Investigating low thyroid stimulating hormone (TSH) level

Anthony P Weetman

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. 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 other bewildering changes in levels of TSH, FT3, or FT4. 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. 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. 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 hyperthyroidism 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...
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. 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.

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.

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. 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

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

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<thead>
<tr>
<th>Low serum TSH level</th>
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<tbody>
<tr>
<td>Detailed history - medical history (recent illness, pregnancy, thyrotoxic symptoms); family history of thyroid disease; drug history (levothyroxine, amiodarone, lithium, interferon alfa)</td>
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<td>Examination - goitre; signs of thyrotoxicosis (tremor, warm and sweaty palms, tachycardia or atrial fibrillation); eyelid retraction or lag</td>
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<td>Measure serum FT4 level, then FT3 if FT4 is normal</td>
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<td>Taking levothyroxine</td>
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<td>Adjust dose</td>
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<td>Repeat TSH measurement in 8 weeks</td>
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<td>Low TSH, normal FT4 and FT3 levels</td>
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<td>First trimester of pregnancy</td>
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<td>Low TSH, raised FT4 or FT3 levels</td>
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<td>Thyrotoxicosis</td>
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<td>Refer to endocrinologist</td>
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<td>Secondary hypothyroidism</td>
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<td>Assess for other signs of hypopituitarism, refer to endocrinologist</td>
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<td>Low TSH, low FT4 or FT3 levels</td>
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<td>Repeat TSH and FT3 measurements after 6 weeks</td>
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<td>Normal TSH and FT3 levels</td>
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<td>Non-thyroidal illness</td>
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<td>Consider treatment if age &gt;65 years or risk factors present</td>
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<td>Annual follow-up</td>
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<td>Low TSH, normal FT3 levels</td>
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<td>Non-thyroidal illness</td>
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<td>Subclinical hyperthyroidism</td>
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<td>Evaluate cardiac and bone risk factors</td>
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<td>Low TSH, raised FT3 levels</td>
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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 radiiodine 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).

1 Association of Clinical Biochemistry, British Thyroid Association, British Thyroid Federation. UK guidelines for the use of thyroid function tests. www.british-thyroid-association.org/Guidelines/
5 Cooper DS, Biondi B. Subclinical thyroid disease. Lancet 2012;379:1142-54.
6 Franklin JA. The thyroid—too much and too little across the ages. The consequences of subclinical thyroid dysfunction. Clin Endocrinol (Oxf) 2013;78:1-8.

10-MINUTE CONSULTATION

Flashes, floaters, and a field defect

Ashraf A Khan,1 Ross J Kelly,2 Zia I Carrim3

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 “cob-web.” 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
Dental pain
Umbilical hernia
Abnormal vaginal discharge
An adult with a neck lump
Diagnostic parotid sialogram

Statistical question
Stratified cluster sampling
Statement a is true, whereas b and c are false.

Further reading

Although the vast majority (up to 85%) 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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