need to be considered to make best diagnostic use of the trophic hormone-target

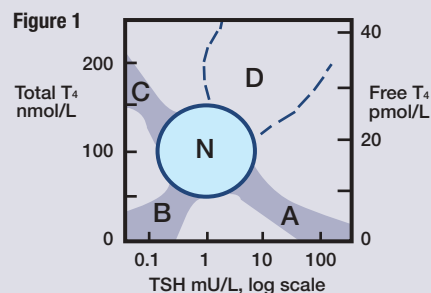
Table 3: Importance of subclinical thyroid dysfunction

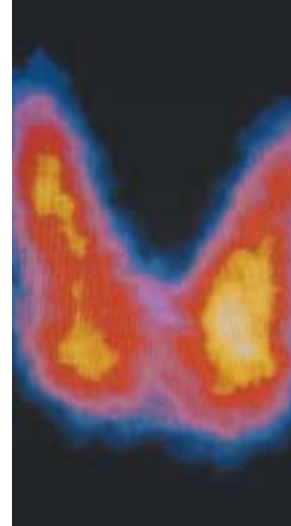
Subclinical thyrotoxicosis (suppressed TSH, normal free T4, free T3)

Progression to overt thyrotoxicosis
Exposure to iodine may precipitate severe thyrotoxicosis
Threefold increased risk of AF after 10 years
Osteoporosis and fracture risks are increased

Subclinical hypothyroidism (Mild thyroid failure)

(increased TSH, normal free T4)
Non-specific symptoms may improve with treatment
Progression to overt hypothyroidism (about 5% per year)
Adverse effect on fetal brain development in pregnancy
Adverse effects on vascular compliance
Independent risk factor for atherosclerotic disease?
Beneficial effect of treatment on lipids?
Increased prevalence of depressive illness?





gland relationship. The first assumption, steady-state conditions, should always be questioned when associated illness or medications perturb the pituitary-thyroid axis. The large difference between the half-lives of TSH (one hour) and T4 (one week) accounts for many transient non-diagnostic abnormalities, especially during critical illness. In several situations, circulating T3, rather than T4, becomes an important, or dominant, determinant of thyroid status. The relevance of serum free T3 measurement is summarised in table 5. Note that serum free T3 is of little value in monitoring T3 treatment because of wide variations that depend on the interval between dose and sampling.

The “TSH first” testing strategy

Because thyroid gland abnormalities are 10-20 times more common than abnormalities due to pituitary dysfunction, TSH changes can generally be regarded as giving an inverse reflection of thyroid status. An algorithm for the assessment of thyroid function based on initial measurement of TSH is shown in figure 2. There are several situations in which TSH alone can give a misleading or ambiguous assessment of thyroid status (table 6). While a normal serum TSH value has high negative predictive value in ruling out either primary hypothyroidism or thyrotoxicosis, an abnormal TSH concentration can be a transient or false finding and should never be used alone as a basis for treatment.

Untreated subjects

Assessment of untreated subjects now commonly begins with measurement of TSH alone, with T4 and/or T3 added only if TSH is abnormal, or if an abnormality of TSH secretion is suspected. According to the algorithm in figure 2, free T4 should be measured to distinguish between overt and subclinical hypothyroidism when serum TSH is elevated, while a suppressed or subnormal TSH level should be followed by assay of both free T4 and free T3 to distinguish subclinical from overt thyrotoxicosis and to identify T3 toxicosis. Given appropriate clinical notes, adequately trained laboratory staff should be able to implement contingency-based testing without the need for further sampling.

Response to treatment

In patients with newly treated thyrotoxicosis, TSH may remain suppressed for several months after normalisation of serum free T4 and T3. Serious over-treatment may result if TSH alone is used for adjustment of anti-thyroid drug dose. Further, during drug treatment thyrotoxicosis may persist due solely to T3 excess. Hence, reassessment of both serum free T4 and free T3 levels is recommended every 3-4 weeks during initial drug treatment of thyrotoxicosis to allow appropriate dose adjustment. During long-term treatment, TSH generally gives a reliable guide to optimal drug dose. Similarly, during long-term replacement or suppressive therapy with thyroxine, serum TSH is the best single index of appropriate

Table 4: The T4-TSH relationship in the assessment of thyroid status

Critical assumptions

1. Steady-state conditions (note different half-lives of TSH and T4)
2. Normal trophic-target hormone relationship
3. Tissue responses proportional to serum free T4 concentration
4. Accurate estimate of active hormone concentration
5. Appropriate reference intervals
6. Adequate assay sensitivity

