17 α -Hydroxylase deficiency with persistence of Mullerian ducts in a genotypic male and paradoxical aldosterone secretion

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Summary: We report a case of congenital adrenal hyperplasia due to 17 α -hydroxylase deficiency in a Chinese genotypic male patient. Despite the male genotype, normal female external genitalia were present and with the introduction of cyclical oestrogen therapy withdrawal bleeding occurred, confirming the presence of functional endometrial tissue. We believe this to be the first report of persistent Mullerian duct structures in a genotypic male with 17 α -hydroxylase deficiency. It could be explained by either impaired secretion or impaired action of anti-Mullerian hormone. Further, contrary to the usual finding of suppressed aldosterone secretion, this patient had measurable levels of plasma aldosterone.

Introduction

17 α -Hydroxylase deficiency causing congenital adrenal hyperplasia is a rare disorder which was first recognized in 1966; only about 120 cases have been reported so far.^{1,2} The enzyme deficiency is present in the adrenals and gonads and affects both sexes. Deficiency of 17 α -hydroxylase causes diminished secretion of glucocorticoids and sex hormones and excess production of 17-deoxycorticosteroids, especially deoxycorticosterone (DOC) and corticosterone.¹ Affected patients usually present with hypertension and hypokalaemia due to excess DOC secretion. Excessive DOC causes retention of sodium and with ensuing blood volume expansion, the renin–angiotensin system is suppressed, which in turn leads to diminished secretion of aldosterone by the zona glomerulosa.² However, the concentration of 18-hydroxycorticosterone which is the immediate precursor of aldosterone has been reported to be elevated.³ More recently it has been reported that circulating aldosterone concentrations may be normal or elevated.⁴

The lack of sex hormones causes sexual infantilism in untreated females and pseudohermaphroditism in males.⁵ Secondary sexual characteristics

in males may range from apparently normal female genitalia and a blind vaginal pouch to hypospadias and a small phallus.^{6–8} In the few reported cases of male pseudohermaphrodites, persistence of Mullerian ducts has not been described.^{6–8}

We report the occurrence of 17 α -hydroxylase deficiency in a Chinese patient with a male genotype. The unusual finding was the persistence of Mullerian duct structures.

Materials and methods

Aldosterone, cortisol, 17 β -oestradiol, progesterone, 17 α -hydroxyprogesterone, testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) were assayed using commercial immunoassay kits obtained from Diagnostic Products Corporation (USA). Plasma renin activity (PRA) was assayed using a kit from Sero Diagnostic S.A. (Switzerland). ACTH was assayed using an Allergo HS-ACTH radioimmunoassay kit from Nichols Institute (USA). The intra- and inter-assay precisions for all of the assays were less than 15%.

Corticosterone, deoxycorticosterone, and 18-hydroxycorticosterone were assayed by Dr Robert Fraser, MRC Blood Pressure Unit, Western Infirmary, Glasgow, Scotland. Dr Fraser also assisted with the additional assay of aldosterone using radioimmunoassay after prior chromatographic separation.

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Case report

A phenotypic female, then aged 17, was admitted to hospital in 1988 for screening, her elder sister having been diagnosed as having 17 α -hydroxylase deficiency following investigation for primary amenorrhoea.

When contacted for screening a history of primary amenorrhoea was obtained. On admission the patient was noted to have an eunuchoidal build. Her height was 163.5 cm and weight 46.5 kg. She had normal, although infantile, female external genitalia and no gonadal tissue could be palpated in the inguinal region. Severe hypertension (blood pressure 250/150 mmHg) and hypokalaemic alkalosis (plasma K⁺ 2.1 mmol/l, plasma HCO₃⁻ 33 mmol/l) were documented. The clinical diagnosis of 17 α -hydroxylase deficiency was confirmed by the finding of undetectable circulating concentrations of cortisol and 17 α -hydroxyprogesterone together with elevated concentrations of progesterone, LH and FSH as summarized in Table I. The aldosterone concentration was also elevated (Table I).

