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Lesson of the week

Unsuspected central hypothyroidism

A Waise, P E Belchetz

Thyroid testing is increasingly used as a tool for identifying cases of thyroid disease in both primary and secondary care even in the absence of a strong clinical suspicion of disease. Patients with unsuspected thyroid disease are, therefore, likely to be identified, and among those identified are a few patients who have pituitary tumours or hypopituitarism. In the United Kingdom there is variation in which tests are offered for first line thyroid testing. In a 1994 survey of endocrinological testing in clinical biochemistry laboratories in the United Kingdom, Barth et al found that 30 different combinations of first line and second line profiles were being used.[1] In a total of 186 replies 34% of laboratories reported offering testing for free thyroxine concentrations and thyroid stimulating hormone, 32% offered testing only for thyroid stimulating hormone, and 18% offered testing for total thyroxine concentration. The cases of the six patients described here highlight the fact that offering testing only for thyroid stimulating hormone (TSH) may be inappropriate.

The first five patients discussed had concentrations of free thyroxine hormone and thyroid stimulating hormone measured using a highly sensitive, third generation method (Amerlite hTSH, Kodak Clinical Diagnostics, Amersham). In the sixth patient these were measured by a two step, second generation method (Beckman Instruments, High Wycombe). Prolactin, luteinising hormone, and follicle stimulating hormone were measured using the Abbott IMX fluoroimmunoassay (Abbott Diagnostics, Maidenhead). Growth hormone was measured using the Nichols Diagnostics immunoassay (Nichols Institute Diagnostika, Bad-Nauheim, Germany). Testosterone was measured by radioimmunoassay. Anterior pituitary function was investigated in five patients using glucagon, thyrotrophin releasing hormone, and gonadotrophin releasing hormone challenge. Insulin was used instead of glucagon in one instance.

Testing only for thyroid stimulating hormone will miss unsuspected cases of central hypothyroidism

Case reports

Case 1

A 75 year old man with a three year history of anaemia was referred by his general practitioner to a general physician. The patient's haemoglobin was 10.8 g/dl with contracted red cells. Hypothyroidism was suggested as a possible cause. On thyroid testing serum concentration of TSH was 1.34 mU/l (reference range 0.15-3.5 mU/l) and free thyroxine concentration was 8 pmol/l (10-30 pmol/l).

The patient's anaemia and the biochemical evidence of central hypothyroidism triggered referral for clinical endocrine assessment. The patient reported a 12 year history of feeling cold and of sexual dysfunction. He was kyphotic and had postural hypotension, sparse body hair, and thin skin. Pituitary stimulation testing confirmed the diagnosis of hypopituitarism and computed tomography identified a pituitary tumour. He received hydrocortisone and levothyroxine sodium (thyroxine sodium) and had transsphenoidal surgery for a non-secretory pituitary adenoma.

Department of Clinical Biochemistry, Friarage Hospital, Northallerton, North Yorkshire DL6 1JG
A Waise
consultant chemical pathologist
Department of Medicine, General Infirmary, Leeds LS1 3EX
P E Belchetz
consultant physician
Correspondence to:
A Waise
a.waise@nahs-tr.northy.nhs.uk

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Case 2

A 43 year old man was having the results of his thyroid tests checked to investigate possible causes of hypercholesterolaemia. On testing, his TSH concentration was 2.42 mU/l and free thyroxine was 7 pmol/l, suggesting central hypothyroidism. Further tests found that a random serum cortisol concentration was 132 nmol/l (250-800 nmol/l), serum luteinising hormone was 1.7 IU/l (2-12 IU/l), serum follicle stimulating hormone was 8.2 IU/l (1-12 IU/l), serum prolactin was 30 μg/l (2-28 μg/l), and testosterone 2.6 nmol/l (10-31 nmol/l). A short tetracosactide test showed a suboptimal response (serum cortisol 475 nmol/l at 60 minutes; expected value >550 nmol/l).

The patient was referred for clinical endocrine assessment. He reported a history of mid-morning sweating and flushing. He had a sallow complexion, sparse body hair, hypogonadism, no postural hypotension, and normal visual fields and optic discs. Pituitary stimulation confirmed hypopitutarism. Computed tomography identified a 2.5 cm cystic pituitary lesion with suprasellar extension. He began replacement treatment and underwent transsphenoidal surgery for resection of a non-secreting pituitary adenoma. He made an uneventful recovery.

