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Diagnosis and management of thyrotoxicosis

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- Diagnosis and management of heritable thrombophilias (*BMJ* 2014;348:g4387)
- HIV testing and management of newly diagnosed HIV (*BMJ* 2014;349:g4275)

Thyrotoxicosis is a common condition associated with excess circulating thyroid hormones that may present in myriad ways and thus will be encountered by practitioners in all medical disciplines. In Europe, it affects around 1 in 2000 people annually.[1] Although thyrotoxicosis typically presents with weight loss, heat intolerance, and palpitations, there are a large variety of additional features, which manifest more variably with advancing age and in people with milder disease. It is important to determine the cause of the thyrotoxicosis, as this determines treatment. Some experts distinguish between thyrotoxicosis and hyperthyroidism by restricting the latter term to describe the conditions associated with excess synthesis and secretion of thyroid hormones from the thyroid gland.

This clinical review summarises the current evidence for the diagnosis and management of adults with thyrotoxicosis.

What are the causes of thyrotoxicosis and who gets it?

Table 1 lists the important causes of thyrotoxicosis and the underlying pathogeneses. Graves' disease is the most common cause, accounting for about 75% of cases. It is typical in women aged 30-50 years but can occur at any age in both sexes. People with a history of other autoimmune disorders, those with a family history of thyroid or other autoimmune disorders, and smokers are at an increased risk of Graves' disease.[2] Several case-controlled studies,[3 4] but not all,[5] have shown an increased reporting of major adverse life events within the year before the diagnosis of Graves' disease, indicating that stress may act as a trigger for the disease. Furthermore, observational studies have shown an increased incidence of a new diagnosis or relapse of Graves' disease in the postpartum period, suggesting that childbirth is an additional risk factor.[6] Finally, people who are recovering from immunosuppression such as during highly active antiretroviral therapy for HIV are also at high risk of developing Graves' disease.[7]

Thyrotoxicosis due to toxic nodular goitre is more common in people aged over 60 years. Those living in iodine deficient regions are particularly at risk.

SUMMARY POINTS

- It is important to determine the causes of thyrotoxicosis as some are self limiting
- The test for antibodies to thyroid stimulating hormone receptor is more sensitive and specific than the test for antibodies to thyroid peroxidase for the diagnosis of Graves' disease
- Stratification of the severity of Graves' disease is good practice, allowing patients with a low probability of remission from treatment with antithyroid drugs to be considered for radioiodine or thyroidectomy at an early stage
- The block-replace regimen of antithyroid drugs must not be used to treat hyperthyroidism in pregnancy
- Radioiodine treatment should be avoided in patients with active thyroid eye disease

SOURCES AND SELECTION CRITERIA

We searched Medline, Clinical Evidence, and the Cochrane library using various combinations of terms: "thyrotoxicosis", "hyperthyroidism", "Graves' disease", "subclinical hyperthyroidism", "thyroiditis", "antithyroid drugs", "carbimazole", "methimazole", "propylthiouracil", "amiodarone", "radioiodine", and "thyroidectomy". We gave preference to high quality observational studies, randomised controlled trials, and systematic reviews published in the past 10 years.

What is the underlying pathophysiology of thyrotoxicosis?

Graves' disease is an autoimmune disease mediated by antibodies that stimulate the thyroid stimulating hormone (TSH) receptor, leading to excess secretion of thyroid hormones and hyperplasia of thyroid follicular cells, resulting in hyperthyroidism and diffuse goitre (table 1). Both genetic and environmental factors (for example, smoking, stress, and dietary iodine) play important roles in the pathogenesis of Graves' disease.[8]

Hyperthyroidism in solitary toxic nodule and toxic multinodular goitres results from over-secretion of thyroid hormones by one or more nodules. Histologically these nodules are benign follicular adenomas.

Thyroiditis (subacute, silent, or post partum) causes release of preformed thyroid hormones into the circulation as a result of inflammatory destruction of the thyroid follicles, resulting in transient thyrotoxicosis.

Gestational hyperthyroidism occurs in the first trimester of pregnancy owing to increased secretion of thyroid hormone in response to placental β human chorionic gonadotrophin, which is structurally similar to TSH.[9] Gestational hyperthyroidism is particularly common in women with hyperemesis gravidarum, which is associated with high levels of β human chorionic gonadotrophin.

Several drugs, including amiodarone, iodine, lithium, interferon α, highly active retroviral therapy, tyrosine kinase inhibitors, and levothyroxine can cause thyrotoxicosis in different ways (table 1).

What are the clinical features and associated conditions?

