

Review

Interpretation of thyroid function tests

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The introduction of sensitive thyrotropin assays and free thyroid hormone measurements has simplified the interpretation of thyroid function tests. However, important pitfalls and difficult cases still exist. In this review, thyroid function test results are grouped into six different patterns. We propose that if assays for thyrotropin, free T3, and free T4 are all done, knowledge of these patterns coupled with clinical details and simple additional tests allow a diagnosis to be made in almost all cases.

There have been considerable improvements in assays for thyrotropin (TSH), free T4, and free T3 over the past 20 years. As a result, interpretation of thyroid function tests is now generally straightforward, and more than 90% of people investigated are diagnosed with normal thyroid gland function. However, there remain a few situations in which the results of TSH, free T4, and free T3 assays tend to point in different directions, as well as cases in whom thyroid function test results seem clear cut but are in fact misleading. Additionally, over the past 6 years, an increasing number of genetic defects has been identified in the pituitary-thyroid axis. These defects are easily misdiagnosed by the unwary and, although rare, can present for the first time in adulthood, with implications for both the patient and their family. My aim is to guide the general physician around these pitfalls with a practical approach.

Thyroid function tests

The choice of first-line thyroid function tests depends on local arrangements and laboratory protocols. In many laboratories, a highly sensitive TSH assay (second or third generation, with a limit of detection <0.1 mU/L)¹ alone is used for initial screening, which is satisfactory so long as its limitations are appreciated. At an increased cost, the sensitive TSH measurement can be combined with a single measurement of total or free thyroid hormone concentrations to address these limitations. T3 or T4 estimation alone as an initial screen, however, will miss subclinical thyroid dysfunction and is not advised. If TSH is abnormal, a free T4 or, when TSH is low, a free T3 assay should be obtained, and in difficult cases when the suspicion of thyroid dysfunction remains high, a combination of all three tests (TSH, free T3, free T4) will usually avoid misdiagnosis. Finally, total-thyroid-hormone assays are still used in some laboratories. Because of the changes in thyroid-binding proteins, however, these tests can cause diagnostic confusion and should be accompanied by a marker of protein binding such as a T3 uptake assay.

Since these issues have been reviewed,² I will

concentrate on diagnostic difficulties that persist even when free-hormone assays, or assays corrected for protein binding, have been done. Note, however, that free-hormone assays by routine methods are still affected by extreme changes in binding-protein concentrations, non-thyroidal illness, and some drugs—eg, anticonvulsants. Recent recommendations for assay performance, taking into account biological variation, include an imprecision (between-site) of less than 10% for all thyroid hormone assays, and less than 20% for TSH assessed at the stated lower limit of detection.^{1,3} Despite recent improvements, many assays fail to meet these criteria. Important bias also exists between commercial methods emphasising the need for results to be compared with normal ranges derived with the same assay.

If TSH alone is the first line test, what diagnoses will be missed? Sensitive TSH assays are widely used and financially justifiable as first-line screening tests. However, they can be misleading when: hypothyroidism is caused by pituitary disease (TSH is usually in the normal range),⁴ hypothyroidism develops within 12 months of treatment for thyrotoxicosis (the TSH value remains suppressed),⁵ thyrotoxicosis is caused by a TSH secreting pituitary tumour,⁶ or individuals are thyroid hormone resistant⁷ (TSH is usually in the normal range in these final two) (panel 1). In these cases testing of free thyroid hormones is recommended in addition to the TSH assay. However, a small number of unsuspected cases of secondary hypothyroidism with undiagnosed secondary hypoadrenalism will still be missed (estimated to be 1 in 20 000 of the population).⁸ Non-thyroidal illness (previously termed the sick euthyroid syndrome) can also result in low thyroid hormone concentrations with TSH values in the normal range, but clinically important diagnoses are unlikely to be missed in such situations.⁹

What additional thyroid tests should be routinely available? Tests enabling measurement of antithyroid peroxidase autoantibodies (anti-TPO, previously referred to as thyroid antimicrosomal antibodies) are often valuable when trying to determine the cause of a thyroid disturbance.¹⁰ However, assays for antithyroglobulin

Panel 1: Conditions in which TSH alone might be misleading

Common

Recent treatment of thyrotoxicosis
Pituitary disease
Non-thyroidal illness

Rare

TSH-secreting pituitary tumour
Thyroid hormone resistance

Lancet 2001; **357**: 619–24

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antibodies, anti-TSH receptor antibodies, thyroxine-binding globulin, and thyroglobulin are only indicated in specific circumstances, and need only be available in regional centres.

