RATIONAL TESTING

Investigating low thyroid stimulating hormone (TSH) level

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

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Previous articles in this series

- Abnormal liver function tests in pregnancy (*BMJ* 2013;347:f6055)
- Investigating hypokalaemia (*BMJ* 2013;347:f5137)
- When to order an antinuclear antibody test (*BMJ* 2013;347:f5060)
- High sensitivity cardiac troponin in patients with chest pain (*BMJ* 2013;347:f4222)
- Investigating microcytic anaemia (*BMJ* 2013;346:f3154)

A 66 year old woman with chronic obstructive pulmonary disease visited her general practitioner with a history of persistent fatigue since a severe chest infection three weeks previously. The infection had responded to antibiotics during a four day hospital admission. Her general practitioner found no physical signs in the chest, although there was a small, multinodular goitre. A measurement of thyroid stimulating hormone (TSH) was requested, and the result was 0.06 mU/L (reference interval 0.4-4.0 mU/L).

What is the next investigation?

The presence of a goitre prompted examination for clinical signs of thyrotoxicosis, but sinus tachycardia, atrial fibrillation, fine tremor, eye signs (lid lag or retraction), and warm palms were absent. A drug history should also be taken: in this setting of a low TSH level, is the patient taking amiodarone or levothyroxine? Less common drug induced causes of a low TSH level are high dose prednisolone, recent treatment with carbimazole, and dopamine infusion.

Thyroid function tests

Laboratories vary in their testing strategy when a request for thyroid function tests is made.[1] Because a serum TSH level within the reference interval excludes primary thyroid disease, and secondary (pituitary or hypothalamic) causes of thyroid dysfunction are uncommon, many laboratories measure only TSH if thyroid function tests are requested. Other laboratories will also measure free thyroxine (FT4) or will add this if the TSH level is outside the reference interval. The term "reference interval" is preferable to "normal range." The reference interval for biochemical tests encompasses the mean plus or minus two standard deviations, and therefore 5% of normal individuals will have values outside the reference interval.

If the TSH level is low the next step is to measure thyroid hormone levels to identify thyrotoxicosis (see figure). If the FT4 level is normal, this does not exclude the diagnosis, as in the earliest phase of hyperthyroidism (2-5% of cases) the serum free triiodothyronine (FT3) level is elevated but the FT4 is normal (T3 toxicosis). In cases of excessive iodine intake, the FT4 level is elevated but the FT3 is normal, which leads some laboratories to measure only FT4 initially if the TSH level is low.

If the FT3 and FT4 levels are normal the most likely explanations are that the patient has subclinical hyperthyroidism or that the TSH abnormality will turn out to be a transient abnormality of no clinical consequence. To distinguish between these two possibilities, repeat the TSH measurement after six weeks. If the TSH returns to within the reference interval, the likely explanation is that the hypothalamo-pituitary axis has been disturbed by a non-thyroidal illness. Any acute, severe illness may alter thyroid hormone deiodination through the effects of cytokines and result in otherwise bewildering changes in levels of TSH, FT3, or FT4.[2] Low TSH values in hospitalised patients are three times more likely to be due to this effect than to hyperthyroidism. It is best to avoid thyroid function testing during and immediately after non-thyroidal illness unless there are clear indications from the history or examination that thyroid dysfunction is likely.

If the TSH level is persistently low with a normal FT3 and FT4 the patient, by definition, has subclinical hyperthyroidism (see below), but this definition also encompasses healthy individuals whose TSH levels are below the reference interval. In one US survey 4% of black people had a low TSH level compared with 1.4% of white people.[3] People who smoke have slightly lower TSH levels, and the distribution of TSH levels in elderly people is wider at both upper and lower limits than younger subjects. In around half of individuals with a low TSH level, values return to within the reference interval when tested over five years.[4] In pregnancy, the TSH level is often low in the first trimester because of the thyrotrophic action of human chorionic gonadotrophin.