Weight loss, heat intolerance, palpitations, tremor, anxiety, and tiredness are common symptoms of thyrotoxicosis (box). Older patients tend to have fewer symptoms; an observational study of over 3000 consecutive patients with thyrotoxicosis found that more than half of patients aged 61 years or older had fewer than three classic symptoms of thyrotoxicosis.[10] Atrial fibrillation is a commonly associated feature of thyrotoxicosis, particularly in older patients. A recent epidemiological study of over 500 000 adults showed a 13% cumulative incidence of atrial fibrillation over eight

Table 1 | Important causes and underlying mechanisms of thyrotoxicosis in adults

Causes	Underlying mechanisms
Graves' disease	Autoimmunity; stimulation of thyrocytes by TSH receptor antibodies
Toxic multinodular goitre	Autonomous thyroid nodules
Toxic nodule	Autonomous thyroid nodule
Thyroiditis:	
Subacute thyroiditis	Release of preformed thyroid hormones; possibly viral infection
Silent thyroiditis	Release of preformed thyroid hormones
Postpartum thyroiditis	Release of preformed thyroid hormones; autoimmunity
Drugs:	
Levothyroxine/triiodothyronine	Exogenous ingestion of thyroid hormones; iatrogenic or factitious
Amiodarone	Release of preformed thyroid hormones (type 2; thyroiditis) or excess thyroid hormone production (type 1; Jod-Basedow phenomenon)
Lithium	Release of preformed thyroid hormones (thyroiditis) or autoimmunity
Interferon α	Release of preformed thyroid hormones (thyroiditis) or autoimmunity
Highly active antiretroviral therapy	Autoimmunity or release of preformed thyroid hormones (thyroiditis)
Tyrosine kinase inhibitors	Release of preformed thyroid hormones (thyroiditis) or autoimmunity
β human chorionic gonadotrophin mediated hyperthyroidism:	
Gestational hyperthyroidism	Stimulation of thyrocytes by β human chorionic gonadotrophin
Choriocarcinoma	Stimulation of thyrocytes by β human chorionic gonadotrophin
Hydatidiform mole	Stimulation of thyrocytes by β human chorionic gonadotrophin
Struma ovarii	Ovarian teratoma with autonomous thyroid tissue
Non-autoimmune familial hyperthyroidism	Constitutive activation of TSH receptor due to germline mutation
TSH secreting pituitary adenoma	Stimulation of thyrocytes by excess TSH secreted by pituitary adenoma

TSH=thyroid stimulating hormone.

years among people with thyrotoxicosis aged more than 65 years.[11]

Thyrotoxicosis is sometimes associated with acute muscle paralysis and severe hypokalaemia, called thyrotoxic periodic paralysis. It is most commonly seen in Asian men with thyrotoxicosis and is often triggered by strenuous physical activity, high carbohydrate load, alcohol, or infection.[12]

Rarely, patients with thyrotoxicosis present with thyroid storm, which is a life threatening condition associated with tachycardia, fever, agitation, altered mental state, features of cardiac failure, and deranged liver function.[13] Poor compliance to treatment, surgery, infection, childbirth, and trauma are common precipitating factors.

How do you determine the cause of thyrotoxicosis?

Figure 1 shows an algorithm for the investigation of patients presenting with symptoms of thyrotoxicosis.

The diagnosis of primary hyperthyroidism is usually based on increased serum free thyroxine levels in the presence of fully suppressed serum TSH (<0.05 mIU/L) levels. If the level of free thyroxine is normal in the presence of suppressed TSH, then the levels of free triiodothyronine must be checked to exclude triiodothyronine (T3) thyrotoxicosis. This should be considered as a mild form of hyperthyroidism and is commonly seen in association with toxic multinodular goitre or a toxic thyroid nodule but can also be a feature of mild Graves' disease. Low or suppressed TSH levels in the presence of normal free thyroxine and free triiodothyronine levels is termed subclinical hyperthyroidism.

Taking a careful clinical history and carrying out a physical examination often provide clues as to the cause of thyrotoxicosis. For example, ophthalmopathy, dermopathy, and acropachy are hallmarks of Graves' disease (fig 2). In the absence of these features, the diagnosis of Graves' disease can be confirmed by checking the serum levels of antibodies to the TSH receptor. A recent meta-analysis has shown that such antibodies measured with immunoassay methods are highly sensitive and specific for the diagnosis of Graves' disease (third generation assay: sensitivity 98%, specificity 99%).[14] In contrast, thyroid peroxidase antibodies are present only in about 75% of cases of Graves' disease. If TSH

Common symptoms and signs of thyrotoxicosis

Symptoms

- Weight loss
- Palpitations
- Breathlessness
- Tremor
- Tiredness
- Heat intolerance
- Excessive sweating
- Increased bowel action
- Anxiety
- Nervousness
- Muscle weakness
- Menstrual disturbances (oligomenorrhoea and amenorrhoea)
- Loss of libido

