Graves' disease in a young woman

VIVIENNE MILLER MB BS, FRACGP, DRACOG, DCH, MACPM, MWAME

Tamsin is a 28-year-old woman whom you have seen several times in the past year for routine care. She is taking no medications and has no known medical problems. Her boyfriend is concerned about her anxiety levels and her weight loss. Tamsin is in a very stressful job and works long hours. She has lost about 4 kg in weight in the past six weeks without changing her diet or exercise.

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Dr Miller is a GP in Sydney, Medical Editor of *Cardiology Today*, medical journalist and author.

What questions would you like to ask her?
Answer: Questions to ask are: Why does she think she has lost weight? Is she nauseated or has she vomited? Could she be pregnant, does she use contraception? Has she had any other symptoms, such as cough, fevers, sweats, increased fatigue, bowel changes, menstrual irregularities, palpitations or tremors? Does she feel as if she is coping or have major problems in her life? How anxious is she, or does she feel depressed? Is she taking any illicit drugs, does she drink alcohol often and has alcohol intake changed? Is she taking complementary or alternative therapies?

Tamsin says she is not pregnant, she is still taking the oral contraceptive pill, and her last period was normal a week ago. She has tried to increase her food intake and is hungry. She does not skip meals but usually eats more in the evenings. She is always tired and sleeps fairly well, but she has noticed recently that she is half-waking at night sweaty and feeling hot. Her work colleagues said to her that a paper she was holding was shaking during a presentation. She said she is stressed and has noticed irregularities in her heart rate intermittently, more so at work and in the evenings when she is resting. She drinks in moderation and is taking a multivitamin. There is no relevant family history of medical illness.

You examine Tamsin. She has seborrhoea around her hairline but her face is otherwise unremarkable. She has a prominent thyroid with no overt palpable lumps within it and no bruits. She looks underweight with a BMI of 19 kg/m² and has mild proximal muscle weakness in her upper limbs. Her temperature is 37.5°C core, her pulse rate is 85 beats/min and regular with the occasional irregular beat. She has a fine bilateral tremor, seen best with the hands and fingers outstretched. Mild lid lag is present bilaterally but no specific features of Graves' ophthalmopathy. Her blood pressure is 145/65 mmHg seated. Auscultation reveals a grade 2/6 midsystolic murmur at the left sternal edge with no radiation. The respiratory examination is normal. Her urinalysis is normal and a pregnancy test is negative. Her abdomen examination is normal and there are no masses.

What investigations would you do initially?
Answer: Initial investigations would include measurement of thyroid-stimulating hormone (TSH), free thyroxine (T_4) and free triiodothyronine (T_3) levels (the latter two acceptable under Medicare as there is a goitre, as well as suspicion of thyroid disease). Urea, electrolytes and creatinine, full blood count, C-reactive protein (CRP), formal blood glucose level, liver function, iron studies and serum corrected calcium should also be assessed. Resting electrocardiography is advisable to confirm ectopic beats as opposed to atrial fibrillation. At this stage, a cardiac echocardiogram would not be indicated and neither is a chest x-ray.

Results show a mildly raised CRP level of 7 mg/L (normal range 0–5 mg/L), undetectable TSH level of <0.01 mIU/L (lower limit 0.50 mIU/L), free T_4 level of 36 pmol/L (normal range 10–20 pmol/L) and a free T_3 level of 10.3 pmol/L (normal range 2.6–6.0 pmol/L). Liver function tests show raised levels of alanine aminotransferase (55 U/L, upper level of normal is 40 U/L) and aspartate aminotransferase (80 U/L, upper level of normal is 35 U/L). Her corrected serum calcium level is at the upper level of normal at 2.51 mmol/L (upper level of normal is 2.55 mmol/L).

What are the differential diagnoses of thyrotoxicosis?
Answer: The differential diagnoses of thyrotoxicosis are Graves' disease, painless autoimmune thyroiditis, postpartum thyroiditis, subacute (de Quervain's) thyroiditis, toxic adenoma, toxic multinodular goitre, medication induced (amiodarone, overdose or inappropriate use of thyroid hormone or iodine), and very rarely TSH tumours (pituitary, trophoblastic tumours) and struma ovarii tumours. In Tamsin's case, Graves' disease or painless thyroiditis are most likely and further investigation is required to differentiate between these.

What are the key investigations to confirm the cause of thyrotoxicosis in this case?

Answer: A positive TSH receptor antibody (TRAb) will confirm Graves' disease. You request from the pathologist TRAb and anti-thyroid peroxidase (TPO) antibody tests. The results show strongly positive TRAb and weakly positive anti-TPO tests. Graves' disease is the definitive diagnosis given the clearly raised TRAb test. A weakly positive anti-TPO antibody test helps to confirm auto-immune thyroid disease but is not specific for Graves' disease. A technetium-99m thyroid uptake scan showing diffuse and increased uptake will also confirm the diagnosis of Graves' disease and often provides a more rapid diagnosis than a TRAb level. However, the diagnosis of Graves' disease seems definite in this case given the TRAb result, and a thyroid uptake scan is not indicated. The liver enzyme abnormalities and the serum calcium level being at the upper range of normal are common in Graves' disease and are caused by the metabolic changes. They resolve as thyrotoxicosis improves.