When can thyroid dysfunction be confidently excluded? In clinical practice, six different patterns of the three main thyroid function tests (TSH, free T3, free T4) are seen. In individuals with thyroid disease, or a strong clinical suspicion of thyroid disease, all three tests should be done on at least one occasion so that a clear diagnosis can be made. If all three are in the normal range, thyroid disease can be confidently excluded. The only exception to this rule is individuals having thyroxine replacement, who could possibly benefit from an increased dose of thyroxine or a combination of thyroxine and triiodothyronine even when TSH, free T3, and free T4 are in the normal laboratory range.^{11,12} This area remains controversial.

Low TSH, raised free T3 or T4

There are six patterns of thyroid function tests. Low TSH, accompanied by raised free T4 and T3 concentrations (panel 2), indicates primary hyperthyroidism, most commonly caused by Graves' disease, multinodular goitre, or toxic nodule. In these cases TSH should be undetectable and thyroid tissue should not be tender. Clinical criteria can usually separate the three common causes of primary hyperthyroidism, however, there is no definitive test for Graves' disease. Thyroid ophthalmopathy and a diffuse uptake on technetium or radioiodine thyroid scanning make the diagnosis of Graves' disease likely, but antithyroid antibodies (including anti-TSH-receptor antibodies) are negative in about 10% of cases. Graves' disease can also develop during recovery from profound anti-T-cell immunotherapy,¹³ and should, therefore, be suspected in this unusual context. Amiodarone causes thyrotoxicosis in up to 10% of individuals treated, and can be difficult to remedy.¹⁴ Lithium induced hyperthyroidism is rare as this drugs leads more often to hypothyroidism.¹⁵

When the history of hyperthyroid symptoms is short (<1 month), response to antithyroid drugs is unusually rapid—eg, euthyroidism is achieved within 2 weeks or hyperthyroidism is diagnosed in the postpartum period, transient thyroiditis should be suspected (subacute, silent,

or postpartum).¹⁶ Thyroiditis can be confirmed by a low uptake on radioiodine or technetium thyroid scanning, and is important since thionamides are ineffective, symptomatic treatment (β blockers) alone usually being sufficient in these conditions. Tenderness over the thyroid gland and a raised erythrocyte sedimentation rate suggests subacute (postviral or De Quervain's) thyroiditis, but can also indicate silent thyroiditis. Silent and postpartum thyroiditis¹⁷ (the latter occurring within 9 months postpartum) are related autoimmune conditions, which can arise repeatedly,¹⁸ and are sometimes, confusingly, painful. Anti-TPO antibodies are on occasion detectable and can be useful, in the absence of histology, to differentiate postviral and silent thyroiditis.¹⁶ The causes of thyrotoxicosis with a low radioiodine uptake include thyroxine ingestion (therapeutic or factitious), ectopic thyroid tissue (including struma ovarii), amiodarone therapy, and excess iodine ingestion (typically seen in multinodular goitre-Jod-Basedow effect).¹⁶ An increase in thyroid tissue favours the last condition.