Signs

- Weight loss
- Tachycardia
- Atrial fibrillation
- Fine tremor
- Skin erythema
- Sweaty palms and palmar erythema
- Onycholysis
- Prominent eyes and eyelid retraction
- Muscle weakness
- Systolic hypertension, wide pulse pressure
- Thyroid bruit
- Signs of cardiac failure

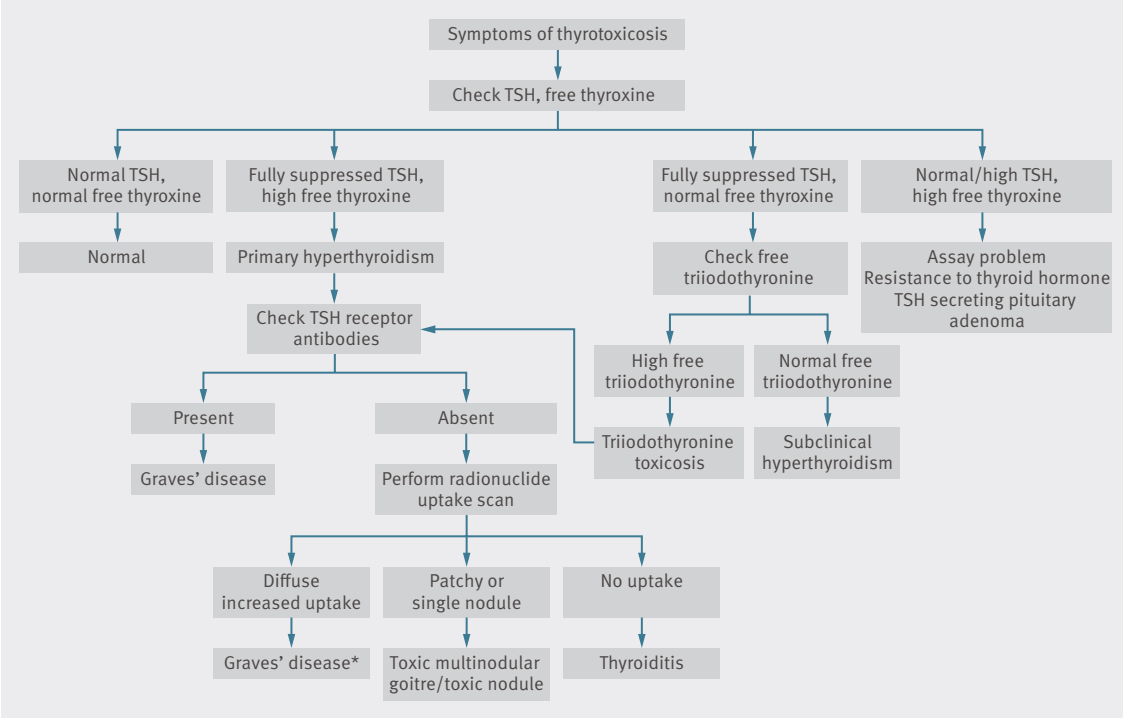

Fig 1 | Algorithm for investigation of thyrotoxicosis. TSH=thyroid stimulating hormone. *Patients might also have non-autoimmune familial hyperthyroidism

receptor antibodies are not present, a scan of radionuclide thyroid uptake (with radioactive technetium or iodide) can be helpful to distinguish the different causes of thyrotoxicosis (fig 3). In subacute thyroiditis, inflammatory markers such as erythrocyte sedimentation rate and C reactive protein are usually increased.[15]

When should general practitioners refer?

All patients with new onset thyrotoxicosis warrant assessment in secondary care, to establish the cause and to agree on a management plan. Prepregnancy consultation for counselling and optimisation of treatment for those who are currently receiving antithyroid drugs or who have received radioiodine therapy or thyroidectomy in the past is also worthwhile.

What are the treatment options?

Graves' disease

The treatment options for hyperthyroid Graves' disease include thionamide drugs, radioiodine, or thyroid surgery (thyroidectomy). β blockers (for example, propranolol modified release 80 mg once or twice daily) are useful for the control of symptoms in all patients with thyrotoxicosis but are contraindicated in those with asthma. Anticoagulation is also warranted in most patients with thyrotoxicosis who have atrial fibrillation. A randomised controlled trial of antithyroid drugs, thyroidectomy, or radioiodine in Graves' disease showed no significant difference in patient satisfaction with the three treatment options.[16] Each modality has its own advantages and drawbacks, and patient preference is often a deciding factor.

