Endgames

Endocrinology ~ An elderly lady with weight loss and diarrhoea

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Case History

An 80 year old lady presented in July 2006 with a 2 month history of diarrhoea. She complained of passing loose stools approximately 4 times a day, and having to get up at night to open her bowels. She had noticed that her appetite had been poor and as a consequence, thought that she had lost approximately one stone in weight. She had noticed that the diarrhoea began shortly after one of her regular medications, dothiepin, had been stopped by her GP. Her only past medical history was hypertension, angina and a benign breast lump. She was a non-smoker and did not drink any alcohol. Her regular medications were as follows: aspirin 75mg OD, atenolol 50mg BD, bendroflumethiazide 2.5mg OD, doxazosin 6mg OD and simvastatin 40mg OD.

An outpatient CT colonography was arranged by a gastroenterologist and was reported as normal.

Routine blood tests were requested at the initial consultation and the results were as follows (normal ranges and units shown in brackets):

Hb 13.1 (13.0 – 18.0 g/dl)
Plt 150 (150 – 450 x 10^9/L)
WCC 5.4 (4 – 11 x 10^9/L)
Na 139 (135 – 145 mmol/L)
K 3.8 (3.4 – 5.0 mmol/L)
Ur 6.9 (3.1 – 7.9mmol/L)
Cr 105 (70 – 110 mmol/L)
Adjusted Ca 2.32 mmol/L
Bilirubin 13 (0 – 19 µmol/L)
Alk phos 60 (35 – 120 U/L)
ALT 24 (0 – 45 U/L)
TSH <0.05 (0.3-4.7 mIU/L)
Free thyroxine 19 (11-23 pmol/L)
Free T3 6.6 (3.5-6.5 pmol/L)
Thyroid peroxidise antibody 39 (0 – 60 kU/L)

Her thyroid function was subsequently monitored (table 1).

Table 1: thyroid function test results from July 2006 to October 2007 (normal ranges shown in brackets, abnormal results are shown in bold)

	July 2006	Sept 2006	Nov 2006	Oct 2007
TSH (0.3-4.7)	**<0.05**	**<0.05**	**<0.05**	**<0.05**
FT4 (11-23)	19	18	19	23
FT3 (3.5-6.5)	**6.6**	**6.7**	6.5	**6.9**

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Questions

1. What is the biochemical abnormality at initial presentation?

2. What do the subsequent thyroid function tests show?

3. What are the potential causes of a suppressed TSH with normal T4 and T3?

4. What are the risks associated with this biochemical pattern?

5. What treatment would you offer this lady?

Answers
Short answers

1. This lady has presented with mild T3 thyrotoxicosis (TSH suppressed, FT4 normal, FT3 raised just above the upper limit of normal).

2. At subsequent follow up appointments, her thyroid function varies from T3 thyrotoxicosis (T3T) to subclinical hyperthyroidism (SH).

3. T3T is almost always due to endogenous hyperthyroidism, whereas potential causes of SH may be endogenous or exogenous and include:

Endogenous causes (T3T or SH):

- Graves' disease
- Autonomously functioning thyroid adenoma
- Multinodular goitre

Exogenous causes (SH only):

- Excessive thyroid hormone replacement therapy in hypothyroid individuals
- Intentional thyroid hormone suppressive therapy for differentiated thyroid carcinoma or nodular thyroid disease
- Iatrogenic e.g. Drugs (glucocorticoids, opiates, levodopa, amiodarone) and IV contrast agents containing iodine
- Pregnancy (due to placental hCG stimulation of the thyroid)
- Non-thyroidal illness (sick euthyroid syndrome)

4. The associated risks of T3T and SH include:

- Atrial fibrillation and stroke disease
- Cardiovascular disease
- Dementia
- Fracture
- Premature death

5. T3T can be regarded as the earliest or mildest form of overt hyperthyroidism and should generally be treated in the same way as full-blown thyrotoxicosis. Treatment options for SH include:

- Monitoring only
- Beta blockers
- Antithyroid drugs e.g. carbimazole
- Radioactive iodine

Long answers

While T3T may be symptomatic, SH is often a laboratory diagnosis, characterised by the biochemical findings of low or undetectable serum thyroid stimulating hormone (TSH) level with normal levels of thyroxine (T4) and tri-iodothyronine (T3), and little in the way of symptoms.

Both T3T and SH may result from endogenous overproduction of thyroid hormones (e.g. Graves' disease, an autonomously functioning thyroid adenoma, toxic multinodular goitre). However, SH may also be owing to intentional or unintentional over-administration of thyroid hormones. This biochemical picture is also seen in normal pregnancy [1], in sick euthyroid syndrome[2] and in patients taking glucocorticoids[3] amiodarone[4], levodopa [5], opiates[6], and following injection of IV contrast agents containing iodine[7].

T3T and SH are more common in women than in men (female:male = 1.5:1). T3T is uncommon, but SH affects between 1 and 2% of women over the age of 60[8, 9], and up to 3% of people over 80 years of age[10].

SH was once considered a benign biochemical abnormality. However, in recent years, evidence has accrued which demonstrates that persistent SH is associated with significant morbidity and mortality due to cardiovascular and cerebrovascular disease. In a study of community-dwelling over 60 year olds, at the 5 year follow-up point, the circulatory mortality in study participants with a TSH <0.5 was 25% compared with 15% in participants with a TSH within normal limits. This represents a 10% fall in survival in those with SH compared to those with normal thyroid function[11]. This finding has been replicated across a cohort of the "oldest old" in the Leiden 85-Plus Study [12].