During pregnancy, pronounced biochemical hyperthyroidism usually results from Graves' disease, but a mild rise associated with vomiting in the first trimester can be caused by overstimulation of the TSH receptor by very high human chorionic gonadotropin concentrations or human chorionic gonadotropin variants (gestational thyrotoxicosis or molar pregnancy). Striking anti-TPO-negative thyrotoxicosis, which recurs in subsequent pregnancies and spontaneously resolves postpartum, raises the rare possibility of familial gestational hyperthyroidism. In this recently identified condition, a *K183R* mutation in the TSH receptor increases its ability to be activated by human chorionic gonadotropin.¹⁹

A possibility of a dominant germline activating TSH-receptor mutation exists in thyrotoxicosis that persistently recurs after thyroidectomy, or treatment with radioiodine, and in patients with other family members, particularly children, affected.²⁰ These cases are rare but the diagnosis is worth making, because it allows screening of other family members and aggressive treatment (total thyroidectomy plus radioiodine). Affected individuals are anti-TPO negative. Age of onset varies from the neonatal period to adulthood, and a smooth or multinodular goitre can develop.^{20,21} Closely similar somatic mutations are responsible for 80% of toxic nodules.

Low TSH, normal free T3 or T4

Low TSH and normal free T3 and T4 test results are usually seen with thyroxine ingestion (panel 3). A less common alternative is subclinical primary hyperthyroidism, typically seen in elderly people. Further investigation normally reveals a multinodular goitre. If TSH is wholly suppressed, this situation can require treatment since the risk of atrial fibrillation²² and osteoporosis is increased.²³

Among patients in hospital, high-dose steroid or dopamine and dobutamine infusions, both of which can suppress pituitary TSH release, or non-thyroidal illness⁹ should be considered. Repeat thyroid function tests

Panel 2: Low TSH, raised free T3 or free T4

Common

Primary hyperthyroidism:

Graves' disease
Multinodular goitre
Toxic nodule

Relatively common—with low radioiodine uptake

Transient thyroiditis:

Postpartum
Silent (lymphocytic)
Postviral (granulomatous, subacute, De Quervain's)

Rare—with a low radioiodine uptake

Thyroxine ingestion
Ectopic thyroid tissue or struma ovarii
Iodine induced
Amiodarone therapy

Rare—with a positive pregnancy test

Gestational thyrotoxicosis with hyperemesis gravidarum
Hydatidiform mole
Familial gestational hyperthyroidism

Rare—familial or resistant to treatment

Activating germline TSH-receptor mutation

Panel 3: Low TSH, normal free T3 or free T4

Common

Subclinical hyperthyroidism
Thyroxine ingestion

Rare

Steroid therapy
Dopamine and dobutamine infusion
Non-thyroidal illness

Panel 4: Low or normal TSH, low free T3 or free T4**Common**

Non-thyroidal illness
Recent treatment for hyperthyroidism (TSH remains suppressed)

Rare

Pituitary disease (secondary hypothyroidism)
Congenital TSH or thyrotropin-releasing hormone deficiency

showing a return to normal after recovery should confirm these diagnoses.

Low or normal TSH, low free T3 or T4

Low or normal TSH and low free T3 or T4 test results represent a typical pattern in unwell patients with non-thyroidal illness, the most common combination of results being a low free T3 with a TSH in the normal range (panel 4). However, in individuals without obvious concomitant disease, pituitary disease with second hypothyroidism should be considered.⁴ Non-endocrinologists are frequently surprised to find TSH in the normal range in this situation, since the pituitary fails to respond adequately to low thyroid hormone concentrations. The diagnosis is important, because concomitant hypoadrenalism could be life threatening, and an unsuspected large pituitary tumour can cause local pressure effects. A history of pituitary or cranial irradiation, even 20 years previously, can provide the explanation. Short Synacthen testing, follicle-stimulating hormone, Luteinising hormone, and measurement of gonadal steroids, and magnetic resonance imaging of the pituitary are indicated. If all these tests are normal, especially in a baby, the very rare conditions of congenital thyrotropin-releasing hormone-deficiency or TSH-deficiency should be considered.^{24,25}

It is noteworthy that within 2 to 3 months of treatment for hyperthyroidism, TSH concentrations can remain suppressed even in the presence of low concentrations of free T3 or T4, giving a similar pattern to pituitary disease.⁵ The patient's medical history should provide the diagnosis, but an unsuspecting clinician could wrongly assume that the individual is still thyrotoxic (suppressed TSH) when, in fact, they are profoundly hypothyroid.

