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CASE REPORT

Adrenogenital syndrome due to 11-β-hydroxylase deficiency with skeletal abnormalities and pulmonary stenosis

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ABSTRACT. This report describes a 13-year-old female patient with 11-β-hydroxylase deficiency who was found to have short fourth metatarsals and pulmonary stenosis. The unusual association between these abnormalities and this rare form of congenital adrenal hyperplasia is presented.

INTRODUCTION

The adrenogenital syndrome due to 11-β-hydroxylase deficiency was first described in 1955 by Bongiovanni and Eberlein (1). Many cases were subsequently reported, but the occurrence of this syndrome remains extremely rare when compared to the much more common variant, 21-hydroxylase deficiency (2). The association of skeletal abnormalities and congenital cardiac defects with the 11-β-hydroxylase variant has not heretofore been reported. We present in the following report the case of a Jordanian girl affected by this syndrome who was also found to have short metatarsals and pulmonary stenosis.

CASE REPORT

A 13-year-old female was admitted to Jordan University Hospital in April 1979 with the problem of ambiguous genitalia. She was born in August 1966 and was the product of a full term normal delivery to a multiparous mother. At birth she was registered by the midwife as a 'normal female'. Two months later, the mother noticed that the clitoris was enlarged as compared to that of the patient's older sister. At that time the patient was examined by the family physician who assured the mother that the size of the clitoris was 'within normal limits'. At three years of age, pubic hair started to appear and then, gradually, most parts of the body including the face became covered with dark hair. The patient was admitted in 1970 to the Emergency Hospital in Amman during the Jordan civil war, when excision of the clitoris and closure of the vagina were performed, as reported by the mother. No medical data from that admission could be obtained as the records of that hospital were destroyed during the war. The family history revealed no other members who have a similar condition. On physical examination in 1979, she was 135 cm. in height, the BP was 170/110 mm Hg, and the pulse rate was 90/min. There was an abnormally low-pitched voice, masculine habitus, adult male hair distribution and flat chest (Fig. 1). An ejection systolic murmur was heard in the left fourth intercostal space. The clitoris had been amputated and the vagina was still closed. Routine laboratory studies including CBC, urinalysis, blood sugar, urea, uric acid, SGOT, alkaline phosphatase, proteins, cholesterol, creatinine, serum calcium and phosphate, urine calcium and phosphate, and creatinine clearance were all within normal limits. The serum sodium ranged from 140 to 144 mmol/l and the serum potassium from 2.5 to 3.5 mmol/l, on multiple occasions. The ECG and chest X-ray were normal.

Hormonal studies

Serum concentrations of LH, FSH, T_4, T_3, TSH and cortisol were assayed by radioimmunoassays using commercially available kits (Amersham Radiochemicals, England) and were all found to fall within the normal range. The results of serum cortisol and 24-hour urinary excretion of 17-hydroxycorticoids (17-OHCS) and 17-ketosteroids (17-KS) before, during and after a 5-day dexamethasone suppression test are shown in Table 1. It is evident that the patient had markedly elevated urinary 17-OHCS and 17-KS which were easily suppressible with dexamethasone administration. Serum aldosterone, 11-deoxycorticosterone (DOC), 11-deoxycortisol (Compound S) and 17-hydroxyprogesterone measurements were kindly performed by Dr. G.F. Joplin at the Hammersmith Hospital of London, England (4). The results are shown in Table 2. Serum concentrations of compound S and DOC were markedly increased while that of 17-hydroxyprogesterone was normal.

It was surprising to find that the concentration of serum aldosterone was not markedly suppressed in the face of the greatly elevated concentrations of DOC. However, another assay for serum aldosterone at a different laboratory revealed a similar value (5).

Radiologic studies showed an advanced bone age of

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Table 1 - *Results of 5-day dexamethasone suppression test on serum cortisol and 24-hour urinary excretion of 17-ketosteroids (17-KS) and 17-hydroxycorticoids (17-OHCS). Total daily dose of dexamethasone was divided into equal 6-hourly doses p.o.*

	Dose of dexamethasone (mg/day)	Serum cortisol (ng/ml) 08:00	Urinary 17-KS (mg/24 h)	Urinary 17-OHCS (mg/24 h)
Baseline	0	120	114	144
Day 1	2	—	—	—
Day 2	2	21	8.9	22.0
Day 3	8	20	5.2	10.0
Day 4	8	19	4.2	9.0
Day 5	8	12	3.7	4.7

