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Female phenotype in a male child due to 17-α-hydroxylase deficiency

The finding of testicles in a normal looking girl usually leads to a diagnosis of testicular feminization, i.e. congenital insensitivity to testosterone (due to lack of conversion to dihydrotestosterone). However, a similar picture may be encountered in some patients who have a congenital defect of testosterone synthesis (Givens *et al.*, 1974) and in whom adrenal insufficiency may cause severe illness. Serious illness in a child wrongly diagnosed as a case of testicular feminization led to discovery of 17-α-hydroxylase deficiency.

Methods

Pregnanediol and pregnanetriol were estimated in urine by gas-liquid chromatography after enzymatic hydrolysis (Moolenaar and Van Seters, 1971). 11-Hydroxycorticosteroids in serum were estimated according to Mattingly (1962), cortisol and corticosterone by a competitive protein-binding technique (Dr. H. J. Degenhart, Sophia Children's Hospital Rotterdam), and testosterone, progesterone, and follicle stimulating hormone by radioimmunoassay.

Case report

A girl of 3 years was admitted to this hospital in a semicomatose condition. 6 months earlier she had been admitted to another hospital with inguinal hernia. A testicle was then found in the hernial sac, and karyotyping showed a 44,XY pattern, a diagnosis of testicular feminization being made. The external genitals were of normal female appearance; the vagina was present; neither uterus nor ovaries could be felt.

When admitted to our hospital the child had been ill for 24 hours and was found to have otitis media

TABLE

Concentrations of main steroids in blood and urine

	Untreated	Treated with dexamethasone		Normal values in children
		1 mg/d for 2 days	0·25 mg/d for 70 days	
Urine				
17-oxosteroids mg/24 h (μmol/24 h)	0·6–1·2 (2·1–4·2)	1·0–1·3 (3·5–4·5)	0·9–1·9 (3·1–6·6)	0·1–3·0 (3·5–10·4)
17-oxogenic steroids mg/24 h (μmol/24 h)	2·4 (8·3)	3·2–3·9 (11·1–13·5)	1·2–2·7 (4·2–9·4)	1·5–9·6 (5·2–33·3)
Pregnanediol mg/24 h (μmol/24 h)	0·99 (3·1)	0·32 (0·99)	0·37 (1·2)	0·01–0·14 (0·03–0·45)
Pregnanetriol mg/24 h (μmol/24 h)	0·04 (0·12)	0·02 (0·06)	0·01 (0·03)	0·02–0·16 (0·06–0·48)
Serum				
11-OH steroids μg/100 ml	45–57	4·9	4·6	10–20 (0·28–0·55)
Cortisol μg/ 100 ml (nmol/l)	⩽0·3 (8·28)			10–20
Corticosterone μg/100 ml	47			1–2
Testosterone ng/100 ml (nmol/l)	<5 (0·17)			14–23 (48·6–79·8)
Testosterone after Pregnyl ng/100 ml (nmol/l)	<5 (0·17)			
Progesterone ng/ml (nmol/l)	4·3 (13·67)	0·8 (2·5)	0·3–0·6 (0·95–1·9)	<0·5 (1·59)
Follicle stimulating hormone mIU/ml			17·0	4·3–0·8
Blood pressure (mmHg)	145/100	100/70	100/70	

and mastoiditis. The severity of the symptoms was judged to be out of proportion to the severity of the infection. Further investigation disclosed hypertension (blood pressure 145/100 mmHg) and hypokalaemia (2·6 mmol/l) with a strongly negative potassium-balance and hypoglycaemia (1·6 mmol/l; 29 mg/100 ml).