Raised TSH, low free T4 or T3

This combination of results always indicates primary hypothyroidism (panel 5). In iodine sufficient areas, almost all cases are due to thyroablative therapy for thyrotoxicosis or thyroid cancer (by radioiodine or surgery) or, if they arise spontaneously, autoimmune thyroiditis (manifest as atrophic thyroiditis or Hashimoto's disease).²⁶ Hypothyroidism can develop 20 years or more after radioiodine therapy. Hyperthyroidism can also develop years after thyroid surgery²⁷ or carbimazole-induced remission in Graves' disease (but not multinodular goitre), presumably because of a spontaneous conversion of the autoimmune reaction to a destructive process or as a result of loss of thyroid stimulating antibodies. Antithyroid microsomal antibodies are said to be present in more than 90% of cases of chronic autoimmune thyroiditis,²⁸ but negative results might be more common in routine clinical practice. Notably, cases of spontaneously resolving transient thyroiditis do occur (panels 2 and 5), which if sampled during the hypothyroid phase can give the same pattern of thyroid function tests. Differentiation between autoimmune (postpartum, silent) and postviral types of transient thyroiditis is needed, since the former is likely to recur. However, thyroxine therapy is rarely necessary in

either type of thyroiditis. Cytokine therapy (interferons, interleukin-2, and granulocyte-macrophage colony stimulating factor), amiodarone, and lithium can all also precipitate primary hypothyroidism, especially in patients with underlying subclinical autoimmune thyroiditis.^{14,15,26,29} In Riedel's thyroiditis, a rare disorder in which the thyroid gland is replaced by fibrosis, hypothyroidism happens in around 30% of cases. Thyroid autoantibodies might be present in this case but the role of autoimmunity in the pathogenesis is not established.³⁰

When thyroid function tests suggest primary hypothyroidism, but anti-TPO antibodies are not detectable, rarer causes should be considered. A previous history of neck irradiation should first be excluded. Measurement of urinary iodine excretion should then be considered. Iodine deficiency with associated endemic goitre (urinary iodine excretion <45 µg daily) is the most common cause of primary hypothyroidism worldwide, and should be strongly suspected in iodine-deficient areas. Physicians practising in iodine-sufficient areas need to consider the diagnosis in recent immigrants, particularly those from mountainous areas of the world as well as those from south Germany, Italy, and Zaire.³¹ Vast excesses of iodine (urinary iodine >1000 µg per day) can also cause hypothyroidism and have been reported from water-purification systems or from gross dietary excess, but this cause is rare.³² If dietary iodine intake is adequate (>100 µg daily) but endemic goitre is common, as reported for example in Sheffield, parts of Spain, Bohemia, Virginia, Kentucky, and Tasmania, dietary goitrogens that inhibit thyroid hormone biosynthesis should be suspected.³³

The final category of causes of primary hypothyroidism is that of congenital defects of thyroid gland function.³⁴ Results of studies of patients identified in neonatal screening programmes have revealed mutations in the TSH receptor,³⁵ and in the paired box containing gene *PAX 8*,³⁶ and thyroid transcription factor 2 *TTF2*³⁷ as causes of thyroid hypoplasia with hypothyroidism, in one

Panel 5: Raised TSH, low free T4 or free T3 (primary hypothyroidism)**Common**

Chronic autoimmune thyroiditis*
Post radioiodine
Post thyroidectomy
Hypothyroid phase of transient thyroiditis

Rare (anti-TPO negative, no radioiodine or surgery)

Post external-beam irradiation to the neck
Drugs: amiodarone, lithium, interferons, interleukin-2
Iodine deficiency
Iodine excess-iodide goitre in Japan (water purification units)
Goitrogens
Amyloid goitre (large, firm goitre with systemic amyloidosis)
Riedel's thyroiditis†

Congenital—thyroid tissue absent

Thyroid dysgenesis possibly associated with TSH-receptor, *PAX-8*, and *TTF2* mutations

