CASE TWO

Short case number: 3_17_2
Category: Endocrine & Reproductive Systems.
Discipline: Medicine
Setting: General Practice
Topic: Hyperthyroidism_Graves Disease

Case

Shelley Hunter, a 35-year-old female presents with a recent history of feeling very agitated and nervous all the time. She has noticed that on occasions her heart is racing and she doesn't seem to 'feel the cold' as much as she used to.
You observe that she appears to have a 'startled look', when you mention this she comments that her friends have mentioned something about her eyes as well.

Questions

1. You are concerned that Shelley may have a problem with her thyroid, what are the key features of the history that you would explore with Shelley that would support a diagnosis of hyperthyroidism?
2. What are the key features on examination that support a diagnosis of hyperthyroidism? What are the clinical features specific to Graves's disease?
3. What results on thyroid function testing would support a diagnosis of hyperthyroidism?
4. You explain to Shelley that she most likely has Graves Disease – What is the underlying pathophysiology of Grave's disease? Briefly outline other causes of hyperthyroidism.
5. In considering further investigation of Shelley, outline the different types of thyroid autoantibodies and their prevalence in different thyroid conditions.
6. Briefly describe the use of radio-iodine uptake tests in the assessment of hyperthyroidism.
7. Shelley asks about treatment of the condition; Summarise the mechanism of action of antithyroid drugs and the main side effects of each type of medication.
8. Radioactive iodine or surgery are other management options for thyroid disease,
   a) Briefly outline the mechanism of action of radioactive iodine.
   b) Summarise the indications for and possible complications of surgery.
9. Briefly outline what is meant by the term 'thyroid storm' and explain why it is considered an emergency situation.

Suggested reading:

- Kumar P, Clark ML, editors. Kumar & Clark's Clinical Medicine. 9th edition. Edinburgh: Saunders Elsevier; 2016.
- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014.

ANSWERS

1. You are concerned that Shelley may have a problem with her thyroid, what are the key features of the history that you would explore with Shelley that would support a diagnosis of hyperthyroidism?

Italics = common

General *Weight loss despite normal* or *increased appetite*
Heat intolerance
Fatigue, apathy
Osteoporosis (fracture, loss of height)
Gastrointestinal Diarrhoea, steatorrhoea, *hyperdefecation*
Anorexia
Vomiting
Cardiovascular *Palpitations*
Dyspnoea on exertion
Angina
Ankle swelling
Exacerbation of asthma
Neuromuscular Anxiety, *irritability, emotional lability*, psychosis
Tremor
Muscle weakness
Periodic paralysis (predominantly in Chinese)
Dermatological *Sweating*
Pruritis
Alopecia
Reproductive Amenorrhoea/oligomenorrhoea
Infertility
spontaneous abortion
Loss of libido, impotence
Ocular *Grittiness, red eyes*
Excessive lacrimation
Diplopia
Loss of acuity

Hyperthyroidism Hx

MSK - Tremor

CVS - Tachy
- Palps

Systemic - Weight loss - Tremor
- Heat intolerance - Sweating

Sleep - Less

OBGYN - Period changes (less freq / Absent)

Psych - Anxious

Skin - Sweaty Palms.

2. What are the key features on examination that support a diagnosis of hyperthyroidism? What are the clinical features specific to Graves's disease?

Italics = most common, **Bold = Graves**

General *Weight loss*
Goitre with bruit
Cardiovascular *Sinus tachycardia*
Atrial fibrillation
Systolic hypertension/

increased pulse pressure
Cardiac failure

Haematological Lymphadenopathy (rare)

Neuromuscular *Tremor*
Hyper-reflexia
Ill-sustained clonus
Proximal myopathy
Bulbar myopathy (particularly in the elderley)

Dermatological *Palmar erythema*
Pretibial myxoedema
Finger clubbing (thyroid acropachy)
Spider naevi (rare)
Onycholysis (rare)
Pigmentation (rare)
Vitiligo

Reproductive Gynaecomastia

Ocular *Lid retraction, lid lag*
Chemosis
Exophthalmos
Periorbital oedema
Corneal ulceration
Ophthalmoplegia
Papilloedema

