Congenital hypothyroidism in Klinefelter's syndrome

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SUMMARY Congenital hypothyroidism has been found in four patients with Klinefelter's syndrome. It is likely that this reflects more than chance concurrence of these conditions.

In spite of a number of reports of abnormal thyroid function in patients with Klinefelter's syndrome (recently reviewed by Hsueh *et al.*, 1978), there have been only isolated instances of clinical thyroid disease in this condition. Current knowledge of the prevalence of congenital hypothyroidism and of Klinefelter's syndrome suggests that the occurrence of both conditions in one person should be rare. The discovery of one such patient led to a review of the records of all 420 patients with Klinefelter's syndrome held in the MRC Cytogenetics Registry and the discovery of three further cases.

Case reports

CASE 1

This case was born in 1908. Pregnancy and birth were said to be normal and there was no family history of mental deficiency or thyroid abnormality. At the age of 3 years he was noted to be developing slowly and was given thyroid extract. He started school at 9 years, and from 16 worked for many years in a local village shop. He was admitted to institutional care at the age of 62.

He has always been able to feed and dress himself normally and has always been continent. There has been no abnormality of hearing, speech, or vision. He is said to be shy, introverted, and attention seeking. Mental age as an adult (by Columbia MM scale) was assessed as 5 years 9 months and Wechsler Adult Inventory Score as 62.

On examination (Fig. 1), he had a broad flat nose, widely set eyes, periorbital puffiness, dry, rough skin, moderate gynaecomastia, and protuberant abdomen. There was no goitre. Height was 131.8 cm, arm span 127 cm, sitting height 77 cm, and weight 48.5 kg. Pulse was 70/min (on thyroxine) and reflexes were normal. There was no focal neurological deficit and the visual fields were full. He had early cataracts. No testicular or epididymal tissue was

Received for publication 3 April 1979

Fig. 1 Frontal view of case 1. Note short stature, gynaecomastia, and cretinous facies.

palpable in the scrotum and secondary sexual hair was sparse.

Investigations (in 1978, after withdrawal of thyroxine for 6 weeks): haemoglobin 12.8 g/dl; MCV, 84 fl; urea and electrolytes, normal; cholesterol, 4.8 mmol/l (normal 3.9-6.2); serum thyroxine (T_4), 15 nmol/l (normal 45-160); triiodothyronine (T_3), 0.34 nmol/l (normal 1.5-3); thyroid stimulating hormone (TSH), >98 mU/l (normal 1.2-5.3);

antibodies not detected against thyroglobulin or microsomes; 4-hour I^{131} uptake, 1.8% (normal 10–25%); thyroid scan, gland normal in size and position.

Plasma cortisol (8 h), 0.54 $\mu\text{mol/l}$ (normal 0.3–0.7); (24 h), 0.1 $\mu\text{mol/l}$; Synacthen test, cortisol (0^h) 0.43 $\mu\text{mol/l}$, (30^h) 0.83 $\mu\text{mol/l}$; urinary 17-oxogenic steroids, 14 $\mu\text{mol/24 h}$ (normal 35–70); plasma ACTH, <35 ng/l (normal).

Plasma testosterone, 0.65 nmol/l (normal 10–35); oestradiol, 68.3 pmol/l (normal <150); progesterone, <1.7 nmol/l (normal <2); 17- α -hydroxyprogesterone, 5.75 nmol/l (normal <30); urinary 17-oxosteroids, 16 $\mu\text{mol/24 h}$ (normal 35–70); serum follicle stimulating hormone (FSH), 80 units/l (ref. range 0.42–4.78); luteinising hormone (LH), 22.2 units/l (ref. range 1.86–13.18).

Growth hormone (GH), 1.4 mU/l suppressing to less than 0.9 mU/l at 40 min in oral glucose tolerance test with rise to 5.6 mU/l at 5 h; serum prolactin, 348 mU/l (normal up to 360 mU/l).

Electrocardiogram: T-wave flattening V3–4; chest x-ray: kyphosis, unfused epiphyses at inferior angles of scapulae; hand x-ray: generalised demineralisation, short bones, all epiphyses fused; lower limb x-rays: normal; skull x-ray (Fig. 2): enlarged pituitary fossa.

Buccal smear: chromatin positive; karyotype: 47,XX+marker (analysis of 38 peripheral blood lymphocyte metaphases).