Congenital—thyroid tissue present

Iodine transport defects—low radioiodine uptake or saliva iodine
Iodine organification defect

Congenital—high radioiodine uptake, positive perchlorate discharge

Thyroglobulin synthetic defect—low thyroglobulin concentration
TSH-receptor defects
Resistance to TSH with other (unspecified) defects

*If goitre rapidly enlarging, especially in spite of thyroxine therapy, consider lymphoma on a background of autoimmune thyroiditis. †Thyroid autoantibodies can be present.

case with associated primary hypoadrenalism.³⁸ Mutations in the sodium/iodide transporter (symporter)³⁹ or in the thyroid peroxidase enzyme⁴⁰ result in hypothyroidism with a goitre and, in the second case, a positive perchlorate discharge test. Many thyroglobulin synthesis defects have been described that lead to varying degrees of hypothyroidism and goitre but very low thyroglobulin concentrations.⁴¹ Cases of resistance to hypothyroidism with TSH in which there were no TSH-receptor mutations have also been described.⁴²

Of particular clinical importance is the identification of patients with less profound degrees of thyroid dysfunction caused by congenital defects, because such individuals could present later in childhood or in adulthood. Raised TSH concentrations (6–120 mU/L) but normal free T4 or T3 have been reported in familial cases of TSH resistance caused in some,⁴³ but not all,⁴⁴ cases by TSH-receptor defects. Indeed, the same TSH-receptor mutation can be associated with both mild and profound hypothyroidism.^{43,45} Mild hypothyroidism is also common in Pendred syndrome—the triad of sensorineural deafness (typically with the Mondini cochlear defect), goitre, and positive perchlorate discharge tests—and has been reported with some thyroglobulin synthetic defects.⁴¹ There could, therefore, be more inherited defects of thyroid function in the hypothyroid population than at first suspected. Familial cases that are negative for antithyroid antibodies should be further investigated with radionuclide or ultrasound scanning, to identify the location and size of the gland, a perchlorate discharge test, to diagnose iodide organification defects (including Pendred's syndrome) and a thyroglobulin value. Referral to a specialist centre for genetic analysis should then be considered.

Raised TSH, normal free T4 or T3

This is the pattern of thyroid function normally seen with mild thyroid failure (subclinical hypothyroidism) (panel 6). It is common in the population, affecting 5–10% of all women, and in most cases is associated with positive anti-TPO antibodies. Subclinical hypothyroidism is caused by autoimmune hypothyroidism that has not yet progressed to severe thyroid impairment,⁴⁶ although it can also follow radioiodine treatment or thyroidectomy.

Although subclinical autoimmune hypothyroidism is by far the most common cause of this pattern of thyroid function tests, alternative diagnoses should be considered under certain circumstances. If the TSH concentration is raised to a value usually associated with a low free T4 or T3—eg, over 20 mU/L—or does not return to normal with T4 therapy, the presence of a heterophile—eg, anti-mouse immunoglobulin—interfering with the TSH assay is likely.⁴⁷ Repeat estimation, with a different assay, or the addition of blocking agents such as mouse serum, can

rapidly provide confirmation. Such interfering antibodies persist for years, so the patient should be made aware and the medical records marked to ensure only assays in which interference does not occur are used. Individuals with heterophile antibodies could have completely normal thyroid function, but are often prescribed thyroxine and then accused of poor compliance because intermittent T4 therapy in true hypothyroidism can generate this same pattern of thyroid function tests.