After recovery from the infection hormonal studies were undertaken. The results are summarized in the Table, and are characteristic of 17-α-hydroxylase deficiency, with high levels of progesterone in the blood (4·35 ng/ml) and of pregnanediol in the urine (0·99 mg/24 h). The ratio between pregnanediol and pregnanetriol in urine was high at 25 (in normal children 1–3). The excretion of oxogenic steroids and oxosteroids was low; excretion in normal children may be too low to enable subnormal excretion to be recognized. The blood level of 11-hydroxycorticosteroids was high (45–57 μg/100 ml), due to increased amounts of corticosterone. The blood level of cortisol was very low at ⩽0·3 μg/100 ml (8·28 nmol/l). The very low blood testosterone concentration was unaffected by administration of chorionic gonadotrophin (Pregnyl); in boys with normal testicles testosterone increases markedly after one injection (Zachmann, 1972). The high level of follicle stimulating hormone, estimated only during treatment with dexamethasone, was most likely due to the small amounts of circulating testosterone. The decreased levels of 11-hydroxycorticosteroids and progesterone, and the normalization of blood pressure by dexamethasone provided further confirmation of the diagnosis.

Orchidectomy was performed. Histology showed normal infantile testicular tissue, comparable to that of a newborn with undifferentiated tubular cells; Leydig cells were present. In the testicular hilus only rudimentary epididymal tubules were encountered (Prof. A. Schaberg, Dept. of Pathology) (Fig.).

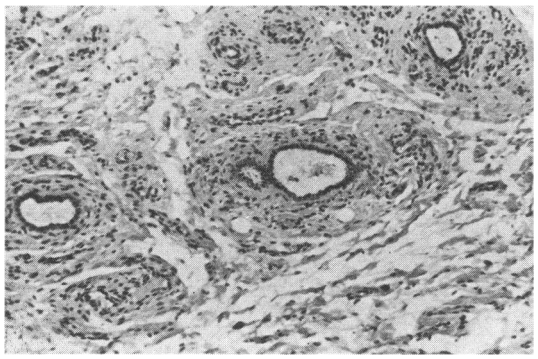

FIG.—*Rudimentary epididymal tubules.* (×85.)

Discussion

Nine cases of 17-α-hydroxylase deficiency have been reported, all in adults. 5 patients described by Biglieri, Herron, and Brust (1966), Goldsmith, Solomon, and Horton (1967), Mallin (1969), and Linquette *et al.* (1971) were female (XX), and 4 described by Mantero *et al.* (1971), Alvarez, Cloutier, and Hayles (1973), and H. Van Slooten (personal communication, 1975), were male (XY). The female patients were detected because of hypertension and sexual infantilism. The male patients all presented as females; they also showed hypertension and sexual infantilism. In none was the diagnosis based upon the finding of testicles.

All the reported cases showed increased production of desoxycorticosterone (DOC) and corticosterone, and decreased production of cortisol. High blood pressure and hypokalaemia are the result of the increased levels of DOC and possibly other precursors of aldosterone, and these normalize if dexamethasone is given. Clinical signs of cortisol deficiency have not been mentioned in published case reports. Low aldosterone excretion has usually been reported, probably secondary to the high level of DOC. Decreased excretion of androgens and oestrogens have been mentioned in most reports.

In all reported males (XY) with 17-α-hydroxylase deficiency the lack of testosterone in early fetal life has led to complete female development of the external genitals. The case published by New and Suvannakul (1970) is the only one with ambiguous genitals; however, hormone studies in this patient were not compatible with a severe deficiency of 17-α-hydroxylase activity: the deficiency was either partial or another endocrine disorder was present.

The presence of an epididymis has been mentioned in a few male patients. In our case only a few poorly developed epididymal tubules were seen. Though exploratory laparotomy was not performed, investigation under anaesthesia failed to disclose the presence of a uterus. It may be assumed that the fetal testes had produced Müller-inhibiting-factor.

The clinical and laboratory findings in our patient are very similar to those of other reported patients, but the case is remarkable for several reasons. In the first place the child originally was diagnosed as a case of testicular feminization. Secondly, she is the only reported patient in whom deficiency of 17-α-hydroxylase has been detected in childhood. Thirdly, the child exhibited clinical signs of adrenal insufficiency during an infection.