3. What results on thyroid function testing would support a diagnosis of hyperthyroidism?

TSH	T_4	T_3	Most likely interpretation(s)
Undetectable	Raised	Raised	**Primary thyrotoxicosis**
Undetectable	Norm[1]	Raised	**Primary T_3-toxicosis**
Undetectable	Norm[1]	Norm[1]	**Subclinical thyrotoxicosis**
Undetectable	Raised	Low, norm or raised[2]	Sick euthyroidism/non-thyroidal illness
Undetectable	Low	Low	Secondary hypothyroidism i.e. pituitary or hypothalamic disease Transient thyroiditis in evolution
Normal	Low	Low[3]	Secondary hypothyroidism
Mildly elevated 5-20 mU/l	Low	Low[3]	Primary hypothyroidism Secondary hypothyroidism
Elevated > 20 mU/l	Low	Low[3]	Primary hypothyroidism
Mildly elevated 5-20 mU/l	Norm[4]	Norm[3]	Subclinical hypothyroidism
Elevated 20-500 mU/l	Norm	Norm	Artefact Endogenous IgG antibodies which interfere with TSH
Elevated	High	High	Non-compliance with T_4 replacement-recent 'loading' dose **Secondary thyrotoxicosis**-TSH-secreting pituitary tumour Thyroid hormone resistance

[1]Usually upper part of reference range.
[2]Depending on the assay system.
[3]T3 is not a sensitive indicator of hypothyroidism and should not be requested.
[4]Usually lower part of normal range.

4. You explain to Shelley that she most likely has Graves Disease – What is the underlying pathophysiology of Grave's disease? Briefly outline other causes of hyperthyroidism.

PATHOPHYSIOLOGY OF GRAVES

Graves thyrotoxicosis results from the production of **IgG antibodies directed against the TSH receptor** on the thyroid follicular cell, which stimulate thyroid hormone production and, in the majority, goitre formation. These antibodies are termed thyroid-stimulating immunoglobulins or **TSH receptor antibodies (TRAb**) and can be detected in the serum of 80-95% of patients with Graves' disease. The concentration of TRAb in the serum is presumed to fluctuate to account for the natural history of Graves' thyrotoxicosis. The ultimate thyroid failure seen in some patients is thought to result from the presence of blocking antibodies against the TSH receptor, and from tissue destruction by cytotoxic antibodies and cell-mediated immunity.

In Caucasians there is an association of Graves' disease with HLA-B8, DR3 and DR2, and with inability to secrete the water-soluble glycoprotein form of the ABO blood group antigens. Family studies show that 50% of monozygotic twins are concordant for thyrotoxicosis, as opposed to 5% of dizygotic twins.

The trigger for the development of thyrotoxicosis in genetically susceptible individuals may be infection with viruses or bacteria, although there is no proof. In regions of iodine deficiency, iodine supplementation may result in the development of thyrotoxicosis, but only in those with pre-existing subclinical Graves' disease. Smoking is weakly associated with Graves' thyrotoxicosis, but strongly linked with the development of ophthalmopathy.

CAUSES OF HYPERTHYROIDISM

Graves' disease
Multinodular goitre
Autonomously functioning solitary thyroid nodule
Thyroiditis Subacute (de Quervain's)
Post-partum
Iodine induced Drugs (e.g. amiodarone)
Radiographic contrast media
Iodine prophylaxis programme
Extrathyroidal Factitious hyperthyroidism
Struma ovarii (Ovarian teratoma containing thyroid tissue)
TSH induced TSH-secreting pituitary adenoma
Choriocarcinoma and hydatidiform mole (HCG is thyroid stimulating)
Follicular carcinoma ± metastases

