# Managing an elderly woman with Graves' disease

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*The immediate management and investigation of an acute endocrine presentation in general practice is discussed in this section. It is inspired by, but not based on, a real patient situation.*

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***Jeannette, a 71-year-old previously fit and well woman, presents to you, her GP, with a three-day history of anxiety, tremors, dizziness and palpitations. Jeannette's family have noticed that she has increasing agitation at home and difficulty with concentration. On further questioning, Jeanette has experienced some chest tightness and shortness of breath, but no cough, sputum or other infective symptoms such as fevers, chills or rigors over the past two weeks. She also has general malaise, but normal bowel and urinary functions.***

***What are the possible causes of Jeannette's symptoms?***

***Answer:*** Jeannette's symptoms could be caused by several possible acute illnesses. In her age group, infective illnesses are a common explanation for a behavioural change. Although she has no overt infective symptoms, pneumonia and urinary tract infection should be excluded.

Other causes that should be considered include new-onset atrial fibrillation, electrolyte disturbances, endocrine disturbances especially hyperthyroidism, myocardial ischaemia, pulmonary emboli, adverse drug effects including medication commencement or withdrawal, and vitamin deficiencies.

***What features should you look for on physical examination?***

***Answer:*** You examine Jeannette to exclude any life-threatening causes, particularly any suggestion of pulmonary embolus, myocardial ischaemia or sepsis that might warrant urgent referral to the emergency department.

On general inspection, she is well but diaphoretic. She has a fine tremor in her hands and sweaty palms. Her pulse is irregularly irregular with a heart rate of 85 beats per minute. Her blood pressure is 120/70 mmHg, with saturations of 95% on room air and a normal temperature of 37.1ºC.

Cardiac examination confirms tachycardia, but there are no murmurs. She has normal chest auscultation. Abdominal examination is unremarkable and her legs show mild pitting oedema to just above the ankles. She has no signs of proptosis or exophthalmos but she does have a diffusely enlarged palpable goitre. There are no palpable thyroid nodules.

In summary, she has a tachyarrhythmia with a goitre and mild heart failure.

***What is the likely cause of Jeannette's symptoms?***

***Answer:*** Jeannette has typical symptoms and signs of hyperthyroidism complicated by atrial fibrillation. The most common cause of hyperthyroidism is Graves' disease, which has some



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### 1. Unique clinical features of Graves' disease

**Ophthalmopathy features**
This is defined by an inflammatory process in the extraocular muscles, orbital fat and connective tissue. Diplopia may occur due to impaired extraocular muscles, and proptosis (exophthalmos) may lead to corneal exposure leading to irritation, ulceration and even optic neuropathy or blindness. Oedema in the periorbital space and conjunctiva (conjunctival injection) commonly occur. Smoking is a known risk factor.

**Skin manifestations**
Dermopathy, a rare manifestation, is an infiltrative disease with the most common site being over the shins (pretibial myxoedema). It can also occur in scar tissue. It appears as raised, hyperpigmented orange peel textured papules. Other skin manifestations include smooth textured skin, excessive sweating and warmth, onycholysis, hyperpigmentation and hair loss or thinning (telogen effluvium). Vitiligo or alopecia can also be seen in association with autoimmune causes of hyperthyroidism. Cutaneous reactions may also occur with use of thionamide therapy.

**Cardiovascular features**
These include tachycardia, widened pulse pressure, hyperdynamic circulation, hypertension, cardiomyopathy with high or normal output heart failure and arrhythmias. Atrial fibrillation occurs in 10 to 20% of patients with hyperthyroidism, but is more common in older people. Most will revert to sinus rhythm with appropriate treatment of hyperthyroidism. Most patients with hyperthyroidism and atrial fibrillation should be anticoagulated.

**Respiratory features**
These include tracheal obstruction with large goitres, pulmonary hypertension and respiratory muscle dysfunction leading to hypercapnoea and reduced exercise tolerance. Proximal muscle weakness is common as is hyper-reflexia.

**Other features**
These include weight change due to the alterations in appetite and metabolic state (usually weight loss), and neuropsychiatric symptoms with a behavioural change, which is very common in older patients. Insomnia, agitation or even depression or psychosis may occur. Women may become oligo- or amenorrhoeic. Erectile dysfunction may occur in men along with gynaecomastia due to upregulation of hepatic sex hormone binding globulin production with consequent reduction in free (active) sex hormones leading to relative hypogonadism.