Case 3

Thyroid tests were ordered by a general practitioner for a 73 year old man because he had reported feeling cold and tired during an assessment for hip surgery. His TSH concentration was 1.88 mU/l and free thyroxine was 7 nmol/l, suggesting central hypothyroidism. Further investigations generated by the laboratory showed that his serum cortisol concentration was 211 nmol/l and prolactin was >1200 μg/l.

The patient had a clinical endocrine assessment. He reported a six month history of a lack of energy, a loss of about 6.5 kg in weight, and a 15 year history of sexual dysfunction. He was pale and had a sallow complexion, sparse body hair, bilateral gynaecomastia, and testicular atrophy. He also had optic atrophy and bilateral temporal hemianopia. Pituitary stimulation testing confirmed the diagnosis of hypopituitarism and computed tomography identified a macroadenoma. He was treated with hydrocortisone and levothyroxine sodium and later with bromocriptine. He had surgery for the pituitary macroadenoma and remains on cabergoline for a residual tumour.

Case 4

A 76 year old retired auxiliary nurse was being seen by her general practitioner for a two month history of feeling unwell, faint and giddy in the morning. She had had a mastectomy for breast carcinoma and a thyroidectomy for hyperthyroidism. She was taking tamoxifen, atenolol, and omeprazole. Thyroid testing was requested. She was hyponatraemic. Her free thyroxine concentration was 6 nmol/l and TSH was 0.94 mU/l, suggesting central hypothyroidism. Further testing found that her luteinising hormone concentration was <1.0 IU/l, follicular stimulating hormone was <0.5 IU/l, and prolactin was 27 μg/l.

At the time of clinical assessment of her endocrine functioning she looked pale, had no axillary hair, and had sparse pubic hair. She was hypertensive but had no visual field defect, and her optic discs were flat. Pituitary stimulation confirmed hypopituitarism but computed tomography did not show definite evidence of a pituitary tumour. She was started on hydrocortisone and levothyroxine sodium after which she developed diabetes insipidus and required treatment with desmopressin.

Case 5

A 54 year old plant operator was being seen by his general practitioner for tiredness, depression, and possible hypothyroidism. His TSH concentration was 0.84 mU/l and free thyroxine was 7 nmol/l, suggesting central hypothyroidism.

He was referred for clinical endocrine assessment. This identified a history of impotence and lack of libido. He also had angina, asthma, and hypertension. He was obese, bearded, and showed no abnormality of hair growth or symptoms of hypogonadism. His visual fields were intact. His response to short tetracosactide testing was suboptimal (serum cortisol 468 nmol/l at 60 minutes). Pituitary stimulation testing confirmed hypopituitarism and computed tomography identified a pituitary tumour with suprasellar extension. He began treatment with hydrocortisone, levothyroxine sodium, and testosterone replacement. Over the next few weeks he complained of blurred vision and scotomas. He then underwent transsphenoidal surgery and radiotherapy for a pituitary adenoma.

Case 6

A 69 year old man was thought to be clinically hypothyroid during treatment for a small basal cell carcinoma. His thyroid testing suggested central hypothyroidism (free thyroxine 6 pmol/l (10-25 pmol/l); TSH 3.43 mU/l (0.3-5.0 mU/l)). Further tests carried out on the same sample showed that his serum cortisol concentration was 19 nmol/l (150-650 nmol/l), luteinising hormone was <1.0 IU/l, and follicle stimulating hormone was 3.4 IU/l.

During clinical endocrine assessment he made no specific complaints. He was pale, had a sallow complexion, axillary hair was absent, and pubic hair was sparse. Pituitary stimulation testing confirmed the diagnosis of hypopituitarism, but there was no evidence of a tumour on imaging. He was started on replacement treatment; he reported feeling less lethargic and that long standing aches and pains had resolved.

Discussion

All patients described here had clinical and biochemical evidence of pituitary failure when they were seen for a clinical endocrine evaluation. Four had radiological evidence of pituitary tumours. In all patients TSH was detectable and within the normal reference range for adults. Concentrations of free thyroxine were low in all patients. All had evidence of deficiencies in growth hormone and adrenocorticotrophic hormone. All of the men had testosterone deficiency. All patients had the expected response to replacement treatment and to surgery. After replacement treatment TSH concentrations remained undetectable (<0.05 mU/l) in four patients; these patients underwent pituitary surgery with or without radiotherapy. In those who did not have surgery or radiotherapy TSH concentrations remained detectable (0.16 mU/l in patient 4 and 0.74 mU/l in patient 6).