What is Graves' disease?

Answer: Graves' disease is responsible for about 70% of cases of thyrotoxicosis and is most common in women aged 20 to 40 years. It occurs in about one in 100 individuals, is more common if there is a family history of autoimmune thyroid disease, and is five to ten times more likely in women than men. It is due to autoimmune stimulation of the entire thyroid gland by an activating TSH receptor antibody (presumably because of genetic and environmental triggers) resulting in over-production of thyroid hormone. The metabolic effects of excess thyroid hormone affect other parts of the body and include complications such as eye changes, supraventricular tachycardias, liver function abnormalities and, especially if longstanding and untreated, osteoporosis, cardiomyopathy, myopathy and severe weight loss. Thyroid eye disease caused by immune-mediated swelling and inflammation in eye muscles can lead to proptosis of the eyes, which may be asymmetrical, and to diplopia.

What are the classic physical signs of Graves' disease?

Answer: Classically, there is a diffuse enlargement of the thyroid showing a 'butterfly' shape in the neck and possibly a bruit; proptosis may be unilateral or bilateral ('thyroid stare'), lid lag and lid retraction are due to the sympathetic nervous system stimulation and are not specific to Graves' disease. Proptosis is more common in smokers. Often there is conjunctivitis, due to drying of the eye from altered tear film distribution, and uncommonly there may be pretibial myxoedema, a red, subcutaneous lumpiness over the shins. There is typically a fast pulse rate, raised systolic blood pressure and there may be a flow murmur. There may be evidence of proximal myopathy, sweatiness and a fine tremor of the hands. Patients may have no signs of goitre or eye disease, but still have severe thyrotoxicosis.

You arrange referral to an endocrinologist. How would you initially manage Tamsin?

Answer: If she has never had asthma and has no other contraindications, then propranolol (10 mg three times daily) and the thionamide neomercazole (10 mg twice daily in her case, but larger doses would be needed if free T_3 and T_4 levels were higher) can be prescribed. Neomercazole is preferred to propranolol if the patient is not pregnant, as the latter is more likely to cause abnormal liver function. Thyroid function tests (TFT) and full blood count should be reviewed in about three weeks. Not all patients require beta blockers (e.g. if there is no anxiety, tremor or palpitations). Free T_4 and free T_3 levels normalise more quickly than the TSH levels. It takes clinical experience and individualised patient care to titrate the neomercazole dose to maintain euthyroidism.

What would you warn Tamsin about regarding these medications?

Answer: She may have symptoms of low blood pressure if the dose of propranolol is too high. If she has inadequate control of tremor and anxiety she may increase propranolol to 20 mg three times daily and, on your review, even to a higher dose. Neomercazole has a very rare idiosyncratic side effect of reducing white cells levels and she needs to report urgently any severe sore throat, mouth ulcers or raised temperatures in the next few months. A rash can occur in patients taking antithyroid drugs. Tamsin should be advised not to get pregnant while her Graves' disease is not well controlled.

How can Tamsin be managed in the long term, especially if she wants to conceive?

Answer: She could discuss further with the endocrinologist ongoing medical therapy, or definitive therapy with radioactive iodine or total thyroidectomy. However, this is reserved for those who relapse and those with thionamide drug side effects or persistent Graves' disease. Definitive therapy would usually necessitate long-term thyroxine replacement therapy, certainly in cases of total thyroidectomy.

The dose of neomercazole should be tapered over some weeks to 5 to 10 mg daily as a maintenance dose once the Graves' disease is under control; this may be continued for several years but can be ceased if she is euthyroid with a negative TRAb after at least one year of therapy.

Pregnancy is possible if Graves' disease is well controlled, but careful discussion and counselling is needed. Graves' disease tends to improve during pregnancy but commonly relapses postpartum. Rarely, it get worse during pregnancy, so ideally she should consult with her endocrinologist and GP before she conceives and receive endocrine consultant care during her pregnancy. Neomercazole can be taken during pregnancy if given in low doses from the 2nd trimester onwards. Propylthiouracil is the preferred agent in the 1st trimester, but neomercazole is the agent of first choice in all other situations, unless the patient is allergic. Risks of miscarriage and birth defects are lower on antithyroid drugs than with untreated Graves' disease, and slightly lower for propylthiouracil in the 1st trimester than with neomercazole. Some women choose definitive therapy if they want to conceive soon, but as a guide they should avoid pregnancy for six months after radioactive iodine treatment. Hypothyroidism in the 1st trimester must also be avoided, so TSH levels are maintained around 2.5 mIU/L or below in women taking thyroxine therapy in pregnancy. Thyroxine dose requirements frequently rise early during pregnancy by as much as 30%.

Outcome: Tamsin had two weeks off work and with treatment she noticed a rapid improvement in fatigue levels and felt more in control after commencing neomercazole. Her sleep also improved and she gained 2 kg in weight after three weeks of therapy. Propranolol was ceased, after weaning the dose, when her thyroid function had returned normal. Her neomercazole dose was reduced as TFTs, improved, and she continued a maintenance dose of 5 mg daily for 12 months, ceasing when her TRAb was negative and her TFTs had been normal for some months. ET