CASE 2

This case was previously described by Boyle and McGirr (1965).

In 1918, at the age of 7½ months, he was given thyroid for delay in development. Medication was

stopped after a few months. At the age of 4 years, he was investigated in a paediatric unit for delayed development and a diagnosis of cretinism was made. In 1962 he was admitted to a mental institution. He had been receiving thyroid medication until 6 months before admission and had become slow and lethargic since then.

On examination, he had puffy eyes, dry skin, delayed ankle jerks, no goitre, small testes, and gynecomastia. Height was 170 cm, span 170 cm. *Investigations* (in 1967, on admission to mental institution): electrocardiogram, low voltage; 24 h I^{131} uptake, 1% with no response to exogenous TSH; protein bound iodine (PBI), 0.7 $\mu\text{g/100 ml}$ (55.16 nmol/l) (normal 4–8 $\mu\text{g/100 ml}$, 300–600 nmol/l); urinary 17-hydroxycorticosteroids, 7.14 mg/24 h (normal 4–12). Normal response to metyrapone. Urinary 17-ketosteroids, 1.3 mg/24 h (normal 6–28); urinary FSH excretion, 40 mU/24 h. Skull x-ray, normal; buccal smear, chromatin positive; karyotype, 47,XXY.

CASE 3

This case was previously described by Kibel (1965).

He was born prematurely in 1955. He was noted to have poor weight gain, constipation, and developmental delay. At 3 years he was thought to be a typical cretin with mental retardation, dry skin, alopecia, and no goitre. There was a systolic murmur, and both testes were palpable.

Investigations (at the age of 3 years): x-rays: stippling of femoral head epiphyses with epiphyseal delay (bone age 1 year). PBI, 3 $\mu\text{g/100 ml}$ (236 nmol/l); serum calcium, 11.6–12.8 mg/100 ml (2.9–3.2 mmol/l) (normal 9–11 mg/100 ml, 2.2–2.75 mmol/l). He was referred at 3½ years for further investigations and a buccal smear was found to be chromatin positive with karyotype 47,XXY in marrow cells and skin fibroblasts.

He later made good physical progress on thyroid but remained mentally retarded.

CASE 4

He was born in 1955 and presented at 7 years 6 months with growth retardation; height age was 4 years 10 months and bone age 2 years 6 months. On examination, he 'looked hypothyroid', had bilateral clinodactyly, and normal penis and testes.

Investigations (in 1962): x-rays: punctate appearance of femoral head suggestive of hypothyroidism; blood film: macrocytic anaemia; marrow: normoblastic. PBI, 1.6 $\mu\text{g/100 ml}$ (126.08 nmol/l); cholesterol, 385 mg/100 ml (9.97 mmol/l). Buccal smear was chromatin positive on two occasions. Chromosome analysis: peripheral blood leucocytes showed 46,XY on one occasion and 46,XY/47,XXY

Fig. 2 Lateral skull x-ray of case 1. Note enlargement of pituitary fossa.

mosaicism on the second occasion. Culture of skin fibroblasts showed a 46,XY/47,XXY complement on two occasions.

He was treated with 1-thyroxine and grew from 96.5 to 134.6 cm over 6 years. At a chronological age of 10½ years he had a height age of 7 years. Intellectual improvement was also noticed.

In 1976 he presented with advanced hypothyroidism, thyroxine having been stopped one year previously. Serum T_3 , <1 nmol/l; serum T_4 , 23 nmol/l; serum TSH, >100 mU/l. Height at this time was 164.5 cm and weight 69.6 kg. He made a further good response to thyroxine.

Discussion

The diagnosis of hypothyroidism is confirmed in all these patients. In cases 1, 2, and 3 the condition was almost certainly present from birth, whereas in case 4 the onset may have been later in childhood.

Case 1 presents some unusual features which justify further consideration. The early history of mental retardation and his short stature are consistent with cretinism, inadequately treated at an early age. Since there is no evidence of autoimmunity, and the absence of a goitre makes it unlikely that a hereditary enzyme defect is responsible, the thyroid failure is probably the result of idiopathic juvenile hypothyroidism. In support of this diagnosis the scan showed a gland of normal size and position.