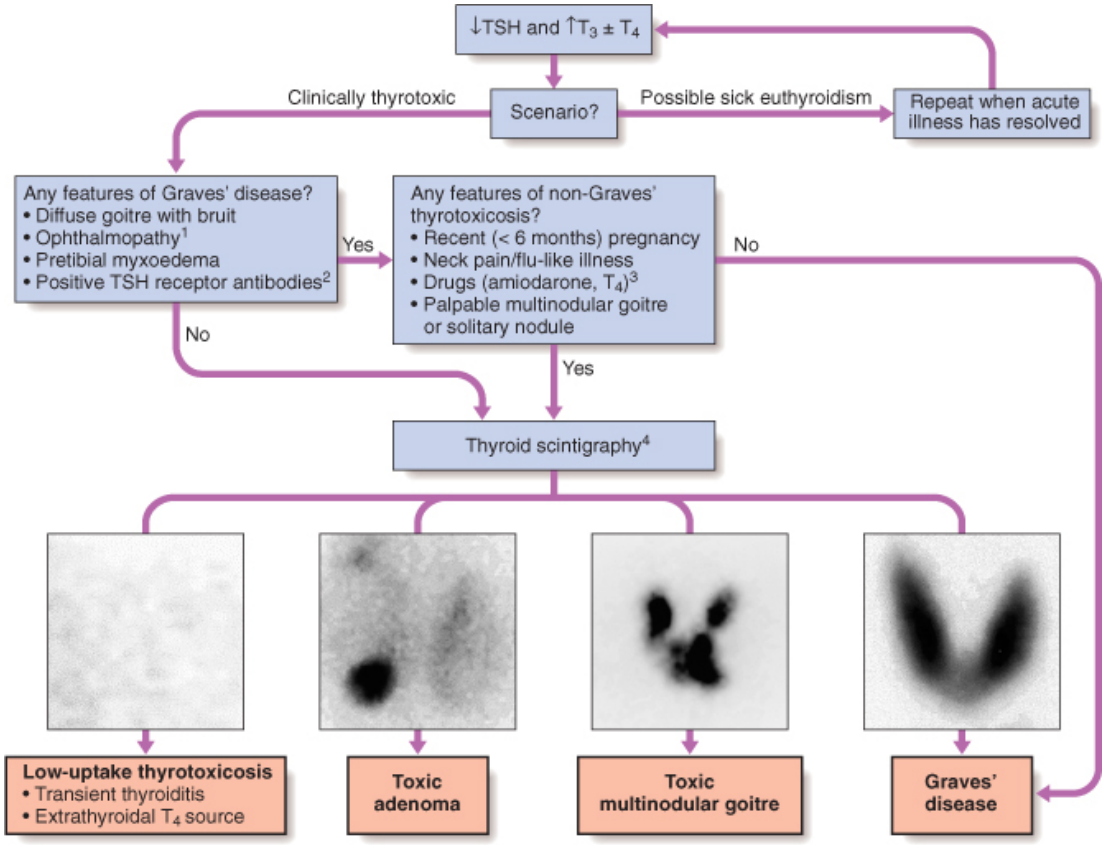
5. In considering further investigation of Shelley, outline the different types of thyroid autoantibodies and their prevalence in different thyroid conditions.

TYPES AND PREVALENCE OF THYROID AUTOANTIBODIES (%)

	Antibodies to:		
	Thyroid peroxidase[1]	**Thyroglobulin**	**TSH receptor[2]**
Normal population	8-27	5-20	0
Graves' disease	50-80	50-70	80-95
Autoimmune hypothyroidism	90-100	80-90	10-20
Multinodular goitre	30-40	30-40	0
Transient thyroiditis	30-40	30-40	0

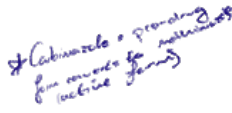
[1]Thyroid peroxidase antibodies are the principal component of what was previously measured as thyroid 'microsomal' antibodies.
[2]TSH receptor antibodies (TRAb) can be agonists (causing Graves' thyrotoxicosis) or antagonists (causing hypothyroidism).

6. Briefly describe the use of radio-iodine uptake tests in the assessment of hyperthyroidism.

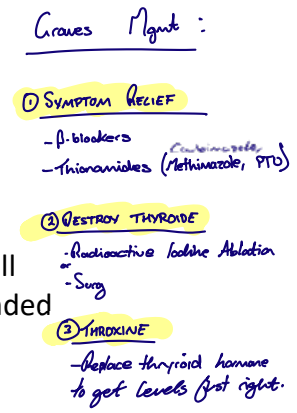


Radio-iodine uptake tests measure the proportion of isotope which is trapped in the whole gland, but have been largely superseded by ^{99m}technetium scintigraphy scans which also measure trapping, are quicker to perform with a lower dose of radioactivity, and provide a higher resolution image.

- Graves' disease there is diffuse uptake of isotope.
- MNG there is relatively low, patchy uptake within the nodules; such an appearance is not always associated with a palpable thyroid.
- Toxic adenoma there is lack of uptake of isotope by normal dormant gland due to suppression of serum TSH.
- Low-uptake thyrotoxicosis (viral, post-partum or iodine-induced thyroiditis) there is negligible isotope detected in the region of the thyroid, although uptake is apparent in nearby salivary glands



7. Shelley asks about treatment of the condition; Summarise the mechanism of action of antithyroid drugs and the main side effects of each type of medication.