The diagnosis of testicular feminization in a child should thus not be made before a defect of steroid biosynthesis has been excluded.

Summary

The discovery of testicles in a 3-year-old girl with XY karyotype led to a diagnosis of testicular feminization. Subsequently, however, hypokalaemia,

hypertension, and severe prostration during a mild infection suggested adrenal involvement, and investigations showed a 17-α-hydroxylase deficiency. Diagnosis of testicular feminization should not be made without excluding a defect of testosterone synthesis.

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Acute renal failure and gout as presenting features of acute lymphoblastic leukaemia

The 'preleukaemic' syndrome of pancytopenia and hypoplastic bone marrow has been described (Melhorn, Gross, and Newman, 1970). Hyperuricaemia (Sinks *et al.*, 1966), gout (Whitaker *et al.*, 1963), and uric acid nephropathy (Pochedly, 1973) are recognized complications of treating leukaemia. In our patient all these symptoms preceded the clinical onset of frank leukaemia. This has only been described once before (Appleyard, 1971). In this latter case renal failure was not the presenting feature but a later complication.

Case report

A 2½-year-old girl had been well until 6 months before admission. During this period she was fractious, developed polyuria and nocturia. Before admission her right foot and left wrist became painful, she vomited, became dehydrated, lethargic, and two bruises appeared. On admission she was pale, febrile, irritable, and dehydrated with Kussmaul respirations and hypotension. There was no lymphadenopathy, hepatosplenomegaly, renal enlargement, and the nervous system was normal. Her right foot, left ankle, left wrist, right third proximal interphalangeal joint were warm, swollen, and tender. She was oliguric. Her blood urea was 91 mmol/l (548 mg/100 ml), sodium 128 mmol/l (128 mEq/l), chloride 93 mmol/l (93 mEq/l), potassium 5·6 mmol/l (5·6 mEq/l), and bicarbonate 5 mmol/l (5 mEq/l). Treatment with intravenous saline and sodium bicarbonate corrected her dehydration and the renal failure improved without dialysis (Fig. 1). The joint symptoms resolved as the renal failure improved and the serum uric acid levels fell (Fig. 1).

Thrombocytopenia had been noted earlier, but within 4 days pancytopenia developed (Fig. 2). A bone marrow smear showed generalized hypocellularity with a relative increase in lymphoid and reticulum cells. There was no evidence of lymphoblastic change or malignancy. She was treated with blood transfusion and antibiotics and the pancytopenia gradually resolved (Fig. 2). The progress of the haematological and renal changes are shown in Figs. 1 and 2.

Other investigations were normal. Urine contained no crystals and was sterile. No viruses were isolated and blood cultures were sterile. *X*-rays showed no evidence of leukaemia and no abnormalities. Intravenous pyelogram on day 4 was normal. Renal biopsy on day 17 showed changes compatible with recovering tubular necrosis and two granulomata identical in appearance with those described in uric acid nephropathy.

She remained well until day 52 when she developed pains in several distal joints. She became restless, lethargic, vomited, and was readmitted on day 58 in acute renal failure (Fig. 1). She was reluctant to move either elbow, the left wrist, the proximal interphalangeal joints of the right 4th and 5th fingers and the left 5th toe. All were swollen and inflamed. Both kidneys were palpable and the liver was slightly enlarged. There was no splenomegaly, lymphadenopathy, or bruising. The acute renal failure and acidaemia were managed conservatively with dietary restriction and intravenous fluids (Fig. 1) and the serum uric acid levels fell.

Fig. 2 shows the results of blood tests at this time. The differential white cell count on day 60 showed immature red and white cells. Bone marrow examination on day 63 showed changes of acute undifferentiated leukaemia. On day 66 treatment was started with prednisolone 40 mg/m² per day and allopurinol; the