Table 5: Indications for measurement of serum free T3

Required

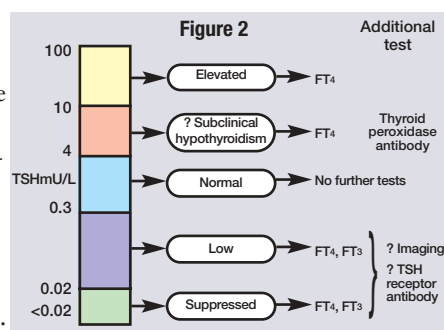
- Potential thyrotoxicosis with suppressed TSH and normal serum free T4
- During antithyroid drug therapy to identify persistent isolated T3 excess
- Diagnosis of amiodarone-induced thyrotoxicosis

Useful

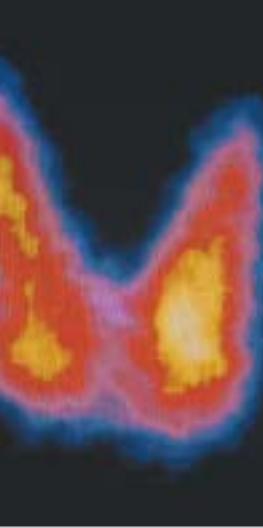
- Early recurrence of thyrotoxicosis
- Extent of T3 excess during suppressive therapy with T4, or after T4 overdose

Not required or misleading

- Diagnosis of hypothyroidism
- During critical illness
- During routine T4 replacement
- Screening of asymptomatic subjects
- Monitoring of T3 treatment



Algorithm for the assessment of thyroid function based on initial assay of serum TSH. Abnormal TSH values lead to further assays as shown. If pituitary dysfunction is suspected, during the early treatment of thyroid dysfunction, during critical illness and with drugs that influence the pituitary-thyroid axis, a free T4 assay is required irrespective of serum TSH.



dose, generally reflected by a low-normal TSH value of about 1mU/L, often with a slightly increased level of serum free T4. The full benefit of thyroxine replacement may not occur until TSH is lowered towards 1mU/L — a value in the high “normal” range may still be well above the normal set-point for that individual.

During suppressive therapy with T4, for example, in the management of differentiated thyroid cancer, the TSH target is lower, in the range 0.03-0.1mU/L. Periodic assessment of free T4 and free T3 in addition to TSH is useful to limit the degree of thyroid hormone excess, thereby avoiding adverse effects on the cardiovascular system or on bone density. In the treatment of hypothyroidism due to pituitary or hypothalamic disease, serum TSH is of no value in assessing T4 dose, which should be judged from clinical response and serum free T4.

Table 6: Serum TSH alone can give a false or uncertain indication of thyroid status

Abnormal TSH secretion
Pituitary dysfunction
Thyrotoxicosis
Subclinical
During antithyroid drug treatment
Hypothyroidism
Subclinical
Early treatment
Medications
Dopamine, glucocorticoids
During severe or critical illness

Important medications

Amiodarone is the most complex and difficult drug that affects thyroid status, sometimes with poor correlation between circulating thyroid hormone levels and clinical severity. In iodine-replete regions, the predominant amiodarone-induced thyroid abnormality is hypothyroidism, which is especially prevalent in those with associated autoimmune thyroiditis. Amiodarone causes two forms of thyrotoxicosis, one due directly to iodine excess and the other attributed to a unique type of thyroiditis. Both forms require detailed specialist care.

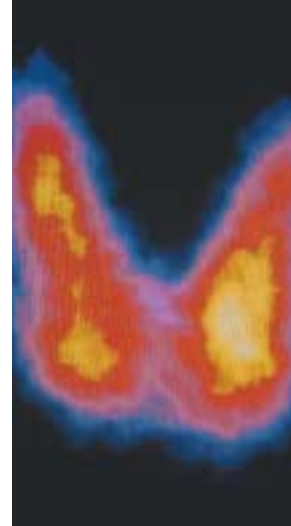
Lithium, used in the management of bipolar illness, has multiple effects on the pituitary-thyroid axis, the most important being inhibition of hormone release. Lithium can exacerbate autoimmune thyroid disease with development of goitre and eventual hypothyroidism. Serum TSH, free T4 and T3 assays generally give a true index of thyroid status during lithium treatment. Hypothyroidism can generally be managed with thyroxine substitution, while lithium is continued.

Phenytoin commonly results in subnormal serum total T4, with an apparent lowering of free T4, not accompanied by the anticipated increase in TSH. Such findings are hard to distinguish from central hypothyroidism due to pituitary deficiency.