Definitive treatment of thyrotoxicosis depends on the underlying cause, and may include antithyroid drugs, radioactive iodine or surgery

In all patients with thyrotoxicosis a non-selective β-adrenoceptor antagonist (β-blocker), will alleviate but not abolish symptoms within 24-48 hours. Beta-blockers cannot be recommended for long-term treatment, but they are extremely useful in the short term, e.g. for patients awaiting hospital consultation or following ^{131}I therapy.

COMPARISON OF TREATMENTS FOR THE THYROTOXICOSIS OF GRAVES' DISEASE

Treatment	Common indications	Contraindications	Disadvantages/complications
Antithyroid drugs Eg. carbimazole propylthiouracil	First episode in patients < 40 yrs	Breastfeeding (propylthiouracil suitable)	> 50% relapse rate usually within 2 years of stopping drug Hypersensitivity rash 2% Agranulocytosis 0.2%
Subtotal thyroidectomy	Large goitre Poor drug compliance, especially in young patients Recurrent thyrotoxicosis after course of antithyroid drugs in young patients	Previous thyroid surgery Dependence upon voice, eg.pera singer	Hypothyroidism (25%) Transient hypocalcaemia (10%) Permanent hypoparathyroidism (1%) Recurrent laryngeal nerve palsy[1] (1%)
Radio-iodine	Patients > 40 yrs[2] Recurrence following surgery irrespective of age Other serious comorbidity	Pregnancy or planned pregnancy within 6 months of treatment Active Graves' ophthalmopathy[3]	Hypothyroidism, approx. 40% in first year, 80% after 15 years Most likely treatment to result in exacerbation of ophthalmopathy[3]

[1]It is not only vocal cord palsy due to recurrent laryngeal nerve damage which alters the voice following thyroid surgery; the superior laryngeal nerves are frequently transected and result in minor changes in voice quality.
[2]In certain parts of the world, ^{131}I is used more liberally and prescribed for young women in the 20-40 age group.
[3]The extent to which radio-iodine exacerbates ophthalmopathy is controversial and practice varies; some use prednisolone for 4 months to reduce this risk

8. Radioactive iodine or surgery are other management options for thyroid disease,
   a) Briefly outline the mechanism of action of radioactive iodine.

Radioactive iodine, ^{131}I, is administered orally as a single dose and is trapped and organified in the thyroid. Although it will decay within the thyroid in a few weeks, the effects of its radiation are long-lasting, with cumulative effects on follicular cell survival and replication. The variable radio-iodine uptake and radiosensitivity of the gland means that the choice of dose is empirical; it is effective in 75% of patients within 4-12 weeks. During the lag period, symptoms can be controlled by a β-blocker or, in more severe cases, by carbimazole. However, carbimazole reduces the efficacy of ^{131}I therapy because it prevents organification of ^{131}I in the gland, and so should be avoided until 48 hours after radio-iodine administration. If thyrotoxicosis persists after 12-24 weeks, a further dose of ^{131}I should be employed. The disadvantage of ^{131}I treatment is that the majority of patients eventually develop hypothyroidism and long-term follow-up is, therefore, necessary.

b) Summarise the indications for and possible complications of surgery.

Subtotal thyroidectomy:

Patients must be rendered euthyroid with antithyroid drugs before operation. Potassium iodide is often added before surgery to inhibit thyroid hormone release and reduce the size and vascularity of the gland, making surgery technically easier

Complications of surgery are rare (see prev question). One year after surgery, 80% of patients are euthyroid, 15% are permanently hypothyroid and 5% remain thyrotoxic. Thyroid failure within 6 months of operation may be temporary. Long-term follow-up of patients treated surgically is necessary, as the late development of hypothyroidism and recurrence of thyrotoxicosis are well recognised.

9. Briefly outline what is meant by the term 'thyroid storm' and explain why it is considered an emergency situation.

Thyrotoxic crisis ('thyroid storm')

This is a rare, life-threatening increase in the severity of the clinical features of thyrotoxicosis. The most prominent signs are:

- Fever
- Agitation
- Confusion
- Tachycardia or AF (and possibly cardiac failure in the older patient)

It is a medical emergency and, despite early recognition and treatment, the mortality rate is 10%.

Thyrotoxic crisis is most commonly precipitated by infection in a patient with previously unrecognised or inadequately treated thyrotoxicosis. It may also develop shortly after subtotal thyroidectomy in an ill-prepared patient or within a few days of ^{131}I therapy when acute irradiation damage may lead to a transient rise in serum thyroid hormone levels.