CASE REPORTS

Primary thyroid failure presenting as a pituitary tumour

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Summary

A 20-year-old female was referred as a pituitary tumour with failure to grow. Primary hypothyroidism from the age of 8 had been diagnosed at the age of 11, when the patient was put on thyroid replacement therapy. Routine investigations showed normal anterior pituitary function, and confirmed the diagnosis of primary hypothyroidism. A needle biopsy of the pituitary gland revealed an empty fossa. The possible relation of the empty sella with the primary hypothyroidism is discussed. A chromosome anomaly, deletion of the short arm of an X chromosome, was found and its contribution to the delayed growth is discussed.

FAILURE to grow in childhood may be associated with a number of conditions. These include deficiency of growth hormone or of thyroxine, chromosomal abnormalities of various types and systemic illness such as malabsorption. A patient is presented here, who showed evidence of several of these causes of growth retardation.

Case history

A 20-year-old girl was referred with growth failure and radiological signs of a pituitary tumour.

She had been a full term delivery, weighing 3.2 kg at birth. Apart from recurrent otitis media she developed normally until the age of 8 years when she

stopped growing. At the age of 11, she was investigated in another hospital for the failure to grow and she was found to be hypothyroid (PBI 1.8 µg/100 ml, serum cholesterol 425 mg/100 ml). A moderate expansion of the pituitary fossa was found but a metyrapone test was normal. Her height was below the third percentile.

She was then treated with L-thyroxine 0.2 mg daily but this produced little growth. At the age of 13, a diagnosis of hypopituitarism was made, in another hospital, on the basis of a negative metyrapone test and absence of growth hormone and cortisol response in an insulin tolerance test which probably induced insufficient hypoglycaemia (after 0.075 u insulin/kg body weight, blood glucose was reported 92, 56, 47, 70 and 84 mg/100 ml at fasting, 30, 60, 90 min and 2 hr, and plasma cortisol 25.6, 22.5 and 26.9 µg/100 ml in the fasting and 30 min and 1 hr, and growth hormone (GH) < 1.0 ng/ml in all samples). During these investigations the patient was taking 0.2 mg L-thyroxine daily and the serum PBI was 9.8 µg/100 ml, while the skeletal age was 11-12 years according to Greulich and Pyle (1950), or only slightly delayed from the chronological one of 13 years. A metabolic trial of human growth hormone was reported to show a strongly positive nitrogen balance, suggesting normal responsiveness to human GH, but no treatment was given.

At the age of 15 years she was still below the third percentile for her height but menstruation started spontaneously. At the age of 18 years, frontal headaches developed. Sequential skull X-rays showed a progressive enlargement of the pituitary fossa. The skeletal age was compatible with 18 years.

On referral to Hammersmith Hospital at the age

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of 20, she was 138 cm tall, i.e. over 2 standard deviations below the normal mean, and weighed 52 kg (Fig. 1). A short neck and wide carrying angle were noted. Heel to pubis length was 72 cm and pubis to vertex was 66 cm. Skeletal age was in excess of 18 years. Breast development and sexual characteristics were normal. The fundi were normal and there was no evidence of papilloedema. Apart from the pituitary and thyroid disorders noted below no clinical or biochemical evidence was found of any other systemic disease.

A jejunal biopsy was performed while she was on partial replacement therapy (0.1 mg/day) and was

found to be normal. There was no biochemical evidence of intestinal malabsorption.

Pituitary and thyroid findings during her Hammersmith Hospital admissions

On her first visit, while on replacement dosage of L-thyroxine 0.1 mg daily there were still some residual features of hypothyroidism, including slow relaxing reflexes and dry skin. Sella tomography and air encephalography confirmed an enlarged sella turcica but no air was recognized in the sella. Formal testing of pituitary function showed normal reserve of adrenocorticotrophic hormone (ACTH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and of growth hormone (GH) (Tables 1 and 2)

TABLE 1. LH/FSH-releasing factor test (100 µg i.v.)

	Time (min)			Response
	0	20	60	
Serum LH µu/ml*	4.2	8.6	6.2	Normal
Serum FSH µu/ml*	8.0	11.1	9.4	Normal

* As MRC Pituitary Standard for LH and FSH 69/104.

FIG. 1. The patient at 20 years.