Thionamide drugs

The thionamide drugs, propylthiouracil, carbimazole, and its active metabolite methimazole, have been in use to treat thyrotoxicosis for more than 60 years. A meta-analysis of randomised controlled trials showed long term remission of hyperthyroid Graves' disease in about 50% of those treated with thionamide drugs for a prolonged period.[17] Carbimazole or methimazole are preferred in most situations, as a small risk of serious liver injury (about 1 in 10 000 adults) has recently been highlighted during propylthiouracil use.[18] In addition, carbimazole or methimazole can be taken once daily rather than every eight or 12 hours as is the case for propylthiouracil, and the longer half life leads to more rapid control.

Table 2 | Considerations in administering the block-replace versus titrated regimens of antithyroid drugs

Factors	Block-replace	Titrated dose
Stability	Easier to maintain stable euthyroidism	Prone to fluctuating hypothyroidism and hyperthyroidism
Monitoring	Fewer thyroid function tests and clinic visits	More thyroid function tests and clinic visits
Side effects	High risk	Low risk
Optimal remission*	Ranges from 6-12 months	Ranges from 12-18 months
Ease of use	More complex regimen with less likelihood of compliance and more prone to drug errors	Simpler regimen with better compliance and less prone to drug errors
Prediction of remission	Not possible to predict remission by dose changes	Prediction of early remission by successful dose reduction
Cost of drugs	High	Low

*No significant difference in early or late remission rates between either regimen.

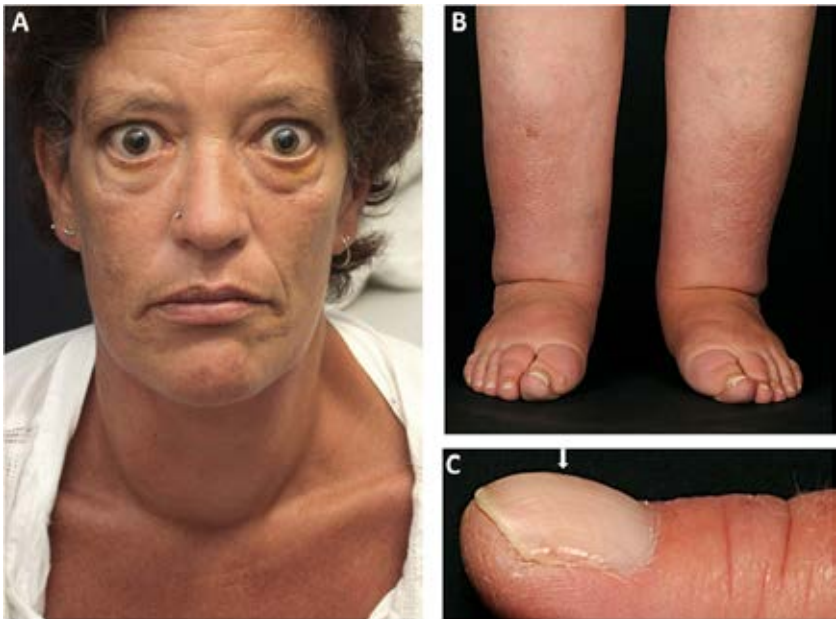

Fig 2 | Extrathyroidal manifestations of Graves' disease: (A) thyroid eye disease with periorbital swelling, eyelid retraction, and exophthalmos (the patient also has a bilateral, symmetrical goitre); (B) thyroid associated dermopathy (pretibial myxoedema) with non-pitting oedema as a result of diffuse waxy induration of skin on both legs; and (C) thyroid acropachy (arrow) with clubbing and swelling of the finger

Thionamides reduce levels of circulating thyroid hormones by acting as a preferential substrate for iodination by thyroid peroxidase, the key enzyme in thyroid hormone synthesis. Most patients with hyperthyroid Graves' disease are rendered euthyroid (as judged by normal free thyroid hormone levels) by 4-8 weeks treatment with methimazole (15-30 mg daily) or carbimazole (20-40 mg daily). Patients with severe hyperthyroidism (free thyroxine >70 pmol/L), large goitre, or recent exposure to iodide (including contrast media used for computed tomography) may need to be treated for longer, or with larger thionamide doses.

After euthyroidism is achieved, two different regimens can be employed. In the first regimen, termed "block-replace," the dose of thionamide is kept constant (for example, carbimazole 40 mg daily), thus blocking thyroid hormone production, and levothyroxine is then added in a suitable dose to maintain euthyroidism (for example, 100 µg daily for women, 125 µg daily for men). In the second regimen, termed "titrated," the thionamide dose is progressively lowered at regular intervals to allow endogenous synthesis of thyroid hormone to continue in a regulated fashion. Table 2 lists the advantages and disadvantages of the two methods. In both regimens the remission rate is approximately 50% if treatment is continued for between six and 18 months and then stopped.[19] The most important disadvantage of treatment with either regimen is the uncertainty of whether patients will relapse after treatment is stopped and the potential adverse effects of the drugs.