Chromosomal analysis performed on two separate samples on two occasions, revealed a 46 XY karyotype confirming that the patient has a male genotype. Ultrasonography of the pelvis demonstrated the presence of an infantile uterus and vagina. Following treatment with dexamethasone (0.25 mg in the morning, 0.5 mg at night) and cyclical oestrogen therapy, blood pressure and plasma K⁺ returned to normal and the progesterone concentration fell to 2.4 nmol/l.

Although the aldosterone concentration fell to 58 pmol/l, the PRA initially remained undetectable. Withdrawal bleeding occurred following oestrogen therapy, confirming the presence of functional endometrial tissue. Permission for further investigation aimed at locating and identifying the gonads has, to date, been refused although ultrasonography suggested the possible presence of gonadal tissue within the pelvis.

In view of the paradoxical aldosterone result she was reinvestigated after 1 year, informed consent having been obtained. Whilst still on treatment the following results were obtained: progesterone 3.0 nmol/l, 17 α -hydroxyprogesterone less than 0.3 nmol/l, cortisol less than 28 nmol/l, PRA in supine position 0.14 ng/ml/hour and the corresponding aldosterone 165 pmol/l. ACTH was undetectable.

To stimulate the renin-angiotension-aldosterone axis, dexamethasone treatment was then withdrawn for 1 week and a low sodium (10 mmol/day) and high potassium (100 mmol/day) diet given. One day before investigation, 40 mg of frusemide was given orally. The following morning blood was taken in the supine position and at 30, 60 and 120 minutes after adopting the upright posture. The plasma ACTH had risen to 71 pg/ml and cortisol remained less than 28 nmol/l. In the supine position the PRA was 0.3 ng/ml/hour and the aldosterone was 533 pmol/l. The PRA after 30, 60 and 120 minutes in the upright position were 2.35, 4.11 and 5.14 ng/ml/hour, respectively. The respective aldosterone concentrations were 519, 743 and 718 pmol/l. The five aldosterone specimens ob-

Table I Concentrations of hormones at presentation and after treatment with dexamethasone

Hormone (reference range)	Off treatment	On treatment 3 months	On treatment one year
Cortisol (morning 138–690 nmol/l)	< 28	–	–
Corticosterone (2.3–23.0 nmol/l)	71.4	–	–
DOC (0.12–0.49 nmol/l)	7.0	–	–
18-Hydroxycorticosterone (0.083–0.69 nmol/l)	8.54	–	–
17 β -Oestradiol (183–807 pmol/l)	< 40	–	< 40
Progesterone (0–1.27 nmol/l)	27	–	3.0
17 α -Hydroxyprogesterone (0.3–14.4 nmol/l)	< 0.3	2.4	2.2
ACTH (9–52 pg/ml)	–	< 0.3	UD
FSH (0–20 IU/l)	89	–	–
LH (0–38 IU/l)	49	–	–
Aldosterone: (supine: 28–445 pmol/l)	793	–	165
PRA: (supine: 0.12–1.59 ng/ml/hour)	< 0.07	58	0.14
		< 0.07	

– = not assayed; UD = undetectable.

tained during this investigation were also assayed by a chromatographic method in Dr Fraser's Laboratory (normal range: < 500 pmol/l), and the results obtained were lower than with the direct assay (DPC coat-a-count). The results (pmol/l) were as follows (DPC vs chromatographic assay): (1) 165 vs 56; (2) 533 vs 111; (3) 519 vs 167; (4) 743 vs 305; and (5) 718 vs 250.

Discussion

To our knowledge this is the first report of persistent Mullerian structures in a genotypic male pseudohermaphrodite with 17α -hydroxylase deficiency. Anti-Mullerian hormone (AMH) produced by fetal Sertoli cells,⁹ a glycoprotein with a molecular weight of approximately 140 kDa, is responsible for the suppression of Mullerian duct development in normal males. Impairment of fetal testosterone production because of 17α -hydroxylase deficiency, results in failed masculinization and a phenotypic female habitus. However, Mullerian structures are usually absent, presumably due to normal testicular production of AMH. Josso *et al.*¹⁰ reported that testicular dysgenesis could result in deficient production of testosterone from Leydig cells along with AMH from Sertoli cells, and in the persistent Mullerian duct syndrome there could be failure of production, synthesis of an inactive form or impaired peripheral action of AMH.^{10,11} Hutson¹² described a 12 year old girl with 17α -hydroxylase deficiency with normal female genitalia and testes inside inguinal herniae, however there was no mention of persistent Mullerian structures. Whilst de Gennes *et al.*¹³ reported the presence of bilateral streak gonads and impaired development of Mullerian duct derivatives in a girl with 46 XX genotype and 17α -hydroxylase deficiency, a causal link could not be established between the abnormalities. Whether there was coexisting deficiency of, or resistance to, AMH in our patient can only be left to conjecture. Taken together, however, it is tempting to speculate that 17α -hydroxylase deficiency might in some way interfere with the development and hormone secretion of fetal gonads, resulting in the association of these rare disorders in the same patient.