Each year about 20-30 people per million population develop pituitary tumours.[2] The onset is usually

insidious: symptoms of insufficiency are non-specific and progression of the disease is slow. The patients described here presented with symptoms or problems that prompted their doctors to suspect hypothyroidism. Details of patients' clinical history only came to light at the time of their clinical endocrine assessment as did the results of the physical examinations; they were not apparent at the time the patients were first seen.

The results of thyroid function tests may be abnormal in patients with acute or severe non-thyroidal illness, the so called the sick euthyroid state. However, the assays used to investigate the patients described here may identify low concentrations of TSH or raised free thyroxine concentrations during the acute phase of critical illness; TSH concentrations may be slightly raised during recovery.

If a patient has a low concentration of thyroxine and a normal TSH concentration the need for further assessment is more likely to be apparent than if the patient is only tested for TSH. In cases in which only the TSH concentration is used for first line testing, thyroxine measurements are performed only if TSH is clearly too high or too low. This approach saves money for the laboratory. In the laboratory where the analyses were carried out for these six cases, the cost of early detection for patients with pituitary tumours or hypopituitarism is about £5000 ($7000) per case per year. This could be reduced to £3800 if combined first line testing was limited to patients seen in primary care or hospital outpatient departments. However, it is essential to consider the implications of delayed diagnosis for patients with undiagnosed pituitary tumours or hypopituitarism and the consequential long term morbidity and mortality. This must be weighed against any benefit gained from implementing a first line strategy of offering only a single test. Any comparison needs to take into account the patient's quality of life and the decrease in morbidity associated with early identification and treatment.

First line thyroid testing of TSH and free thyroxine concentrations should be offered for all likely presentations of thyroid disorders including central hypothyroidism and central hyperthyroidism. A policy of testing only for free thyroxine concentrations in patients with hypopituitarism would seem to be more sensitive than testing only for TSH. However, this policy may be inappropriate in some clinical situations because of the small proportion of falsely raised results that are inherent in the design of the assays.

Caldwell et al proposed a testing strategy based on what was then the recently introduced second generation TSH assay.[3] They suggested that if TSH concentrations were normal then no further action was needed. However, others pointed out that cases of hypopituitarism would be missed by such a strategy.[4] Patients with central hypothyroidism occurring secondary to pituitary disorders may have low serum thyroxine in combination with normal or high concentrations of TSH.[5 6] This is thought to be the result of the discrepancy between the biological and immunological activity of TSH.[7]

First line testing that includes only TSH concentration may be adequate to identify patients who are already under the care of specialists and for whom a high index of suspicion might mean that secondary hypothyroidism is likely to be identified on clinical grounds. However, these patients are usually seen in primary care first; if TSH testing is the only test used then central hypothyroidism has to be suspected clinically otherwise the diagnosis is likely to be missed. Since many patients with central hypothyroidism are likely to be elderly, routine thyroid evaluation in this group should also use combined testing.[8]

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Contributors: AW had the idea of putting these case histories and findings together, arranged for further testing for the patients, and was involved in the clinical management of the patients. Four patients were later reviewed and managed by PEB. AW drafted the manuscript, which was critically reviewed by PEB. AW will act as guarantor for the paper.

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Are fillers educational?

I have not seen a patient present with polymyalgia rheumatica for many years—perhaps over 15.

Thus, call it coincidence, but seven days after reading about two relatives with polymyalgia (*BMJ* 2000;320:1641) I saw a woman in general practice with marked weakness, headaches, lassitude, and a slowly rising erythrocyte sedimentation rate. She explained how the symptoms had come on quickly and had affected mostly her upper limbs but that her legs were also weak. After several discussions with her, repeat blood tests, and a short phone call to the local geriatrician, we decided that her condition was indeed polymyalgia rheumatica.

We hope that she is now heading for a steroid induced recovery, and I hope that osteoporosis prophylaxis will be sufficient to prevent her bones from becoming weaker.

The answer to the question in the title? Yes, they most certainly can be, though it is best if they can be timed so that they appear a few days before your next memorable patient. The feature is still one of the first articles I read in the *BMJ*.

Surinder Singh *general practitioner, south east London*

We welcome articles of up to 600 words on topics such as *A memorable patient*, *A paper that changed my prctice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to.