A pruritic rash, which is often transient, is seen in about 5% of patients taking antithyroid drugs. The much rarer but occasionally lethal problem of thionamide induced agranulocytosis occurs in about 1 in 300 people.[20] It usually presents with sore throat, mouth ulcers, and high fever. All patients embarking on antithyroid drug treatment should receive clear verbal and written information about this adverse effect with advice to stop the drug and have a blood test for full blood count if they develop these warning symptoms. Agranulocytosis occurs most commonly in the first three months of treatment (median 30 days) and is rare after six months.[21 22] An observational study of more than 5000 Japanese patients found agranulocytosis in 0.8% of patients who started treatment with 30 mg methimazole compared with 0.2% of those starting with 15 mg,[23] suggesting that drug dose is an important risk factor.

Whether using titrated or block-replace regimens, trials have shown that prolonged treatment beyond 18 months has no advantage in remission rates,[19] and the drugs should generally be stopped at this stage, with testing of thyroid function at 4-6 weeks to detect early relapse. The ideal patients to treat with antithyroid drugs for Graves' disease are those with a high chance of remission after treatment. Thus women, age over 40 years, small thyroid size, no extrathyroidal manifestations, mild hyperthyroxinaemia, or triiodothyronine thyrotoxicosis at presentation and a low titre of TSH receptor antibodies are most likely to have a successful outcome from drug treatment.[24] After relapse, a long term, small dose of thionamide is an acceptable option where definitive treatment with radioiodine or surgery is not feasible.

Radioiodine

Radioiodine (iodine-131) is a β and γ radiation emitter, which is rapidly concentrated by the thyroid after oral ingestion. The β radiation has a 2 mm radius of activity and induces DNA damage leading to death of thyroid cells. Six weeks to six months after radioiodine treatment most patients with Graves' disease are rendered sequentially euthyroid and then hypothyroid.[25] A pragmatic fixed dose that results in euthryoidism or hypothyroidism in 70-90% of patients is

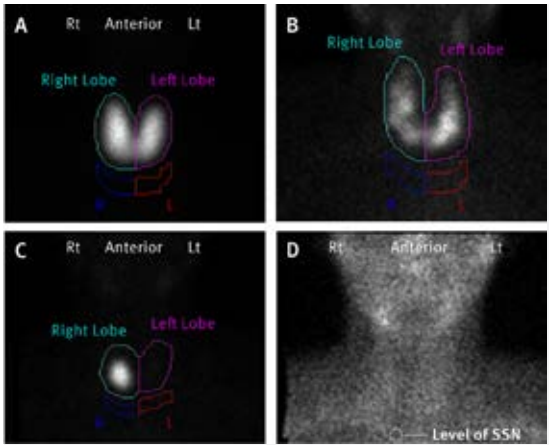

Fig 3 | Radionuclide uptake scans in thyrotoxicosis from different causes: (A) bilaterally symmetrical diffusely increased uptake in Graves' disease (patients with non-autoimmune familial hyperthyroidism show similar results); (B) asymmetrical patchy uptake in toxic multinodular goitre; (C) localised focal uptake in solitary toxic nodule (note diminished uptake in rest of thyroid); and (D) absence of uptake during thyrotoxic phase of subacute, painless, or postpartum thyroiditis (patients with thyrotoxicosis due to exogenous levothyroxine ingestion show similar results)

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Thyroid disease manager (www.thyroidmanager.org/)
—a web based comprehensive and up to date textbook with chapters on different thyroid disorders (free registration is required to access chapters)

NICE clinical knowledge summaries (http://cks.nice.org.uk/hyperthyroidism#!topicsummary)
—this website is particularly useful for primary care practitioners and contains current evidence based best practice guidance on the management of more than 300 common conditions, including hyperthyroidism

American Thyroid Association and American Association of Clinical Endocrinologists guidelines on management of hyperthyroidism (http://thyroidguidelines.net/sites/thyroidguidelines.net/files/file/THY_2010_0417.pdf)
—a useful evidence based guideline on management of hyperthyroidism

The Endocrine Society clinical practice guideline on management of thyroid dysfunction during pregnancy and post partum (http://press.endocrine.org/doi/pdf/10.1210/jc.2011-2803)—a comprehensive guideline on management of thyroid disorders (including hyperthyroidism) in pregnancy

Resources for patients

NHS Choices (www.nhs.uk/Conditions/Thyroid-over-active/)
—provides information on a wide range of health problems, including thyrotoxicosis

British Thyroid Foundation (www.btf-thyroid.org/) and Thyroid Eye Disease Charitable Trust (www.tedct.co.uk/)
—national charities and patient support organisations for patients with thyroid diseases, including thyrotoxicosis and thyroid eye disease