Hutson^{12,14} has proposed a two-stage control of testicular descent: an abdominal stage which is controlled by a non-androgenic hormone, namely AMH and an inguinal stage which is androgen dependent. Scott¹⁵ also concluded that AMH rather than androgens may be responsible for the abdominal phase of testicular descent. From the aforementioned studies, one might expect to find the testes in the abdomen in our patient. However, all further imaging investigations were resolutely refused.

Aldosterone production is usually suppressed; presumably as a consequence of reduced activity of the renin-angiotensin system, hypokalaemia, chronic elevation of ACTH levels and high circulating levels of atrial natriuretic factor. However, in our patient aldosterone was detected by the direct aldosterone radioimmunoassay, the value being in the upper part of the normal range despite suppressed renin values. Other studies have also reported elevated concentrations of aldosterone.^{4,16} The aldosterone results could be explained by cross-reaction with other steroids.¹⁶ A comparison of the results obtained with the direct aldosterone assay (DPC coat-a-count) and by the method incorporating a chromatographic purification partially support this conclusion. While on treatment cross-reactivity accounted for a difference of approximately 100 pmol/l, but the disparity increased to about 400 pmol/l off treatment, presumably as a result of enhanced production of other steroids with ACTH stimulation. Measurable aldosterone was, however, still present even with chromatographic separation. This, in the untreated stage, could be due to enhanced corticosterone methyloxidase type II activity and hence aldosterone production by the zona fasciculata, as has been reported in Japanese patients.⁴

With glucocorticoid replacement therapy the aldosterone concentrations decreased whilst PRA and potassium levels rose. Kater *et al.*¹⁷ found that aldosterone concentrations rose following treatment for 1 week or longer during which time blood pressure, sodium, potassium, DOC and corticosterone concentrations were normalized. It is possible that aldosterone along with 18 -hydroxycorticosterone is secreted from the zona fasciculata under the influence of ACTH and that suppression of ACTH by dexamethasone leads initially to a rapid drop in aldosterone. This statement is also supported by the fact that the zona glomerulosa is refractory to the action of renin after prolonged suppression.¹⁸ Consistent with this, the patient's sister had markedly raised PRA (6.31 ng/ml/hour) but suppressed aldosterone (42 pmol/l) after 3 months' dexamethasone treatment.

Also noteworthy is the fact that when the patient was taken off treatment and given a low salt diet and diuretic, PRA increased appreciably and the erect aldosterone as measured by chromatographic techniques showed a three-fold rise compared to the supine value (305 pmol/l vs 111 pmol/l). This, albeit subnormal, response to renin-angiotensin stimulation is in accordance with Scaroni's¹⁹ findings of a transient increase of aldosterone following glucocorticoid withdrawal and prolonged recovery of aldosterone levels during long-term treatment in these patients.

In summary, a Chinese genotypic male patient with 17α -hydroxylase deficiency has been des-

cribed. Mullerian duct structures are retained, as confirmed with ultrasonography and occurrence of withdrawal bleeding following oestrogens. In contrast to most patients, aldosterone was detectable at presentation, and was, at least temporarily, suppressed with institution of glucocorticoid therapy.

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Note added in proof

A similar case to the above was published in the *Postgraduate Medical Journal* last year: Malcolm, P.N., Wright, D.J. & Edmonds, C.J. Deficiency of 17 α -hydroxylase associated with absence gonads. *Postgrad Med J* 1992, **68**, 59–61.

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