If the FT4 level is low in a patient with a low TSH this may indicate the presence of secondary hypothyroidism due to a pituitary or hypothalamic disorder. In almost all such patients there will be evidence of hypogonadism (amenorrhoea, impotence, loss of body hair) and other features suggesting the underlying problem. Urgent referral to an endocrinologist is indicated for pituitary function testing.

Additional tests if thyrotoxicosis is confirmed

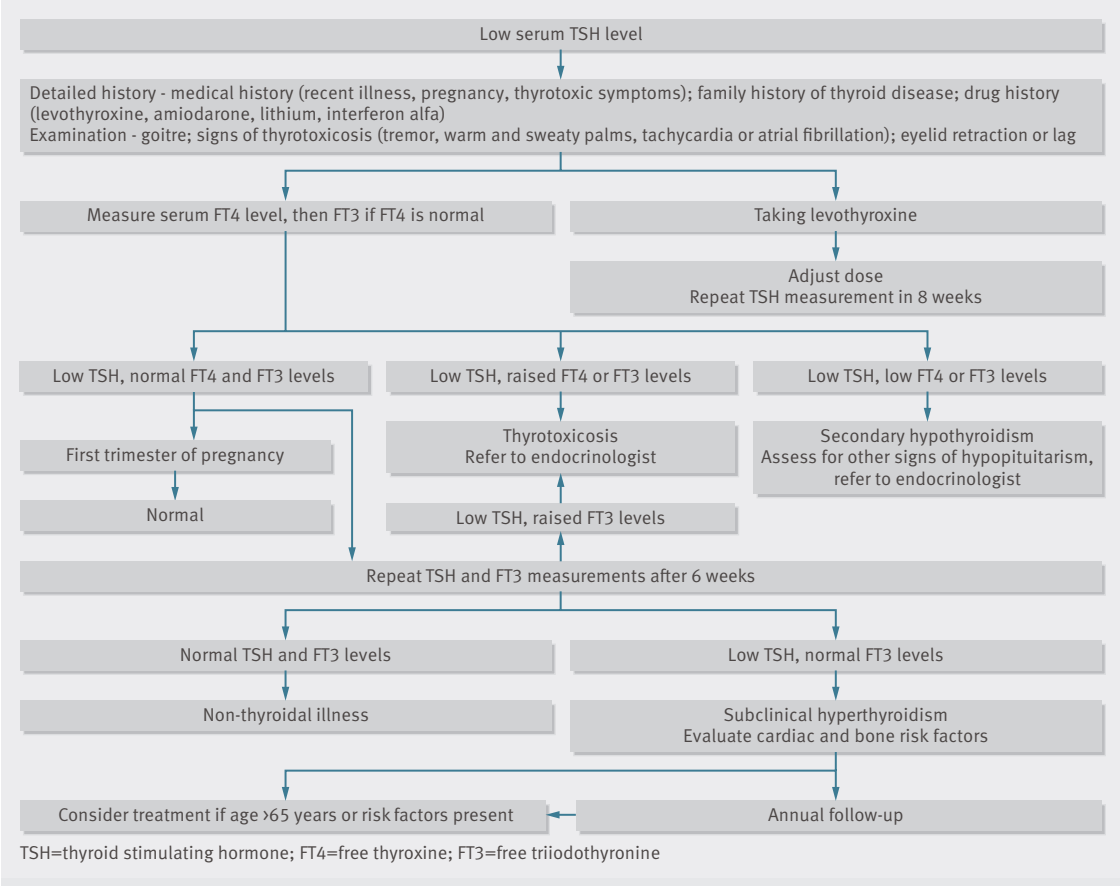
Thyrotoxicosis is not synonymous with hyperthyroidism. The former is any state in which there is excessive circulating thyroid hormone, whereas hyperthyroidism is thyrotoxicosis caused specifically by thyroid overactivity. Thyrotoxicosis without hyperthyroidism may result from excessive levothyroxine intake or transient destructive thyroiditis caused by viruses, drugs (amiodarone, interferon alfa), or autoimmunity (particularly postpartum thyroiditis). The hallmark of viral (subacute) thyroiditis is thyroid pain, and the erythrocyte sedimentation rate is elevated. In the case of postpartum thyroiditis, antibodies to thyroid

LEARNING POINTS

The commonest causes of a low serum level of thyroid stimulating hormone (TSH) are excessive levothyroxine replacement, non-thyroidal illness, and subclinical hyperthyroidism.