British Thyroid Association (www.british-thyroid-association.org/info-for-patients/) and American Thyroid Association (www.thyroid.org/patient-thyroid-information/)
—both websites provide information on different thyroid disorders in a separate section dedicated for patients and families

ONGOING RESEARCH

Selenium supplementation versus placebo in patients with Graves' hyperthyroidism. Copenhagen University Hospital Rigshospitalet, Denmark (www.clinicaltrials.gov/ct2/show/NCT01611896?term=hyperthyroidism&rank=4)

Post-radioiodine Graves' management: the PRAGMA Study. Newcastle upon Tyne Hospitals NHS Trust, UK (www.clinicaltrials.gov/ct2/show/NCT01885533?term=hyperthyroidism&rank=78)

Short term prednisolone to treat moderate and severe subacute thyroiditis. Xinqiao Hospital of Chongqing, China (www.clinicaltrials.gov/ct2/show/NCT01837433?term=thyroiditis&rank=10)

QUESTIONS FOR FUTURE RESEARCH

Is the block-replace regimen superior to the titration regimen for the treatment of Graves' disease with antithyroid drugs?

What is the safest treatment for women with Graves' disease who are pregnant or planning pregnancy?

What is the most appropriate management strategy for asymptomatic mild hyperthyroidism and subclinical hyperthyroidism?

Will new treatments with immunomodulatory biological agents or thyroid stimulating hormone receptor antagonists become an alternative or a useful adjunct to thionamide antithyroid drugs for Graves' disease?

recommended, as attempts to use dosimetry to estimate the optimal individual dose of radioiodine does not improve outcome.[26] Current UK guidance suggests doses of 370 to 550 MBq for routine use in Graves' disease.[27] Patients with large goitres, however, may need higher or repeated doses to achieve euthyroidism. Although radioiodine is commonly used in Graves' disease after a recurrence or side effects from antithyroid drugs,[28] it should also be considered as the preferred treatment for those with severe Graves' disease (particularly young patients aged less than 40 years, men, and those with a large goitre), who are unlikely to achieve long term remission with antithyroid drugs.[24] Radioiodine is also a good treatment for patients who want a predictable cure and for whom the high probability of subsequent lifelong levothyroxine treatment is an acceptable consequence. A recent analysis found that early use of radioiodine is the cheapest long term management strategy for Graves' disease.[29]

In the month after radioiodine treatment there is a small risk of thyrotoxicosis being exacerbated (or even a thyroid storm being precipitated) due to the release of preformed hormone. To reduce this risk it is recommended that patients with large goitres, severe thyrotoxicosis, ischaemic heart disease, heart failure, or arrhythmia should be pretreated with thionamide until they are euthyroid.[27 30] A meta-analysis showed that to obtain optimal outcomes from radioiodine, methimazole or carbimazole should be stopped at least a week before radioiodine therapy.[31] However, it is widely believed that propylthiouracil should be stopped at least two weeks beforehand. Antithyroid drugs can be restarted two weeks after the radioiodine dose, if ongoing control of thyrotoxicosis is critical. Patients should be monitored with regular thyroid function tests for early detection of radioiodine induced hypothyroidism.

Radioiodine is absolutely contraindicated in pregnancy and lactation, and patients are advised to avoid a new pregnancy for six months after treatment.[27] Patients receiving a standard dose of radioiodine in the United Kingdom are also advised to take several precautions to minimise the perceived deleterious effects of ionising radiation to others.[27] For example, close and prolonged contact with children and pregnant women should be avoided for about three weeks (after a 400 MBq dose). Several studies have looked at the risk of cancer after the therapeutic use of radioiodine and the data are strongly reassuring that cancers at all major sites are no different or less common in patients treated with radioiodine than in the background population.[32 33]

Radioiodine is relatively contraindicated in those with active inflammatory Graves' ophthalmopathy, as the release of thyroid antigen and subsequent hypothyroidism may be associated with deterioration of eye disease.[34 35] The risk of deterioration of eye disease is, however, small in patients with inactive ophthalmopathy as long as thyroxine replacement is prompt.[36] The risk of ophthalmopathy is much higher in smokers, but can be abrogated by a short course of prednisolone.[37]

Thyroid surgery

Total (or near total) thyroidectomy is a highly effective and predictable treatment for Graves' disease. Patients with Graves' disease who have relapsed after adequate medical treatment, those with active Graves' ophthalmopathy,

or those with a cosmetically undesirable goitre are all well suited to surgical intervention. Long term complications of thyroidectomy include hypocalcaemia as a result of hypoparathyroidism, which is most often transient, and vocal cord paresis due to operative compromise of the recurrent laryngeal nerve. Patients need to be rendered euthyroid before surgery, and where thionamide antithyroid drugs cannot be used, iodine loading with potassium iodide, Lugol's iodine, or oral cholecystographic contrast media (iopanoic acid 1 g daily) for 5-10 days is sufficient to achieve euthyroidism in almost all cases.[38]

Toxic multinodular goitre and solitary toxic nodule

Antithyroid drugs do not lead to long term remission of thyrotoxicosis in toxic multinodular goitre or solitary toxic nodules. Therefore radioiodine is the treatment of choice for most patients with these conditions. When treatment with radioiodine is not possible, the alternatives are a long term small dose of carbimazole (or methimazole) or thyroid surgery.