SH may progress to T3T or full-blown overt hyperthyroidism with its associated symptoms; the incidence of progression to overt thyrotoxicosis being approximately 5% per year[13, 14]. In addition, the risk of atrial fibrillation (AF), a long established risk factor for cerebrovascular disease, is increased 3 fold in patients with SH[15]. AF risk in one study was little different between SH and overt thyrotoxicosis[16]. SH has also been demonstrated to be associated with dementia. In one population-based study, the risk of dementia or Alzheimer's disease was increased more than 3 fold in participants with a low TSH[17]. Finally, just as overt hyperthyroidism is a risk factor for reduced bone mineral density and fracture, so is SH. A prospective cohort study clearly demonstrated that women over 65 years of age with low serum TSH levels have a 3 fold increased risk of sustaining a new hip fracture and a 4 fold

increased risk of sustaining a new vertebral fracture compared with women with normal TSH levels[18].

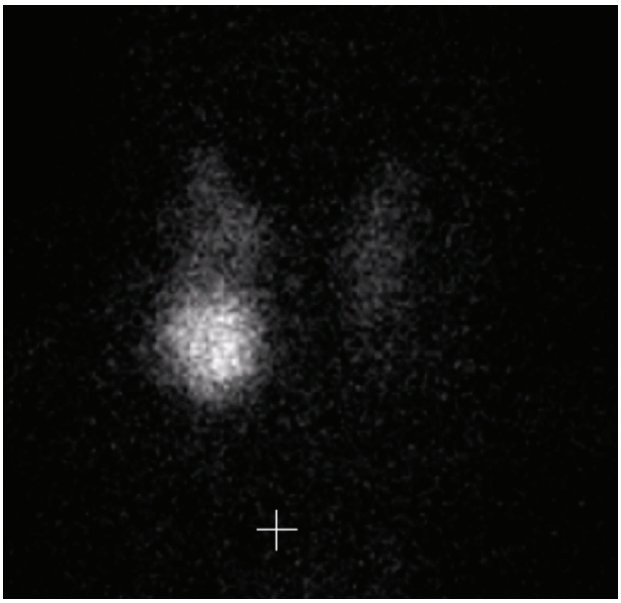
In terms of treatment options, both antithyroid drugs and radioactive iodine are effective at correcting the biochemical abnormalities of SH, however there is no robust evidence to suggest that these treatments lead to a reduction in the associated morbidity and mortality, or an improvement in quality of life and survival. In addition, these treatments have their own drawbacks. For example, carbimazole, one of the most commonly used of the antithyroid drugs, is rarely associated with agranulocytosis which has a mortality of 10% in the elderly[19]. In addition, patients with SH are often older and therefore taking multiple medications. Adding further medications can result in confusion, compliance problems and increases the chances of drug interactions. In contrast, radioiodine therapy is a convenient one-off treatment however it may render the recipient hypothyroid and therefore dependent upon thyroid replacement therapy for life, again increasing the patient's tablet burden. Attempts to establish an evidence base for the treatment of SH through randomised clinical trials have proved difficult thus far.

Despite the lack of evidence, many endocrinologists do treat patients with SH. A recent survey of American thyroid specialists showed that most favoured treating older patients actively, with 66% opting to treat an older woman with SH[20]. A similar survey of UK endocrinologists showed a more conservative approach, with one third of those who responded stating that they would generally treat the patient, particularly if they were in atrial fibrillation or had osteoporosis. Of those offering treatment for SH, 63%, 35%, 1% and 0·4% would recommend radioiodine, thionamide, beta-blocker and thyroidectomy, respectively[21]. Given this uncertainty, options for treatment should be discussed with the patient and the pros and cons of each option explored.

Outcome of the Case

This lady was investigated by the gastroenterologists and no sinister cause for her diarrhoea was found. Dothiepin was restarted, the diarrhoea improved and her weight increased. The gastroenterologists discharged her from their care, after referring her to the endocrine department for investigation of her abnormal thyroid function tests. She was investigated and found to have a solitary toxic thyroid nodule (figure 1). She felt well in herself and therefore declined the offer of radioactive iodine therapy and opted for careful monitoring.

Figure 1: Image from this patient's thyroid ^{99}Tc Pertechnetate scan illustrating a "hot spot" corresponding to a solitary toxic thyroid nodule.



Unfortunately, in October 2007, the patient began to feel very short of breath and complained of palpitations and dizzy spells. A 12-lead ECG showed AF and her thyroid function tests demonstrated worsening T3T (TSH <0.05, FT4 23, FT3 6.9). She was given digoxin for rate control and was anticoagulated with warfarin. She agreed to radioactive iodine therapy and received this in November 2007.

In January 2008 she was clinically euthyroid however her TSH was increasing, therefore she was commenced on a low dose of thyroxine (25 micrograms per day) in anticipation of her becoming hypothyroid. She remained in AF and so was referred for DC cardioversion. In April 2008 she was successfully cardioverted back into sinus rhythm with significant improvement in her symptoms. Immediately after cardioversion, her digoxin was stopped and her atenolol dose was reduced to 50mg once daily. She continued with warfarin for a further 6 months after cardioversion, and having confirmed that she remained in sinus rhythm, this was stopped in June 2008. She is currently well, remains in sinus rhythm and is maintained on 25 micrograms of thyroxine daily.

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Licence for Publication

Competing Interests

All authors declare that the answer to the questions on your competing interest form [http://bmj.com/cgi/content/full/317/7154/291/DC1] are all “No” and therefore have nothing to declare