In a patient who is not taking levothyroxine treatment, a low TSH level should prompt measurement of free thyroxine (FT_4) and free triiodothyronine (FT_3). If these are normal, the TSH level should be measured after six weeks to rule out non-thyroidal illness.

Subclinical hyperthyroidism is common in elderly people, and treatment may be indicated before progression to overt thyrotoxicosis to minimise bone loss and risk of atrial fibrillation



Suggested pathway for investigating a patient with a low serum level of thyroid stimulating hormone (TSH)

peroxidase are present. If there is any doubt about the diagnosis, referral to an endocrinologist is advisable. Thyroid scintiscanning with technetium-99m will reveal little or no thyroid uptake of the isotope: ultrasound investigation of the thyroid is not indicated.

Referral to an endocrinologist is advised in all patients with hyperthyroidism for final diagnosis and treatment. Graves' disease is the commonest cause of hyperthyroidism and is confirmed if typical eye signs are present, but these occur in only a third of cases. Measurement of TSH receptor antibodies is now the easiest test to distinguish between Graves' disease and other causes of hyperthyroidism such as toxic adenoma and toxic multinodular goitre (sensitivity and specificity both around 95%).

Outcome

In this patient, the serum FT3 and FT4 levels were normal (5.3 pmol/L and 17.1 pmol/L respectively) and repeat testing of the TSH at six weeks gave a value of 0.27 mU/L with normal FT3. These results are compatible with mild underlying subclinical hyperthyroidism secondary to multinodular goitre, with the initial biochemical change in TSH exacerbated by the patient's recent non-thyroid illness.

Subclinical hyperthyroidism

Subclinical hyperthyroidism occurs when thyroid overactivity due to Graves' disease or autonomously functioning thyroid nodules is sufficient to suppress pituitary secretion of TSH but insufficient to cause an elevation of circulating thyroid hormones. The condition becomes more common with age and is more common in women.[5] There is progression to overt hyperthyroidism (when the circulating thyroid hormone levels are raised) in 1-3% of elderly patients per year. Progression is greater in younger patients and those with autonomous nodules.

The main risks of subclinical hyperthyroidism relate to its effects on the heart and bone. The risk of atrial fibrillation is nearly doubled in those with low but detectable TSH levels, and is even higher with undetectable TSH levels. Bone mineral density is reduced, with a threefold to fourfold increase in hip fractures in older men and postmenopausal women.[5 6] There is conflicting evidence that dementia is more common with subclinical hyperthyroidism. A recent meta-analysis found a 24% increase in mortality in patients with subclinical hyperthyroidism.[7]

There is no firm evidence from prospective trials on which to base recommendations for treatment. Guidelines published by the American Thyroid Association and American Association of Clinical Endocrinologists recommend that treatment should be considered in patients with a persistently low TSH level (<0.1 mU/L) if they are older than 65 years or are postmenopausal and at risk of osteoporosis.[8] Treatment is also recommended for all patients over 65 years old with TSH levels below the reference interval if there are cardiac risk factors or symptoms of thyrotoxicosis (which begs the question as to whether the term subclinical is appropriate). It remains unclear how best to manage other patients, but the minimum requirement is

annual follow-up with measurement of FT3 as well as TSH to detect overt hyperthyroidism. Patients should also be warned to seek testing if they develop suggestive symptoms between annual tests.