### 2. Causes of hyperthyroidism

**Endogenous excess**
- Graves' disease (autoimmune)
- Hashimoto's disease (autoimmune)
- Toxic adenoma (rarely malignant; autonomous thyroid nodule)
- Multinodular goitre (autonomous thyroid)
- Painless thyroiditis (e.g. postpartum)
- Subacute (painful granulomatous) thyroiditis
- Amiodarone-induced thyroiditis
- Radiation-induced thyroiditis
- Iodine load/contrast-induced thyroiditis

**Exogenous thyroxine**
- Excessive replacement
- Factitious hyperthyroidism

**Rarer causes**
- Pituitary tumour (thyroid-stimulating hormone producing)
- Hyperemesis gravidarum (pregnancy and human chorionic gonadotrophin mediated)
- Molar pregnancy (pregnancy and human chorionic gonadotrophin mediated)
- Metastatic follicular thyroid cancer (ectopic thyroid hormone)
- Ovarian tumour (struma ovarii; ectopic thyroid hormone)

unique clinical features particularly ophthalmopathy and dermopathy (see Box 1).

***You explain to Jeannette that hyperthyroidism is a possible diagnosis and you send her for thyroid function tests. What are the results and can you confirm the diagnosis?***
***Answer:*** The results are as follows:
- thyroid-stimulating hormone (TSH), less than 0.005 mIU/L (reference range 0.400–5.00 mIU/L)
- free thyroxine (T4), 66.0 pmol/L (reference range 10.0–20.0 pmol/L)
- free triiodothyronine (T3), more than 46.1 pmol/L (reference range 2.3–5.7 pmol/L).

A low TSH level with a high T4 and/or T3 level confirms the diagnosis of primary hyperthyroidism.

***What are the causes of hyperthyroidism?***
***Answer:*** The causes of hyperthyroidism can be divided into three main categories: endogenous excess, exogenous thyroxine and rarer causes (see Box 2). Graves' disease is due to an endogenous excess, and is the most common cause of primary hyperthyroidism. Toxic adenomas and multinodular goitres are also due to an endogenous excess where thyroid hormone is produced autonomously. However, these generally result in less severe elevations in free T4 and free T3 levels. Insults to thyroid tissue can result in many different types of thyroiditis.

***What further investigations should be ordered so that the diagnosis can be confirmed?***
***Answer:*** Further investigations and results are as follows:
- thyroid receptor antibody (TRAb), 23 IU/L (reference range <1.8 IU/L)
- thyroglobulin antibody (TgAb), 3.7 kIU/L (reference range <4.1 kIU/L)
- thyroid peroxidase antibody (TPOAb), 200 kIU/L (reference range <5.6 kIU/L).

Patients with Graves' disease will often have a disproportionate rise in T3 compared with T4 due to direct upregulation of intrathyroidal free T3 production. This can lead to more severe manifestations of thyrotoxicosis. To confirm a diagnosis of Graves' disease, measurement of TRAb levels is useful. This



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is elevated in 95% of patients with Graves' disease and may have some prognostic significance in regard to response to treatment and risk of relapse. It is worth noting that a 'thyroid receptor antibody or TRAb' must be specifically requested as opposed to 'thyroid antibodies'; the latter under Medicare testing schedules will result in measurements of TgAb and TPOAb (also called thyroid microsomal antibody [TMAb]) being performed but not the required TRAb. Although TgAb and TPOAb (or TMAb) may also be elevated in patients with Graves' disease, they are not specific for this diagnosis and may also be elevated in other forms of autoimmune thyroid disease such as Hashimoto's thyroiditis.

If TRAb status is negative, a thyroid ultrasound and/or thyroid uptake scan are helpful to confirm the diagnosis of Graves' disease and exclude other causes such as adenoma or multinodular goitre.

An ultrasound may not reliably distinguish between the different causes of hyperthyroidism. A thyroid uptake scan is more useful in determining the function of the gland (Figures 1a and 1b).