In patients taking thyroxine, an apparent increase in thyroxine requirement, signalled by an increase in TSH in a previously stable patient, could be caused by malabsorption of thyroxine.⁴⁸ Poor absorption can be caused by small bowel disease or, iatrogenically by cholestyramine or iron therapy.⁴⁸ A similar change in thyroid function tests has been noted in some individuals on sertraline, but the exact mechanism remains unclear. Amiodarone therapy frequently results in mildly raised TSH values in the first 3 months of therapy, caused by inhibition of T4 or T3 conversion in the pituitary. Affected individuals have normal free hormone concentrations (or slightly raised free T4), and this situation should be distinguished from true amiodarone induced hypothyroidism.¹⁴ Recovery from severe non-thyroidal illness, during which thyroid hormones were depressed, can be associated with a transient overshoot of TSH, resulting in a similar pattern of thyroid function.⁹

In individuals who are negative for thyroid antibodies, an isolated raised TSH could be a result of subclinical defects in thyroid gland function caused by congenital abnormalities. Some individuals with Pendred's syndrome fall into this category, although most have a goitre but a TSH within the normal range.⁴⁹ The prevalence of this condition could be as high as 1 in 10 000, accounting for as many as 10% of all cases of hereditary sensorineural deafness. The abnormality has been located to a gene on chromosome 7, and Pendrin was cloned in 1997. This gene codes for a putative sulphate transporter. However, the connection with impaired organification of iodine in the thyroid (and therefore a positive perchlorate discharge test) remains unclear.⁴⁹

Additionally, as mentioned above, syndromes of TSH resistance,⁴² some with TSH receptor defects,⁴³ and some cases of thyroglobulin synthetic defects,⁴¹ might be detected for the first time in adulthood and can be associated with an isolated raised TSH and normal-sized thyroid gland. No doubt further congenital abnormalities will be identified.

Normal or raised TSH, raised free T4 or T3

Normal or raised TSH and raised free T4 or T3 values is an unusual pattern of thyroid function tests, which is often artifactual but is sometimes seen in two rare but clinically important conditions (see below and panel 7). If results of the free T4 and T3 assays are widely discordant with each other, or with the clinical status, then antithyroid

Panel 6: Raised TSH, normal free T4 or free T3

Common

Subclinical autoimmune hypothyroidism

Rare

Heterophile (interfering) antibody

Intermittent T4 therapy for hypothyroidism

Drugs: amiodarone, sertraline, cholestyramine

Recovery phase after non-thyroidal illness

Congenital

TSH-receptor defects

Resistance to TSH associated with other (unspecified) defects

Pendred's syndrome—some cases (associated with sensorineural deafness and goitre)

Panel 7: Normal or raised TSH, raised free T4 or free T3

Rare—with discordant free T4 versus free T3

Interfering antibodies to thyroid hormones (anti-TPO antibodies usually also present)

Familial dysalbuminaemic hyperthyroxinaemia

Amiodarone

Rare—other

Intermittent T4 therapy or T4 overdose

Resistance to thyroid hormone

TSH secreting pituitary tumour (hyperthyroid)

Acute psychiatric illness (first 1–3 weeks)

Panel 8: Common errors in interpretation of thyroid function tests

Thyroid function test result	Circumstance	Wrong interpretation	Correct interpretation
Low TSH, low FT3 or FT4	Post-treatment for thyrotoxicosis	Persistent hyperthyroidism	Profoundly hypothyroid
Low TSH, high FT3 or FT4	Short history or neck pain	Established thyrotoxicosis	Possible self-resolving thyroiditis
Low or normal TSH, low or normal FT4 or FT3	Patient systemically ill	Hypothyroid	Non-thyroidal illness
Normal TSH (FT3 or FT4 not tested)	Pituitary disease	Euthyroid	Possibly hypothyroid—check FT4 or FT3
High TSH, normal FT4 or FT3	TSH fails to fall with T4	Non-compliance with T4	Possible interfering heterophile or an antibody

FT4, FT3=free T4, free T3.