To ascertain whether thyroid failure had been primary or secondary, she was first equilibrated for over 1 month on her subnormal replacement dosage and then given a standard thyrotrophin releasing factor (TRF) test (200 µg i.v.) (Table 3). The L-thyroxine therapy was then stopped for 1 month, after which she was put on acute replacement therapy with a large dose of L-triiodothyronine (T3) to check the suppressibility of the serum TSH as a pituitary tumour was suspected. Table 3 shows that on partial replacement therapy (0.1 mg/day) the serum TSH was raised and over-responsive to TRF, which is a feature of primary hypothyroidism. The diagnosis was confirmed by finding, after 1 month without thyroxine replacement therapy, a low PBI, a very low thyroid ¹³¹I neck uptake, a very high serum TSH and electrocardiographic changes of hypothyroidism (bradycardia, generalized low voltage, flat T waves).

The rapid and complete suppression then of serum TSH level by T3 made a TSH-producing pituitary tumour unlikely. No thyroid or gastric auto-antibodies could be detected in the plasma. Anti-nuclear factors were negative.

TABLE 2. Insulin tolerance test (i.v. 0.1 u/kg body weight × 2)*

	Time (min)					Response
	Fasting	30	60	90	150	
Blood glucose mg/100 ml	65	11	32	14	25	Normal
Serum GH µi.u./ml WHO I.R.P.	1.1	14	> 50	33	> 50	Normal
Plasma cortisol µg/100 ml	14.9	—	24	26	32.1	Normal

* Two doses of insulin were given at 0 and 60 min.

TABLE 3. Thyroid function tests

(a) On L-thyroxine 0.1 mg/day (over 1 month)

TRF test (200 µg i.v.): (Serum TSH µu/ml MRC Res Std A)	Time (min)			Response
	0	20	60	
	26	62	54	Hypothyroid

(b) After withdrawal of L-thyroxine for 1 month

Serum PBI (µg/100 ml)	1.8	(Normal range 4-8)
¹³¹ I Neck uptake at 48 hr	0.8%	(Normal range 20-50)
Serum TSH (µu/ml)	920	(Normal range <1.0-3.7)

(c) Suppression of serum TSH by L-T3 and L-T4

Date	Dose L-T3 (µg/day)	Serum TSH (µu/ml)
4.10.72	500	920
5.10.72	120	—
6.10.72	120	145
7.10.72	120	36
10.10.72	120	4.2
28.11.72	L-T4 0.3 mg/day	—
7.12.72	L-T4 0.3 mg/day	3
18.5.73	L-T3 60 µg/day	—

TRF Test	Time (min)			Response
	0	20	60	
9.6.73 L-T3 60 µg/day	3.0	7.5	7.5	Normal

A needle biopsy of the enlarged pituitary fossa by the transphenoidal route was performed to seek evidence of a tumour. The needle tapped cerebrospinal fluid.

To check the suppressibility of her TSH further, the patient was stabilized on full thyroid replacement therapy first in the form of L-thyroxine 0.3 mg daily and later on L-triiodothyronine 50 µg/day. Serum TSH on both forms of therapy remained within the normal range. A TRF test was done while she was on 60 µg L-triiodothyronine daily and was also normal (Table 3).

Chromosome studies were done on cultured blood leucocytes in the usual way. Approximately 20% of metaphases had a normal female karyotype. In all remaining cells a partial deletion was noted on the short arms of one C-XX group chromosome. Using the Trypsin-Giemsa banding technique (Seabright, 1971) this was shown to be a deletion of the distal end of the short arm of one X chromosome (Fig. 2).

Chromosome studies were also done on both parents and two sisters. All were normal.

Discussion

This patient has hypothyroidism due to primary thyroid failure as shown by the elevated serum TSH, the low PBI, and the low ¹³¹I neck uptake. Its cause remains obscure since no thyroid antibodies were found in her serum. At age 20, we found her pituitary

functions to be normal despite the enlargement of the sella turcica. Clearly, the diagnosis of hypopituitarism at the age of 13 had been incorrect; her cortisol levels were then normal and the serum GH assay might have been technically faulty and in addition, the hypoglycaemia was barely sufficient for certain stimulation. Defective growth hormone response to insulin-induced hypoglycaemia has been described in severe chronic hypothyroidism (Iwatsubo *et al.*, 1967; Brauman, Smets and Corvilain, 1973; Tunbridge, Marshall and Burke, 1973) but this would be unlikely on her replacement schedule with 0.2 mg/day L-thyroxine. The PBI during the same admission of 9.8 µg/100 ml must also have been erroneous.