***How should Jeannette be managed?***

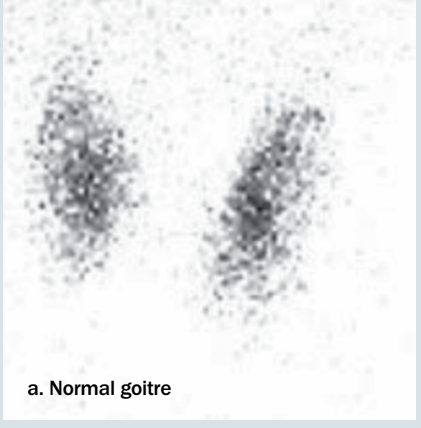
***Answer:*** It is important to be acutely aware of the possibility of thyroid storm, albeit very rare. Few patients will experience this clinical syndrome characterised by exaggerated symptoms of hyperthyroidism. In these cases, patients may become extremely tachycardic with heart failure, hypotension, sudden arrhythmias (including supraventricular and ventricular tachycardia), fevers, agitation, tremor, delirium, psychosis, stupor or coma. Patients with any of these features should be referred for emergency assessment.

Jeannette does not have thyroid storm, so the first objective of her management is to ameliorate her beta-adrenergic symptoms of hyperthyroidism, including palpitations, tachycardia, tremulousness, anxiety and heat intolerance. Nonselective beta blockers such as propranolol are commonly used for symptomatic management because they control heart rate, while improving dyspnoea and exercise tolerance. Historically, high-dose propranolol has been popular in people with hyperthyroidism because in addition to relative nonselectivity it has the added benefit of slowly reducing serum T3 concentrations by as much as 30%. Metoprolol and atenolol are newer agents that also have this T3 lowering effect and are becoming common alternatives; both have relative greater beta-1 selectivity (tachycardia versus tremor and vasodilation). All these beta blockers reduce T3 levels by preventing the conversion of T4 to the active metabolite. Contraindications to beta blockers, such as severe asthma or peripheral vascular disease, should always be considered before starting therapy.

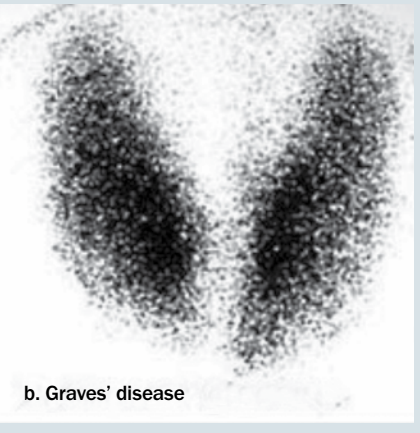
All patients with Graves' disease will need simultaneous pharmacotherapy to reduce the circulating levels of T4 and the active metabolite T3. The conventional drugs for hyperthyroidism are the thionamides carbimazole and propylthiouracil. Carbimazole should achieve a euthyroid state within weeks to months, and the dose is rapidly tapered as the levels of thyroid hormone normalise. Propylthiouracil is used preferentially during the first trimester of pregnancy to avoid teratogenicity associated with methimazole and carbimazole. Due to reports of hepatotoxicity, patients requiring ongoing medical therapy should generally be switched back to carbimazole in the second and third trimesters, once the formative embryonic period has passed. If nonpregnant patients have allergies to carbimazole, then propylthiouracil can be used before definitive therapy, although propylthiouracil should be avoided in children due to the risk of hepatotoxicity. A weaning dose over a treatment period of 12 to 18 months has been found to predict the optimal chance (approximately 50%) of long-term remission. Notable side effects of carbimazole include agranulocytosis and liver toxicity. For this reason, blood tests including full blood count and liver function tests are needed at baseline and during routine monitoring. Other common side effects include allergic type reactions and less commonly antineutrophil cytoplasmic antibody (ANCA) positive vasculitis.

In patients with thyroid storm, carbimazole and propylthiouracil are used at higher than conventional doses and given at shorter intervals. Propylthiouracil, however, is often preferred due to its additional property of blockage of the conversion of free T4 to free T3, the more active thyroid hormone with faster onset of action.

