Coexisting Cretinism and Klinefelter's Syndrome

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Until recently it has been generally assumed that thyroidal function is normal in Klinefelter's syndrome. However, Davis *et al.* (1963) described an abnormally low thyroidal uptake of radioiodine in four chromatin-positive cases of Klinefelter's syndrome. Barr *et al.* (1960) studied 10 patients with the Klinefelter syndrome in a mental institution and found a low uptake of radioiodine in nine of them; moreover, there was little increase in uptake following thyroid-stimulating hormone (T.S.H.) administration. The patients were all, however, euthyroid.

The following case report is of interest in that the patient had cretinism and Klinefelter's syndrome.

CASE REPORT

A man aged 44 had lived in a mental institution for four years after the death of his mother. Both parents were aged 47 at the time of his birth. He was the last of a sibship of eight. There were no facts of obvious relevance in the rest of his family history. All his brothers and sisters were of normal intelligence. At the age of 7½ months his family doctor had noted delayed development and prescribed thyroid tablets for several months. At 4 years he was investigated in a paediatric hospital, and study of his case sheet shows that a diagnosis of cretinism was made. There had been delay in sitting up and he did not walk till 3½ years of age. He was listless, apathetic, and had a cool dry skin.

Since then he had been receiving thyroid extract until six months prior to admission to hospital on 12 September 1962. He had become progressively more slow and lethargic in the last few months.

On examination he was obviously hypothyroid, with puffy eyes and cool dry skin. His voice was croaking. The Achilles tendon reflex was delayed. The thyroid gland was impalpable. Axillary hair was absent and the pubic hair had a female distribution. The penis was of normal size but the testes were small and firm. Gynaecomastia was present. Height=span=170 cm. Pubis-sole=86.3 cm. Muscle tone was poor. X-ray picture of skull was normal.

Haemoglobin was 13 g./100 ml., erythrocyte sedimentation rate 8 mm. in one hour (Westergren); plasma cholesterol 390 mg./100 ml. An electrocardiogram showed low-voltage complexes and T-wave changes compatible with hypothyroidism. Thyroidal radioiodine (¹³¹I) uptake at 24 hours was 1% of the dose (25 µc.). No protein-bound ¹³¹I was detected in the serum 48 hours after the dose. T.S.H. 10 units/day for four days produced no rise in the 24-hour thyroidal uptake of ¹³¹I when the test was repeated.

Basal metabolic rate was 19.5% and 25.9% below standard. The stable serum protein-bound iodine (¹²⁷I) was 0.7 µg./100 ml. The 24-hour urinary 17-hydroxycorticosteroid excretion varied from 7.7 to 14 mg. There was a normal response to the administration of metyrapone (Metopirone), 750 mg. six-hourly for 48 hours (see Table I). The urinary 17-ketosteroid excretion was 1.3 mg./24

TABLE I.—Daily Urinary 17-hydroxycorticoid Excretion in mg.

Before Metyrapone					After Metyrapone	
8-1	10-9	14-0	12-6	7-7	13-4	25-8

TABLE II.—Chromosomal Constitution of S. McC.

No. of chromosomes	> 43	45	46	47*	48
No. of Cells ..	1	1	2	25	1

* All XXY.

hours. Follicle-stimulating hormone (F.S.H.) urinary excretion was <40 mouse units/24 hours.

Sex chromatin was positive. Chromosomal constitution: XXY (see Table II).

DISCUSSION

The diagnosis of cretinism was first suspected by the patient's family doctor because of delay in walking. It was supported some three and a half years later by the presence of listlessness, lethargy, and dry puffy skin noted in hospital.

Forty years later we found that the clinical features of hypothyroidism developed when thyroid tablets were stopped. Further, we noted that there was no increase in the 24-hour thyroidal uptake of ¹³¹I following administration of 10 units of T.S.H. on four consecutive days. The serum protein-bound iodine was 0.7 µg./100 ml. and his B.M.R. was low. The diagnosis of "athyreotic" cretinism appears well founded.

The diagnosis of Klinefelter's syndrome is also soundly based. Thus, in addition to the clinical features of hypogonadism, he had small firm testes, gynaecomastia, a low 24-hour urinary excretion of 17-ketosteroids, and a chromosomal constitution: XXY. The low F.S.H. value does not preclude the diagnosis of Klinefelter's syndrome (Stewart *et al.*, 1959).

Hypopituitarism was excluded by a normal rise in urinary 17-hydroxycorticosteroid excretion following metyrapone administration, by lack of thyroidal response to T.S.H. stimulation, and by a normal skull x-ray picture.

To our knowledge this is the first case to be described of a patient who has cretinism and Klinefelter's syndrome. All the other patients with Klinefelter's syndrome and abnormally low thyroidal ¹³¹I uptakes so far described have been euthyroid (Barr *et al.*, 1960; Carr *et al.*, 1961; Davis *et al.*, 1963). Our patient probably has coincidentally two unrelated diseases; but in the light of previous communications it is just possible that the two disorders may in fact be related and that varying degrees of hypothyroidism may occasionally accompany the Klinefelter syndrome.

Davis *et al.* speculated that with an increasing number of X chromosomes there may be increasing abnormality of thyroid function. This view is based on the fact that two patients with chromosomal constitution XXXY had low thyroidal ¹³¹I uptakes and exhibited poor response to T.S.H. stimulation (Carr *et al.*, 1961), whereas four of their patients—two with XXY and two with one chromatin body on buccal smear—had a good response to T.S.H. stimulation. Another of their patients had no sex chromatin in a buccal smear and had borderline normal thyroidal ¹³¹I uptake. The findings in our patient do not support such a view; although he had only two X chromosomes, his hypothyroidism was severe. We suggest that further cases such as ours may be found by performing buccal-smear studies for sex chromatin on all athyreotic cretins, followed when necessary by chromosomal studies.

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