The patient also had some of the clinical and hormonal features of Klinefelter's syndrome (gynaecomastia, hypogonadism, low plasma testosterone, and raised levels of gonadotrophins), a diagnosis which is confirmed by the finding of a chromatin positive nuclear sex and 47,XX,+mar karyotype. In a man, in the absence of any evidence of true hermaphroditism or adrenal hyperplasia, an XX sex chromosome complement is usually associated with the clinical features of Klinefelter's syndrome. In this case there was also a small marker chromosome which associated with the acrocentric chromosomes and may represent short arm material from D and G group chromosomes. The cytogenetic findings are discussed in full elsewhere (Evans *et al.*, 1979).

The discovery of an enlarged pituitary fossa in our patient raises the possibility of hypopituitarism, but GH secretion was normal and the thyrotrophin- and gonadotrophin-secreting cells were clearly intact. Serum levels of both prolactin and ACTH were also within normal limits. A similar patient was reported by Drury *et al.* (1972). A 27-year-old man with Klinefelter's syndrome and acquired primary hypothyroidism was found to have an enlarged pituitary fossa. Urinary excretion of FSH was raised and it

was inferred that there would be hypersecretion of TSH. There is no other reported instance of benign pituitary enlargement in association with Klinefelter's syndrome and primary hypothyroidism.

Enlargement of the pituitary fossa in hypothyroidism was reported in 1851 by Niepce and has been described in untreated primary hypogonadism by Bower (1968). Defects in the secretion of hormone by the end organs produce a compensatory increase in the trophic hormones, and hyperplasia of the cells producing these hormones in excess could lead, over many years, to enlargement of the pituitary fossa. It is surprising that pituitary enlargement is not seen more often in Klinefelter's syndrome, where there is prolonged hypersecretion of gonadotrophins in almost every case. Kosowicz and Kazimierz (1975) found, in a review of the skull x-rays of 21 patients with Klinefelter's syndrome, that none had an enlarged sella turcica, although all the x-rays were in some other way abnormal. In our case the levels of TSH, FSH, and LH were all greatly raised and this combined stimulus may have led to enlargement of the fossa.

Case 2 has been discussed fully by Boyle and McGirr (1965) who thought that the diagnosis was one of athyreotic cretinism. In case 3, discussed by Kibel (1965), hypercalcaemia was also present, possibly because of the increased sensitivity to vitamin D found in hypothyroidism.

Case 4 was referred, in common with the others, because of growth retardation and he made a satisfactory response to thyroxine. The low serum T_3 and T_4 in conjunction with a high TSH level again confirms that the hypothyroidism was primary in origin.

In the only other reported case of congenital hypothyroidism and Klinefelter's syndrome, Herbeuval *et al.* (1968) describe a 46-year-old mentally defective XXY male in whom hypothyroidism was found to be the result of an ectopic lingual position of the gland.

The chromosomal abnormality in all our patients was discovered while they were under medical attention for their hypothyroidism. They are, therefore, a selected group and cannot be used to calculate a true rate of congenital hypothyroidism in chromatin positive men. However, estimates of the prevalence of congenital hypothyroidism in the general population range from 1:10 000 (Klein *et al.*, 1972) to 1:3000 (J. G. Ratcliffe, 1978, personal communication; Illig and de Vera Roda, 1977). As approximately one male in 1000 has Klinefelter's syndrome and there is no sex difference in the development of congenital hypothyroidism, it can be calculated that the expected rate of concurrence of both these conditions in one person is between 1:6m

and 1:20m males. On the basis of coincidence, therefore, there should only be between 1 and 4 men in the whole United Kingdom with both disorders. This suggests that in our four patients the chromosomal abnormality has in some way predisposed towards the development of early thyroid failure.

Small testes and gynaecomastia are both recognised features of longstanding hypothyroidism (Zondek *et al.*, 1958) and it is quite possible that Klinefelter's syndrome might therefore be overlooked. As Herbeuval *et al.* (1968) suggested, there might be a case for performing a buccal smear examination in male patients with hypothyroidism, in an attempt to determine the true prevalence of this combination of disorders.

We wish to acknowledge the help and advice of the Regional Hormone Laboratories in Edinburgh and Glasgow and Mrs Anna Frackiewicz and her colleagues in the Registry of Abnormal Karyotypes in this Unit. We thank Dr A. S. R. Goonetilleke and Dr McKibben for referring case 1 and for permission to report our findings, and Dr D. Longson for clinical details of case 4. We are grateful to Mrs E. Smith and Mrs S. Lochrie for typing the manuscript.

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