***Jeannette was referred to an endocrinologist after the diagnosis of Graves' disease was made. She was managed with carbimazole 10 mg three times daily initially, which was then titrated down to 5 mg daily as a maintenance dose after normalisation of thyroid function over the following three months. She also started a beta***



a. Normal goitre



b. Graves' disease

**Figures 1a and b. Thyroid uptake scans showing a patient with a normal goitre (a, far left) and a patient diagnosed with Graves' disease (b, left).**



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**Table. Advantages and disadvantages of treatment modalities for hyperthyroidism**

| Therapy | Advantages | Disadvantages |
|---|---|---|
| Thionamides (e.g. carbimazole and propylthiouracil) | • Chance of permanent remission<br>• Lower initial cost | • Minor side effects: rash, hives, arthralgias, transient granulocytopenia, gastrointestinal symptoms<br>• Major side effects: agranulocytosis, hepatitis vasculitis (lupus-like syndrome)<br>• Risk of fetal goitre, hypothyroidism and birth defects if pregnant<br>• More frequent monitoring required |
| Radioiodine | • Permanent resolution of hyperthyroidism | • May result in permanent hypothyroidism requiring long-term replacement therapy<br>• Patient must take radiation precautions for several days after treatment, avoiding contact with young children and pregnant women<br>• Development or worsening of Graves' ophthalmopathy (may need pretreatment with corticosteroids)<br>• Risk of radiation thyroiditis (rare 1%), which can be painful<br>• Patient concerns about long-term risk of malignancy with radiation exposure |
| Surgery | • Rapid, permanent cure of hyperthyroidism<br>• Treatment of choice for patients with large goitres and mass effect | • May result in permanent hypothyroidism requiring long-term replacement therapy<br>• Risk of hypoparathyroidism, recurrent laryngeal nerve palsy and general anaesthetic risks<br>• High cost |

***blocker (propranolol 20 mg three times daily) for rate control. She was reviewed by a cardiologist for her newly diagnosed paroxysmal atrial fibrillation, which resolved after improvement of her thyrotoxicosis. She remains in sinus rhythm, and is taking prophylactic antiplatelet therapy.***

***Jeannette returns to see you several months later for a check up. What further treatment(s) should be offered?***

***Answer:*** If there is recurrent Graves' disease, then definitive treatment may be required in the form or radioactive iodine or surgery (Table), with the ultimate choice of therapy being highly individualised based on the patient's circumstances. Patients with significant Graves' ophthalmopathy may not be suitable for radioactive iodine as this may worsen ophthalmopathy. Intravenous and oral corticosteroids are used as an adjunctive treatment for severe ophthalmopathy.

Measurement of TRAb levels before stopping antithyroid drug therapy is recommended, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating greater chance for remission.

## Summary

Jeannette presented with typical features of Graves' hyperthyroidism. It is important to distinguish the different causes of hyperthyroidism and this can be achieved using serum antibody testing along with thyroid uptake scans.

Pharmacological management of Graves' disease includes use of antithyroid medication, such as carbimazole and prophylthiouracil, while being aware of the rare but potential side effects of agranulocytosis, vasculitis and abnormal liver function. Beta blockers play a large role for symptomatic cases, by relieving hyperthyroid symptoms including anxiety, palpitations and tremors. Once euthyroidism is achieved, patients may need definitive therapy with radioactive iodine or thyroid surgery. The decision for definitive therapy should be considered if there is recurrent disease or the presence of concurrent thyroid nodules with suspicious features, or according to individual patient wishes. **ET**

**Practice points**

- The most common cause of hyperthyroidism is Graves' disease, which has unique clinical features including ophthalmopathy and dermopathy.
- Atrial fibrillation may be a presenting feature of hyperthyroidism in the elderly. With appropriate treatment of thyroid excess, most patients will revert to sinus rhythm.
- Investigating hyperthyroidism involves a combination of blood tests and imaging tests that can help narrow the differential diagnosis. Blood tests include thyroid function testing as well as thyroid receptor antibodies, nuclear medicine iodine uptake scans and/or ultrasound may assist with the diagnosis.
- Treatment of hyperthyroidism involves management of symptoms with beta blockers and reduction of circulating T4 and T3 levels with thionamides. Therapy for 12 to 18 months can achieve long-term medical remission in more than 50% of patients; some will require more definitive therapy with radioactive iodine or surgery.
- Thyroid storm is an uncommon feature of hyperthyroidism but one that should be recognised early to improve outcomes. Endocrinologist involvement and referral of the patient to the emergency department are always needed in these circumstances.

COMPETING INTERESTS: None.



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