Antibody measurements

The terms microsomal and peroxidase antibody (TPOAb) refer to the same moiety, which is the most sensitive marker of immune thyroid damage, usually associated with the lymphocytic infiltration that is most extreme in Hashimoto’s thyroiditis. Positive peroxidase antibody indicates a 4-5-fold increase in the chance of developing overt hypothyroidism and also indicates an increased likelihood of post-partum thyroid dysfunction or amiodarone-induced hypothyroidism. Assays for thyroglobulin antibody are less relevant for the diagnosis of immune thyroid disease, but are crucial for the valid interpretation of serum thyroglobulin assays in the follow-up of differentiated thyroid cancer.

Positive TSH receptor antibody (TRAb) identifies the probable cause of Graves’ disease. The finding of persistently positive TRAb is useful in indicating that apparent remission of Graves’ disease is unlikely to be sustained. TRAb measurement can also indicate the possibility of neonatal thyrotoxicosis in the infant of a mother with autoimmune thyroid disease and may also define the aetiology of atypical eye disease.



Thyroglobulin

Serum thyroglobulin concentrations should always be interpreted in relation to serum TSH. In the long-term follow-up of differentiated thyroid cancer, an undetectable serum thyroglobulin concentration in the presence of a high serum TSH indicates absence of differentiated thyroid tissue, benign or malignant. Thyroglobulin is undetectable in thyrotoxicosis factitia, and generally extremely high in subacute thyroiditis and in amiodarone-induced thyrotoxicosis. Endogenous antibodies to thyroglobulin can invalidate the assay for serum thyroglobulin. These antibodies should be checked to rule out potential interference.

The laboratory-clinical interface

The diverse clinical presentations of thyroid dysfunction mandate laboratory requests from clinicians who may be unfamiliar with current assays. Comments from the laboratory can assist the non-specialist, but the quality of this advice depends on clinical information given by the referring doctor. Review of the clinical context often resolves an apparently anomalous result, so that unnecessary further investigation is avoided.

For references to specific points in this text see *Thyroid Disease Manager Chapter 6b, Clinical Strategies for Thyroid Function Testing*, at www.thyroidmanager.org

The following cases demonstrate important points in the management of thyroid dysfunction

Case 1

A 24 year-old woman presented with a two-year history of progressive weight loss, heat intolerance, nervousness, bowel frequency and oligomenorrhoea. Tremor, sinus tachycardia and proximal myopathy were striking and she had a large smooth goitre 14cm in lateral span, with obvious bruit. There was mild proptosis without diplopia. Test confirmed thyrotoxicosis, with fT4 66pmol/L (ref 10-25) and fT3 20pmol/L (ref 3-8), with suppression of TSH. Treatment with carbimazole, 15mg tds was started and three weeks later testing showed fT4 28pmol/L, with persistent suppression of TSH. Carbimazole dose was decreased to 10mg bd. Three months after starting treatment, she now has persistent symptoms of thyrotoxicosis with sinus tachycardia. Serum fT4 is subnormal at 8pmol/L, with persistent TSH suppression.

Question: What additional measurement is required and how should the dose be adjusted?

The key assay is serum fT3, which has remained high at 12pmol/L, despite the marked decrease in serum fT4. Dose adjustment should continue to be based on serum fT3. This pattern of marked dissociation between serum fT4 and fT3 during antithyroid drug treatment is common with severe Graves' disease with large goitre. TSH suppression may persist for months, after normalisation of both fT4 and fT3, and is not useful for early dose adjustment.

Message: Serum free T3 should be included in the assessment of response to antithyroid drug while there is persistent TSH suppression.

Case 2

A 55-year-old woman is admitted to hospital with a two-day history of abdominal pain, vomiting and features of sepsis. A gangrenous ruptured appendix, with associated peritonitis, is removed at laparotomy. Recovery is complicated by pneumonia and transient oliguric renal failure. Thyroid function, checked after six days during her slow recovery, shows serum fT4 of 5pmol/L, with fT3 <1pmol/L and TSH 6.0mU/L (ref 0.4-4.0). She has no goitre and there are no clinical features of thyroid dysfunction. No treatment is given and testing a week later shows low fT4 of 8pmol/L with TSH 11mU/L.

Question: What treatment or follow-up is appropriate?

The evidence for primary hypothyroidism is still not convincing. However, further testing in three weeks, after recovery, shows fT4 of 11pmol/L with TSH 7mU/L. Peroxidase antibody is strongly positive. Thyroxine replacement is started at 0.05mg daily, increased to 0.1mg daily after two months, with good response.

Message: Transient apparent abnormalities of thyroid function are common during critical illness, and during recovery can be identical to early thyroid failure. In the absence of clinical features, mild changes are usually best followed without treatment, with repeat sampling 3-4 weeks later. Persistently increased TSH, especially with positive peroxidase antibody, is generally an indication for replacement.

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