hormone (anti-T4 and anti-T3) antibodies interfering with the assay should be suspected. Interference can cause considerable confusion, since it is more common in free rather than in total thyroid hormone assays, and autoantibodies develop in individuals who already have autoimmune thyroid disease and disturbed thyroid function.⁵⁰ Furthermore, in postpartum thyroiditis, fluctuations in the concentration of interfering antibodies have been described. Anti-TPO antibodies are invariably present, which could be of some diagnostic value. Interfering anti-TSH antibodies are rare, so that thyroid function can usually be monitored by TSH concentration alone once interference has been confirmed in the laboratory. Discordant free T4 and T3 results are also seen in familial dysalbuminaemic hyperthyroxinaemia, in which the individual is euthyroid but a defect in albumin results in increased affinity for T4. This disease causes interference with both total and analogue free T4 assays, but free T3 concentrations are usually normal.⁵¹ Note that intermittent T4 therapy, particularly ingestion of a single large dose of T4 as in an overdose, can cause raised free T4 and, to a lesser extent, T3 values without suppression of TSH concentrations. Amiodarone therapy, by raising TSH concentrations (see above) and free T4 values (by inhibiting the conversion of T4 to T3 in the periphery), can generate similar, though usually less dramatic, thyroid function test changes.¹⁴

Changes in thyroid function have also been reported in acute psychiatric illness. Although low thyroid hormone concentrations are typically seen in non-thyroidal illness, raised thyroid hormones have been reported in over 16% of acute psychiatric admissions, usually with a raised TSH.⁵² This pattern is particularly described in individuals with schizophrenia, affective psychosis, and amphetamine abuse and rarely persists beyond day 14. The mechanism and relation to the psychiatric condition remain unclear, but it is important to appreciate this transient biochemical change because thyroid function testing is sometimes done on psychiatric admissions.

The two rare but important clinical conditions, in which detectable TSH is associated with raised free T4 or T3, are thyroid hormone receptor mutations that lead to resistance to thyroid hormone and a TSH secreting pituitary tumour. Features that distinguish these two conditions, and favour resistance to thyroid hormone include: family history of thyroid hormone resistance (dominant inheritance); absence of a pituitary lesion shown by computed tomography or magnetic resonance imaging; a normal α -subunit/TSH molar ratio; a normal sex-hormone-binding globulin concentration; a normal or exaggerated TSH response to TRH; and inhibition of TSH secretion following T3 suppression.^{6,7} The concentration of thyroid hormones or of TSH (usually in the laboratory normal range) does not differ significantly between the two conditions. In neither case is thyroablative treatment indicated. Specialist help should be sought in both instances. TSH secreting pituitary

tumours have recently been shown to respond to long-acting somatostatin analogues.

Summary of common pitfalls

Panel 8 summarises the five most common circumstances in which modern thyroid function tests are wrongly interpreted. Amiodarone therapy is frequently cited by general physicians as rendering thyroid function tests difficult to interpret, but in fact the impact of amiodarone on TSH concentration rarely leads to a grossly erroneous misunderstanding of the patient's thyroid status. If TSH alone is used as the initial screening test, for thyroid function testing, the most important circumstance in which a diagnosis of euthyroidism will be wrongly made is in pituitary failure, when the TSH value in the normal range will not automatically trigger free T3 or T4 testing. De novo cases of pituitary hypothyroidism, and even panhypopituitarism can present with very vague symptoms,⁸ but are thankfully rare. The diagnosis can be promptly made if free T3 or T4 concentrations are established, and justify thyroid hormone testing in the presence of persistent fatigue with a normal TSH especially when associated with gonadal dysfunction.

Conclusion

In most cases, interpretation of thyroid function tests with free hormone assays and TSH is straightforward. However, unusual conditions can generate common patterns of thyroid function, easily confused with more straightforward diseases (panels 2, 5, and 6), and unusual patterns of test results (panels 3, 4, and 7). One or more of the following features should prompt further investigation: (1) abnormal thyroid function in childhood; (2) familial disease; (3) thyroid function results inconsistent with the clinical picture; (4) an unusual pattern of thyroid function tests results—eg, widely discrepant free T4 and T3 results or a detectable TSH with raised free T3 or T4; and (5) transient changes in thyroid function. In many cases, correct diagnosis of rare thyroid conditions from their thyroid function tests has very important implications for the management of individual patients and their family members. With the exception of detailed genetic analysis, the tests required to investigate the diagnosis are easily available. The challenge lies in applying them to the right individual at the right time.

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