This patient was reviewed by an endocrinologist and radioiodine treatment was discussed in view of her age. She elected not to have this as she cared for her grandson and could not undertake the necessary radioprotection measures after treatment. She also declined long term antithyroid drug treatment and surgery. A baseline bone density scan was requested, which showed no evidence of excessive bone loss, and annual blood testing for TSH and FT3 was arranged with her general practitioner.

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Patient consent not required (patient anonymised, dead, or hypothetical).

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10-MINUTE CONSULTATION

Flashes, floaters, and a field defect

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This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs.

A 65 year old woman presents to her general practitioner with a three day history of flashing lights in her right eye. She has also noticed a new floater in her temporal field of vision. She describes this as resembling a "fly" or "cobweb." Reassuringly, she has not been aware of a shadow in her field of vision.

Flashes, also known as photopsia, and floaters are a common complaint in primary care. Most patients with this complaint will have a simple, innocuous collapse of the vitreous gel, called a posterior vitreous detachment (figure). However, some may have more serious pathology. A rapid, systematic, assessment can facilitate appropriate management.

What you should cover

Ask about

Photopsia characteristics, duration, and laterality—Intermittent white flashes of light in the temporal visual field, akin to camera or lightning flashes, usually correspond to stimulation of the retina as the shrinking vitreous "tugs" on it. These photopsias can be triggered by eye movement. Coloured lights and zig-zag lines, occurring in the visual field of one or both eyes simultaneously and persisting for minutes or hours at a time, are more likely to be of neurovascular origin (such as migraine).

Size, shape, and distribution of floaters—These are shapes of varying translucency surrounded by a "sea of vision." They are more noticeable against a bright uniform background (computer screen, bright blue sky). They always seem to "move away" when an attempt is made to look at them and then settle back to their original position. They usually exhibit some undulation. Large floaters can interfere with central vision. Thickened strands of vitreous humour (called condensations), blood, and inflammatory debris are the main causes of floaters.

Onset, nature, and duration of change in vision—Flashes and floaters may be accompanied by sudden or gradual loss of field of vision. A progressively enlarging shadow, starting peripherally and advancing centrally, is the most consistent symptom

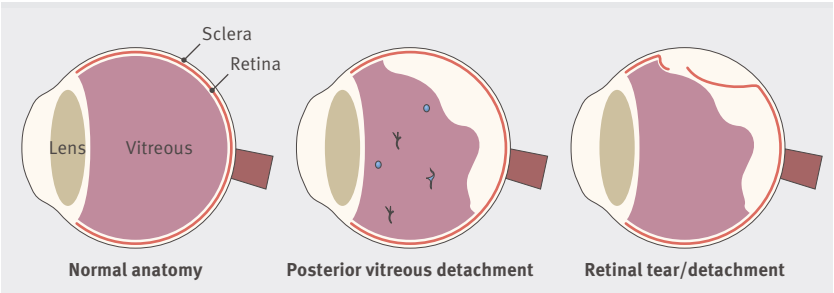

Diagram of the eye showing normal anatomy, posterior vitreous detachment with floaters (small opacities), and retinal detachment caused by a tear

The retinal detachment warning

We propose the following wording: "Your symptoms suggest that the gel in the eye is collapsing and peeling away from the light sensitive film at the back of the eye. As it does so, it can tug on the light sensitive film and cause flashes. In most patients, these flashes resolve, leaving longstanding floaters only. Occasionally, however, the tug can be hard enough to cause a small tear. This allows fluid to build up behind the light sensitive film and cause it to peel off the wall of the eye. This is called a retinal detachment. If you notice a slowly enlarging shadow or curtain effect moving towards the centre from the periphery, this warrants urgent attention"

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Previous articles in this series

- Dental pain (*BMJ* 2013;347:f6539)
- An adult with a neck lump (*BMJ* 2013;347:f5473)
- Abnormal vaginal discharge (*BMJ* 2013;347:f4975)
- Umbilical hernia (*BMJ* 2013;347:f4252
- A pain in the bottom (*BMJ* 2013;347:f4192)

of retinal detachment, which begins with a tear in the retina (figure).