Thyroiditis

Thyrotoxicosis associated with thyroiditis is transient, often progresses through a hypothyroid phase, and then resolves spontaneously. Antithyroid drugs are ineffective and should be avoided. Treatment is often limited to symptom control with β blockers. In subacute thyroiditis, non-steroidal anti-inflammatory drugs and occasionally systemic glucocorticoids may be required to control pain.

Drug induced thyrotoxicosis

Amiodarone induced thyrotoxicosis may result from autoimmunity (type 1) or a destructive thyroiditis with release of preformed thyroid hormones (type 2). Close liaison with a cardiologist is recommended to best manage these patients. The most common form in the United Kingdom is type 2 amiodarone induced thyroiditis, and a recent randomised controlled trial found that the most effective treatment for this was prednisolone.[39] Type 1 amiodarone induced thyrotoxicosis is treated with antithyroid drugs.

Treatment of thyrotoxicosis associated with other drugs, such as lithium, interferon α, highly active antiretroviral therapy, and tyrosine kinase inhibitors depends on whether the underlying mechanism is autoimmunity or destructive thyroiditis. More often than not these conditions are self limiting, and timely investigation saves patients from unnecessary treatment. Consultation between the specialist prescribing the drug in question and an endocrinologist is recommended.

Special situations

Pregnancy and lactation

Graves' disease is the commonest cause of hyperthyroidism presenting in pregnancy; however, it needs to be distinguished from gestational hyperthyroidism mediated by β human chorionic gonadotrophin. The latter is characterised by the absence of ophthalmopathy or a large goitre, absent TSH receptor antibodies, and spontaneous resolution of hyperthyroidism by 20 weeks of gestation.

Antithyroid drugs are the mainstay of treatment for hyperthyroid Graves' disease in pregnancy, and a titrated dose regimen is mandatory as block-replace regimens are

TIPS FOR NON-SPECIALISTS

Patients aged more than 70 years with thyrotoxicosis often manifest minimal classic symptoms and signs. They sometimes present with apathy, lethargy, and depression mimicking a depressive disorder (apathetic thyrotoxicosis)

Diagnosis of thyrotoxicosis should be considered in patients presenting with unexplained weight loss or atrial fibrillation

Rapid onset of thyrotoxic symptoms over one day or two days signals thyroiditis as the likely diagnosis rather than Graves' disease

If β blockers are contraindicated, diltiazem may be used to reduce tachycardia in thyrotoxicosis

WHAT TO TELL PATIENTS WITH NEWLY DIAGNOSED GRAVES' DISEASE WHO ARE STARTING ANTITHYROID DRUGS

It takes at least 5-10 days of treatment before any improvement in symptoms of thyrotoxicosis will be noticed

Agranulocytosis is a rare but serious side effect of antithyroid drugs and usually presents with sore throat, mouth ulcers, and high fever. If these symptoms develop, you must stop the drug and have a blood test for a full blood count

If you have lost weight, expect to gain it again after treatment. Your appetite may be increased at diagnosis and you should curb your food intake quickly once the thyroid condition comes under control

Continuing to smoke increases the risk of thyroid eye disease, delays the onset of action of antithyroid drugs, and increases the risk of relapse of thyrotoxicosis after stopping treatment

Taking antithyroid drugs (in particular, carbimazole or methimazole) in early pregnancy is associated with birth defects in offspring. Tell your doctor if you are planning a pregnancy

A PATIENT'S PERSPECTIVE

At the age of 23 I started to eat more, my bowels opened more frequently, and I felt tired. I put this down to working out too much at the gym. I also noticed that I had lost a few kilograms in weight over a few months, but I had no palpitations. One day, I could not lift the weight that I used to after two months off from the gym. Then I experienced weakness of my lower limbs, such that I struggled to stand and walk. It took me a few days to recover. I thought this was due to the exercise that I had done being too much. However, three months later I had a few episodes of weakness in my lower limbs at night. I did not seek any medical advice until an episode when I fell over in the bath, which returned to normal within 12 hours. My GP had no idea about the cause. I had further episodes after that but the GP was not able to explain what was happening. My friend's dad, who is a neurosurgeon, suggested that I may be suffering from thyrotoxic periodic paralysis. After the blood test for my thyroid function showed thyrotoxicosis, I was treated with carbimazole and propranolol. After the treatment, my appetite has returned back to normal, my bowels do not open as frequently, and I feel a lot less tired. The muscle weakness episodes have also disappeared.

