Lesson of the Week

Primary hypothyroidism presenting as amenorrhoea and galactorrhoea with hyperprolactinaemia and pituitary enlargement

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The combination of amenorrhoea, galactorrhoea, and hyperprolactinaemia in a young woman usually suggests that she has a prolactin secreting adenoma of the anterior pituitary gland. Primary autoimmune thyroid failure, however, is common in young women and may also be associated with hyperprolactinaemia and with galactorrhoea in those whose breasts have been exposed to oestrogen. Hypothyroidism in patients with the amenorrhoea and galactorrhoea syndrome is usually suggested by appropriate symptoms and clinical signs, and treatment with thyroxine renders the patient euthyroid, with resolution of the hyperprolactinaemia. We report on a patient who presented with amenorrhoea, galactorrhoea, hyperprolactinaemia, and suprasellar enlargement of the pituitary. Although she was clinically euthyroid, treatment with thyroxine resulted in resolution of her symptoms and hormonal and radiological abnormalities within six weeks.

Patients with hyperprolactinaemia, with or without pituitary enlargement, should undergo assessment of thyroid function even if clinically euthyroid

Case report

A 26 year old housewife presented with a one year history of secondary amenorrhoea, and at examination milk could be expressed from her breasts. Her menarche had been at 14 years of age, and she had had regular cycles subsequently. Between 17 and 24 years of age she had taken Ovranette (150 μg levonorgestel and ethinyloestradiol 30 μg) and had regular withdrawal bleeds. In 1983 after a planned pregnancy she delivered a healthy girl, but the puerperium had been complicated by severe postnatal depression and she remained amenorrhoeic for one year and had then had six months' oligomenorrhoea.

Investigation elsewhere showed hyperprolactinaemia (prolactin concentrations of 762 and 1288 mU/l (normal <420 mU/l)) and a normal pituitary fossa on plain skull radiography. Her mother had been treated for hypothyroidism.

Responses of growth hormone, cortisol, prolactin and thyroid stimulating hormone to hypoglycaemia (0·1 U insulin/kg), domperidone (10 mg intravenously), and thyrotrophin releasing hormone (200 μg intravenously)

	Minutes						
	0	20	30	60	90	120	Normal
Insulin induced hypoglycaemia							
Glucose (mmol/l)	3·5		1·3	2·2	1·6	1·9	<2·2
Growth hormone (mU/l)	1·4		1·5	>48	27·8	14·4	>20
Cortisol (nmol/l)	252		214	568	569	352	>550
Prolactin mU/l)	1420		1570	1525	1390	1485	>100% basal
Domperidone test							
Prolactin (mU/l)	1097	16398		10593			>100% basal
Thyroid stimulating hormone (mU/l)	620	875		885			<+2 mU/l
Thyrotrophin releasing hormone test							
Prolactin (mU/l)	2464	10998		9900			>100% basal
Thyroid stimulating hormone (mU/l)	960	1065		1365			Basal +2mU/l and >5 mU/l

Conversion: SI to traditional units—Glucose: 1 mmol/l=18 mg/100 ml; Cortisol: 1 nmol/l=36 ng/100 ml.

The patient was referred for investigation of hyperprolactinaemia. On examination she had a small goitre but appeared clinically euthyroid. High resolution computed tomography of the pituitary fossa showed an enlarged gland with 8 mm suprasellar extension. There was homogeneous uptake after the infusion of contrast, and no clear evidence of a discrete microadenoma (figure). Visual fields were normal to confrontation and perimetry. The table shows the results of anterior pituitary hormone assessment. Cortisol and growth hormone responses to hypoglycaemia were normal, but there was no rise in prolactin concentrations. The cortical response to hypoglycaemia was only just within the normal range, but an intact pituitary-adrenal axis was confirmed by a normal rise in urinary excretion of 17 hydroxycorticosteroids during a high dose metyrapone test. Basal thyroid stimulating hormone concentrations were appreciably raised (normal <5 mU/l), and there was a notable increase in both thyroid stimulating hormone and prolactin concentrations after administration of the dopamine antagonist domperidone. Similarly, the responses of thyroid stimulating hormone and prolactin to thyrotrophin releasing hormone were both exaggerated. Surprisingly, in view of the patient's apparent clinical state, the serum free thyroxine concentration was low (2 pmol/l (0·16 ng/100 ml); normal range 8-

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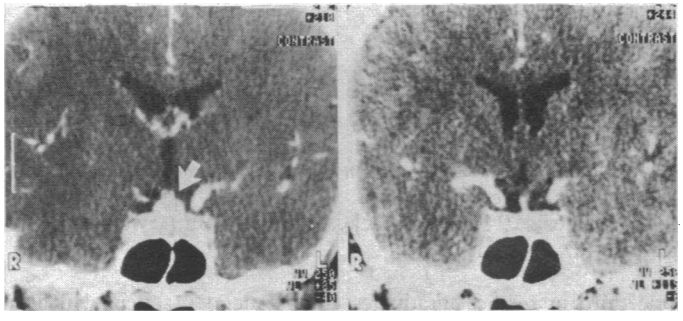
26 pmol/l (0·6-2·0 ng/100 ml)) and thyroid microsomal antibodies measured by haemagglutination of red cells were positive at 1/6400. The serum concentration of 17-β oestradiol was low (45 pmol/l (12 pg/ml); normal follicular phase >70 pmol/l (>19 pg/ml)), and there was no evidence of ovulation (serum progesterone concentration <2 nmol/l (<0·6 ng/ml)).