Risk factors for posterior vitreous detachment—Ask about short sightedness (myopia), previous cataract surgery, and blunt ocular trauma.

General health—Patients with diabetes may develop new floaters as a consequence of vitreous haemorrhage. Systemic inflammatory conditions such as sarcoidosis may be associated with inflammatory debris within the vitreous humour (intermediate uveitis).

Rare causes of isolated photopsias include choroidal malignancy, paraneoplastic retinopathy, and some medications (such as chloroquine).

What you should do

Check vision—Use a Snellen chart to measure unaided visual acuity in each eye. Should this be less than 6/9, use a pinhole occluder to establish if the cause is refractive. If the macula is involved there will be a substantial drop in unaided vision and no improvement with a pinhole.

Assess visual field—Do this for each eye by confrontation; preferably with a 4 mm red hatpin. This is the most important part of the examination. Remember that small field defects are harder to detect with larger targets. Anatomically, most retinal detachments begin in the superior quadrants and would cause corresponding inferior field defects.

Direct ophthalmoscopy—Compare the red reflex in each eye. In the context of preceding or ongoing flashes and floaters, an asymmetrical red reflex may be due to vitreous haemorrhage or retinal detachment. If a prominent circular vitreous condensation near the optic nerve (called a Weiss ring) can be seen on funduscopy this is pathognomic of posterior vitreous detachment. Consider using the direct ophthalmoscope, set to +10D, as a magnifier to examine the anterior segment for signs of inflammation.

FURTHER READING

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Hollands H, Johnson D, Brox AC, Almeida D, Simel DL, Sharma S. Acute-onset floaters and flashes: is this patient at risk for retinal detachment? *JAMA* 2009;302:2243-9.

Although the vast majority (up to 85%[1]) of patients with flashes and floaters will have a simple posterior vitreous detachment, a dilated fundus examination is mandatory to exclude retinal breaks. Tractional retinal breaks cannot be reliably indentified based on symptoms only. In the United Kingdom, dilated fundal examination can be appropriately undertaken by optometrists or general practitioners with special interest in ophthalmology.

Local guidelines for referral should be followed. In the absence of these, we would suggest a dilated fundal examination within two weeks. A retinal detachment warning should also be given to all patients with suspected posterior vitreous detachment (see box). This represents a safeguard against a retinal detachment involving the macula, which carries the worst visual prognosis. Patients with flashes and floaters who have a new visual field defect or drop in visual acuity should be deemed to have a retinal detachment until proved otherwise and referred urgently to an ophthalmologist. Migrainous events associated with visual phenomena should be distinguished from symptoms of a posterior vitreous detachment and managed appropriately in primary care.

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ANSWERS TO ENDGAMES, p 36

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ANATOMY QUIZ

Diagnostic parotid sialogram

A: External auditory meatus (right)
B: Temporomandibular joint (left)
C: Parotid (or Stensen's) duct (left)
D: C3 vertebral body
E: Hyoid bone

STATISTICAL QUESTION

Stratified cluster sampling

Statement *a* is true, whereas *b* and *c* are false.

CASE REPORT

Patterns of inheritance, not always easily visible

1 All modes of inheritance are possible given the pedigree structure—autosomal dominant, autosomal recessive, X linked, mitochondrial, or sporadic.
2 By sequencing DNA from the parents and the affected child.
3 The chances that the parents would have another child with this disease are extremely low because both have a normal (wild-type or reference) sequence for the *UBIAD1* gene. The theoretical risk works out to be less than the risk of being struck by lightning in the United Kingdom (about one in three million).
4 As for all dominantly inherited conditions, if his partner had wild-type *UBIAD1* DNA, their children would have a one in two chance of carrying the mutated gene and manifesting the disease. The exact phenotypic effects might not be completely predictable, however.