Male Chinese student, Exeter, United Kingdom

associated with a risk of fetal hypothyroidism and goitre. There is evidence for a small risk of embryopathy with all antithyroid drugs. A nationwide birth cohort study from Denmark showed birth defects in 9.1% of offspring of mothers treated with carbimazole or methimazole, compared with 8.0% treated with propylthiouracil and 5.4% in untreated women with a previous diagnosis of hyperthyroidism.[40] The spectrum of congenital abnormalities seems different, with aplasia cutis, choanal atresia, tracheo-oesophageal fistula, and omphalocoele with carbimazole or methimazole but potentially less severe facial, neck, urinary tract, and cardiac malformations with propylthiouracil. This risk of congenital defects with antithyroid drugs also has to be balanced against the much rarer risk of serious maternal hepatotoxicity with propylthiouracil.[41] Current guidelines recommend that propylthiouracil is preferred during the first trimester of pregnancy.[9 42] Given the uncertainties relating to birth defects, a full discussion with prospective mothers is warranted. If women of childbearing age present with hyperthyroid Graves' disease and express the wish for future pregnancy, the advantages of early definitive treatment with radioiodine or surgery should be discussed.

Breast feeding is safe with all three antithyroid drugs (daily doses of up to 20 mg methimazole or carbimazole or 300 mg propylthiouracil); however, because of the small risk of severe liver toxicity associated with propylthiouracil, the current guidelines recommend methimazole or carbimazole as the preferred antithyroid drugs for lactating women.[42]

Thyroid eye disease

Radioiodine should be avoided in active Graves' ophthalmopathy. Antithyroid drugs in a block-replace regimen is probably the optimal treatment until the ophthalmopathy becomes inactive.[43 44] If this cannot be tolerated then total thyroidectomy is a good option. Patients with ophthalmopathy may need specific treatment and should be referred early to specialist services.[45]

Subclinical hyperthyroidism

Subclinical hyperthyroidism refers to a state of low or suppressed serum TSH levels with normal circulating free thyroxine and free triiodothyronine levels. It occurs in 2-3% of patients over the age of 80 years,[46] with around 0.7% having the more important abnormality of suppression of serum TSH levels to <0.1 mIU/L. Prospective studies have shown that more than 50% of patients with subclinical hyperthyroidism, and particularly those with a low but not suppressed TSH level (range 0.1-0.4 mIU/L), have a transient abnormality.[47] A low or suppressed TSH level may also be caused by several drugs, including opiates, levodopa, anti-inflammatory doses of glucocorticoid, metformin, and levothyroxine. In addition, persistently low or suppressed serum TSH levels can presage more major systemic illness, such as chronic infection or covert cancer. Although epidemiological studies show that a low serum TSH level is associated with an increased risk of atrial fibrillation,[48 49] and in some studies excess vascular mortality,[47 49] only a few patients have evidence of intrinsic thyroid disease. Current opinion favours consideration of antithyroid treatment in patients aged more than 65 years with a persistently suppressed TSH level (<0.1 mIU/L), particularly in the presence of atrial fibrillation or other cardiac problems.[50] In people with untreated subclinical hyperthyroidism, thyroid function tests should be carried out annually to detect progression to overt thyrotoxicosis.

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References are in the version on thebmj.com.

ANSWERS TO ENDGAMES, p 36

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Axial T2 weighted magnetic resonance image of the base of the brain

A: Vestibulocochlear nerve
B: Facial nerve
C: Basilar artery
D: Meckel's cave
E: Anterior pole of temporal lobe

STATISTICAL QUESTION

Randomised controlled trials: inferring significance of treatment effects based on confidence intervals

Statement *b* is true and *a* is false.

PICTURE QUIZ

A woman with pain and weakness in both legs

1 Both T1 weighted and T2 weighted imaging show a mass that is slightly hypointense relative to the spinal cord. Homogeneous enhancement of the mass and a dural tail sign were also seen after intravenous injection of gadolinium-diethylenetriaminepentaacetate (Gd-DTPA).
2 The main differential diagnoses in this patient are spinal lymphoma, spinal tuberculosis, spinal meningioma, and a metastatic tumour.
3 The correct diagnosis is one that is rarely encountered in clinical practice and does not fall under one of the four main differential diagnoses. It is extramedullary plasmacytoma, which is diagnosed mainly by a combination of histopathological and immunohistochemical analysis.
4 Extramedullary plasmacytomas are highly sensitive to radiotherapy. NCCN guidelines recommend radiotherapy (≥45 Gy) to the involved field.