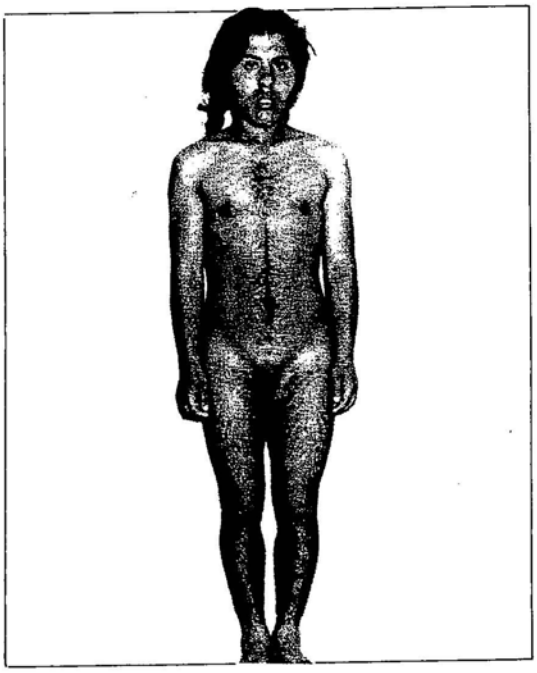

Fig. 1 - *Photograph of the patient on initial presentation, demonstrating severe virilization.*

Table 2 - *Basal concentrations of serum aldosterone, 11-deoxycorticosterone (DOC), 11-deoxycortisol (Compound S) and 17-hydroxyprogesterone (17-OHP).*

	Results	Normal value
Aldosterone	900 pmol/L	100-850
DOC	4,457 pmol/L	91-650
Compound S	295 nmol/L	upto-89
17-OHP	13 nmol/L	upto-18

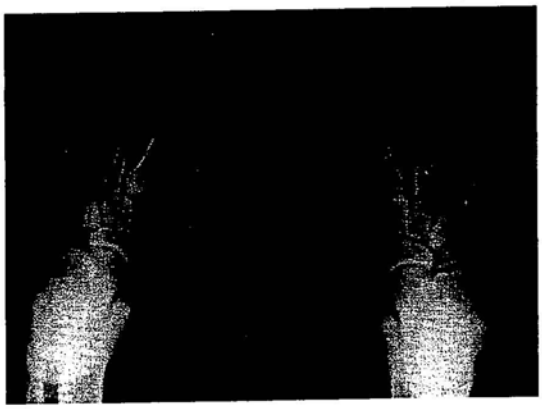

Fig. 2 - *X-ray of both feet showing the short fourth metatarsals.*

18 years and a short fourth metatarsal bilaterally (Fig. 2). The work-up of the heart murmur, that was reported since childhood, included cardiac catheterization which revealed a mild degree of valvular pulmonary stenosis with a gradient of 18 mm Hg. Karyotyping of peripheral blood white cells revealed a normal 46-XX female chromosomal pattern and laparoscopy showed normal uterus, tubes and ovaries. The diagnosis of congenital adrenal hyperplasia due to 11-β-hydroxylase deficiency was made. The patient responded to the treatment with cortisone acetate and her blood pressure dropped to normal. Vulvoplasty was performed on June 17, 1979, after which she started to have regular menstruation. One year after treatment, moderate breast development has occurred.

DISCUSSION

The clinical finding of virilization and hypertension together with the demonstration of markedly increased serum concentrations of compound S and DOC, a

normal plasma 17-hydroxyprogesterone, and the increased urinary excretion of 17-OHCS and 17-KS in this young female establish the diagnosis of congenital adrenal hyperplasia due to 11-β-hydroxylase deficiency.

One would expect to find a markedly suppressed serum aldosterone concentration in the face of a high concentration of DOC. Similarly the plasma renin activity should be suppressed. Unfortunately, we have no data on the latter and, therefore, we have no explanation for the lack of significant suppression of aldosterone in our patient.

The response to treatment with cortisone acetate which was satisfactory regarding control of the hypertension, breast development and the onset of menstruation is in agreement with previous reports (6). However, linear growth has unfortunately already ceased by the time the diagnosis was made.

What was unusual about our patient is the association of short fourth metatarsals and pulmonary stenosis with this type of adrenal hydroxylase deficiency. Short stature and short metatarsal bones are found in pseudohypoparathyroidism and pseudopseudohypoparathyroidism, Turner's syndrome, Gardner's syndrome and other hereditary disorders (7), conditions that are ruled out in our patient by the clinical picture and the results of investigations presented above. A search of the medical literature has failed to uncover a similar report of the particular pattern of skeletal dysmorphism and congenital cardiac lesions in association with 11-β-hydroxylase deficiency as is present in our case.

Whether the association of these congenital skeletal and cardiac abnormalities with 11-β-hydroxylase deficiency is merely a coincidental finding or due to a common genetic factor could not be clarified at present. Nevertheless, because of the relative rarity of this type of adrenal hydroxylase deficiency, the possibility must remain that this association is more than just a chance occurrence.

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