We concluded that the patient had primary autoimmune thyroid failure with associated hyperprolactinaemia and that the pituitary enlargement was due to thyrotrophic hyperplasia. Replacement treatment with thyroxine was begun, increasing to 100 μg daily. One month later the serum free thyroxine concentration was 18 pmol/l (1·4 ng/100 ml) and the thyroid stimulating hormone concentration had fallen to 21·6 mU/l. Serum prolactin concentration was normal at 350 mU/l. The patient felt no different as a result of treatment, although there was no galactorrhoea on expression. Computed tomography showed a normal pituitary gland with homogeneous uptake after contrast and no evidence of suprasellar extension (figure). Two months after the start of thyroxine treatment the serum free thyroxine concentration was 25 pmol/l (1·9 ng/100 ml) and the serum thyroid stimulating hormone concentration was normal at 0·6 mU/l. Menstruation occurred six weeks after thyroxine was started, and subsequent cycles were regular. The response of prolactin to hypoglycaemia was not reassessed after thyroxine treatment because we could not justify further insulin induced hypoglycaemia in a patient with normal anterior pituitary function.



High resolution computed tomogram of pituitary fossa (coronal plane), showing (left) initial 8 mm of suprasellar extension (arrowed) before treatment and (right) resolution after four weeks' treatment with thyroxine 0·1 mg daily.

Discussion

This case emphasises that thyroid state must be assessed in all patients with amenorrhoea and galactorrhoea and hyperprolactinaemia, even if they seem to be clinically euthyroid. It also illustrates the degree of suprasellar extension that may occur in such cases and the rapidity of response to L-thyroxine. It is well known that in longstanding hypothyroidism the pituitary may be enlarged and may show suprasellar extension.[1 2] The lack of clinical features of hypothyroidism, in our patient, however, together with the manner of presentation, might have led the unwary to misdiagnose the condition and treat her inappropriately. The increased pituitary size was presumably a result of thyrotroph hyperplasia,[3 4] although it is not possible to know whether a true thyrotroph feedback adenoma was also present. "Feedback" adenomas secreting thyroid stimulating hormone have been associated with primary thyroid failure,[5-8] but these also resolve with adequate thyroxine replacement treatment. Although the suprasellar extension had resolved after one month's treatment, the serum thyroid stimulating hormone concentration was still raised, though below its initial value. In similar patients the fall in prolactin concentration was reported to take longer than the fall in thyroid stimulating hormone concentration,[9] but in our case prolactin concentrations were normal before thyroid stimulating hormone concentrations. These responses show that the rapidity with which pituitary hyperplasia resolves with adequate and appropriate replacement treatment.

In euthyroid subjects with adenomas that secrete prolactin there is a blunted (<100%) prolactin and exaggerated thyroid stimulating hormone (>2 mU/l) response to acute dopamine antagonism with domperidone compared with the response in control subjects.[10 11] Our patient showed an exaggerated thyroid stimulating hormone response to domperidone compatible with a prolactinoma or primary hypothyroidism,[10] but in addition the prolactin response was greatly exaggerated, which militates against the presence of a prolactinoma but does not exclude it. Similar responses occurred after administration of thyrotrophin releasing hormone.

The cause of hyperprolactinaemia in patients with primary hypothyroidism is unknown. In this patient it is unlikely that the suprasellar extension caused appreciable compression of the stalk as dopamine receptor blockade resulted in considerable increases in circulating concentrations of thyroid stimulating hormone and prolactin, which means that hypothalamic dopamine was still reaching the anterior pituitary gland via the hypophysial-portal system. We recently reported that patients with stalk compression hyperprolactinaemia owing to lesions that are not prolactinomas show reduced or absent thyroid stimulating hormone responses to domperidone.[12] In vitro studies have shown that cultured anterior pituitary cells from hypothyroid rats show a significant reduction in the sensitivity of prolactin to the inhibitory actions of dopamine and dopamine agonists. Furthermore, in hypothyroidism the number and percentage volume of lactotrophs may be increased relative to other anterior pituitary cell types.[13] A variable combination of these two factors may possibly lead to hyperprolactinaemia in association with primary hypothyroidism, and this may have accounted for the condition in our patient.

We are grateful to the department of medical biochemistry for the assay services provided.

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(Accepted 10 March 1986)

What is the significance of breakthrough bleeding occurring in women who have previously been asymptomatic while taking an oral contraceptive in the absence of any change in medication, medical condition, or weight?

It is not uncommon for breakthrough bleeding to occur in women who have previously been asymptomatic on an oral contraceptive. Such patients should be examined vaginally to exclude abnormalities of the pelvic organs and a sample taken for cervical cytology. Assuming that the pelvic organs are normal, I would recommend that the patient is reassured and asked to continue her present contraceptive, as breakthrough bleeding is often transient. If the symptom persists, however, then an alternative oral contraceptive should be prescribed.—G J LEWIS, consultant gynaecologist and obstetrician, Stourbridge.