The patient had for a long time an enlarged pituitary fossa which occasionally has been reported in patients with untreated primary hypothyroidism (Bellini and Neves, 1956; Van Wyck and Grumbach, 1960). In several of these patients pituitary hyperplasia and formation of pituitary tumour was found on histological examination (Russfield, 1958; Caughey and Lester, 1961; Melnyk and Greer, 1965; Herlant *et al.*, 1966). In our patient at the age of 20, the needle biopsy revealed that the sella was empty. The finding of an empty sella in a patient with primary hypothyroidism is extremely rare. There is only one reported case in the English literature (Neelon, Goree and Lebovitz, 1973). Although the

FIG. 2. Trypsin-Giemsa chromosome preparation, showing partial deletion of short arms of one X chromosome.

enlargement of the fossa and the empty sella in our patient must be related to her long-standing but treated hypothyroidism, it is difficult to be sure from her history that the replacement was partial or intermittent until recently. These are the most likely reasons for her sella expansion during adolescence, and relative emptiness when biopsied. Before our patient's pituitary biopsy she must have had sufficient replacement thyroxine to shrink the degree of pituitary enlargement she had evidently had previously.

The anterior pituitary function of this patient was normal, on her current admission, and there were no clinical features of hypothalamic/pituitary dysfunction. In a recent review of sixty described cases of primary empty sella, the endocrine function of two-thirds of the patients was judged to be entirely normal and this is of course the expected finding in all primary cases, i.e. those cases in whom it is not a late stage of a pituitary tumour or follows a radiation or operative damage. The main pituitary endocrine disturbances in the remainder were poor GH response to hypoglycaemia and diminished secretion of gonadotrophins (*Lancet*, 1973).

Her retarded growth at the age of 8 must be attributed in part to her hypothyroidism. But her failure to grow above the third percentile on replacement therapy suggests the concurrence of another factor:

we suspect that her abnormal karyotype has contributed. The previously described cases with deletion of part of an X chromosome have usually been associated with primary amenorrhoea in addition to short stature. The short stature appears with equal frequency with both Xp and Xq deletions (Hecht *et al.*, 1970; Bocian *et al.*, 1971; Lippe and Crandall, 1973). It seems likely that the presence of a normal cell line in our patient may explain the absence of amenorrhoea.

The diagnostic value of elevated basal serum TSH in primary hypothyroidism is well established (Evered *et al.*, 1973) and the elevated serum TSH in our patient, off treatment, undoubtedly confirmed it. The rapid suppression of serum TSH with L-triiodothyronine, to normal levels in this patient served two purposes. First, it demonstrated the normal suppressibility of the unusually high serum TSH and so made a TSH-secreting pituitary tumour unlikely, and second, it provided an index of the adequacy of replacement therapy. The normal pituitary responsiveness was assessed further on two occasions by performing a TRF test while the patient was on replacement therapy (Table 3). It is clear that while the patient was on 0.1 mg L-thyroxine daily the TSH response to TRF was exaggerated and sustained suggesting hypothyroidism. On the contrary, the

TSH response to TRF was within the normal range while the patient was taking 60 µg L-triiodothyronine daily suggesting adequate replacement therapy.

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Problems in the management of mediastinal tumours

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Summary

Five cases of anterior mediastinal tumour are presented. Two cases were asymptomatic, being discovered by routine chest radiography. The remainder presented with dyspnoea, dysphagia and a sinus over the manubrium.

Each case provided a lesson in the management of the mediastinal mass. Pathologies included haemangioma, teratoma, secondary carcinoma from the kidney and a malignant thymoma which caused cardiac tamponade.

Features of interest in the presentation, treatment and pathology are discussed.

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It is concluded that a full investigation of mediastinal swellings is needed before mediastinoscopy is performed; that incision of swellings in the base of the neck should be avoided; and it is suggested that the management of asymptomatic mediastinal haemangioma in adults may be expectant.

Introduction

Mediastinal tumours are not uncommon and several large series have been documented (Blades, 1946; Boyd and Midell, 1968; Brewer and Dolley, 1949; Heuer and Andrus, 1940; Wychulis *et al.*, 1971). Presentation is normally by symptoms due to involvement or pressure on the trachea and neighbouring structures. In no series has there been a large