Deficiency of 17 α -hydroxylase associated with absent gonads

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Summary: A phenotypic female presented initially at the age of 17 years with amenorrhoea and delay of sexual development. Karyotype was male, 46 XY, and as gonads were absent, a diagnosis of congenital anorchia was made. The patient was treated with oestrogen.

At the age of 23 years, she re-presented with tall stature and hypertension. She then had normal female habitus but absent pubic and axillary hair. Re-investigation showed that sex steroids and cortisol were absent and established the diagnosis as 17 α -hydroxylase deficiency. Treatment with hydrocortisone rapidly corrected the hypertension. Ultrasound examination confirmed the absence of gonads but showed that a small uterus was present.

Measurement of serum cortisol is important for recognition of such patients, but further measurements of sex steroids, particularly progesterone, are needed to prove the diagnosis.

We have found no previous reports of absent gonads in 17 α -hydroxylase deficiency. The association remains unexplained.

Introduction

Deficiency of 17 α -hydroxylase is a rare condition accounting for less than 5% of cases of congenital adrenal hyperplasia. It may present at any age with hypertension, hypokalaemia and abnormal sexual development. We report a patient in whom hypertension was initially absent and the gonads were also apparently absent leading to misdiagnosis for many years.

Case report

This patient had first presented at the age of 17 years with primary amenorrhoea and lack of secondary sexual characteristics. She was noted to be thin and tall (1.80 m) but not dysmorphic. She was normotensive (140/80 mmHg). She had no breast development, nor pubic or axillary hair; external genitalia and vagina were recorded as normal pre-pubertal. Her parents and sister were healthy and there was no relevant family history. Investigations including full blood count, urea and electrolytes, thyroid function and serum prolactin were normal. The gonadotrophins were very high (luteinizing hormone (LH) > 100 IU/l, follicle

stimulating hormone (FSH) 38 IU/l). Testosterone (< 0.5 nmol/l) and oestradiol were both low (< 50 pmol/l). The karyotype was normal male, 46 XY. The initial diagnosis was gonadal dysgenesis of the XY type and in view of the risk of malignant change in streak gonads in this condition, laparotomy was performed. No reproductive organs were found and there was no evidence of any gonadal tissue. The diagnosis was revised to congenital anorchia, a sporadic condition in which the affected male develops as a phenotypic female. She commenced treatment with oestrogen but because she moved away, she was not followed up and was not seen again in a hospital clinic until she came to ours.

At the age of 23 years she consulted her general practitioner because she felt that her height was excessive. She was found to be hypertensive and, in view of her past history, was referred to our endocrine clinic. She claimed to have been entirely healthy and doing a busy job; she had stopped the oestrogen treatment herself about one year before because she felt it was of no further benefit to her although she had developed her secondary sexual characteristics during the treatment. She now appeared as a normal phenotypic female but with a blood pressure of 160/130 mmHg. Her height was 1.87 m and body weight 68 kg. Our initial investigations showed a normal blood count and no abnormalities in serum urea, electrolytes, proteins,

cholesterol, creatinine clearance or urinary catecholamine excretion. Serum potassium at 3.8 mmol/l was at the lower limit of our reference range. LH and FSH were both high and oestradiol, testosterone, androstenedione and DHEA were low (Table I). On X-ray, epiphyseal fusion at the knee was almost complete.

On review of the history and the results of the initial investigations, in particular, that cortisol and sex steroids were undetectable, the possibility of a metabolic defect was suspected. Further investigation showed that adrenocorticotrophic hormone was raised and progesterone, normally undetectable in the male, was 12.1 nmol/l. The urinary steroid profile (Table II) revealed metabolites only from intermediates in the aldosterone pathway, that is, from pregnenolone, progesterone and corticosterone only. These features confirmed a defect at the level of 17 α -hydroxylase.

Treatment with hydrocortisone 20 mg morning and 10 mg evening and ethinyloestradiol was begun. Her blood pressure fell to 130/95 mmHg within a few weeks. A recent ultrasound examination of the abdomen, pelvis and inguinal regions after she had been taking ethinyloestradiol 30 μ g daily for a year confirmed that no gonads were present but a small uterus of 2 cm length and 1 cm width was demonstrated in the pelvis.

Discussion

The 17 α -hydroxylase defect is rare, with fewer than 50 cases described in the world literature.¹ A deficiency of 17 α -hydroxylase impairs production

Table I Values for serum hormones at the initial clinic visit and on subsequent investigation

	Observed value	Female reference range (Follicular phase)
TSH	1.6	(0.3–6.5) mIU/l
LH	31.7	(2.5–14.0) IU/l
FSH	77.4	(1.0–10.0) IU/l
Prolactin	116	(0–400) mIU/l
Oestradiol	< 70	70–370 pmol/l
Testosterone	< 0.3	(0.9–2.7) nmol/l
Androstenedione	< 1	(2–12) nmol/l
DHEA	< 0.5	(0.7–11.5) μ mol/l
SHBG	95	(25–110) nmol/l
Hydroxyprogesterone	2.6	(1.4–12) nmol/l
Progesterone	12.1	< 3.2 nmol/l
Cortisol	< 70	160–520 nmol/l
ACTH	84	(10–80) ng/l

TSH = thyroid stimulating hormone; SHBG = sex hormone binding globulin; DHEA = dehydroepiandrosterone sulphate.

of 17-OH pregnenolone and 17-OH progesterone. Consequently sex steroids and cortisol are absent or reduced while the production of progesterone and corticosterone is enhanced. A variety of clinical features occur, ranging from sexual infantilism in genotypic females² to ambiguous or female external genitalia in genotypic males.^{3,4} The variety may reflect a variable genetic basis and varying degrees of deficiency of either or both of the 17 α -hydroxylase and 17, 20-lyase activities of

Table II Urinary steroid profile

Steroid	Observed value (μ mol/24 h)	Normal adult (mean $\pm$ s.d.)
Pregnanediol	4.64	1.87 $\pm$ 0.62
5-Pregnene-3 β ,20 α -diol	2.58	0.16
3 α ,20 α -Dihydroxy-5 β -pregnane-11-one*	0.20	
3 α ,20 α -Dihydroxy-5 α -pregnane-11-one*	8.37	
5 β -Pregnane-3 α -11 β -20 α -triol*	0.41	
5 α -Pregnane-3 α -11 β -20 α -triol*	0.83	
5-Pregnene-3 β ,16 α ,20 α -triol	1.53	
Tetrahydro-11-dehydrocorticosterone**	12.9	0.29 $\pm$ 0.14
Tetrahydrocorticosterone**	5.90	
Allo-tetrahydrocorticosterone**	15.8	1.03 $\pm$ 0.60
Hexahydro-11-dehydrocorticosterone**	4.05	
Hexahydrocorticosterone**	1.57	
Allo-hexahydrocorticosterone**	5.77	

The only steroids detected were those derived from pregnenolone, progesterone and corticosterone either directly (**) or via 21-hydroxylation by gut flora during enterohepatic circulation (*). No metabolites of androgens or cortisol were detected. Many of the metabolites quoted above are absent or normally occur in such small amounts that a normal adult range is not available.

P450_{17α} coded on chromosome 10.⁵ For example, patients with 46 XY karyotype and female phenotype have been shown to have duplications in the CYP 17 gene.^{4,5} In patients with 17α-hydroxylase deficiency, the uterus and/or fallopian tubes may be absent and, in addition, ovarian abnormalities sometimes occur.¹ In one reported case the gonads were absent but this was probably due to surgical removal at an earlier operation for bilateral inguinal herniae repair.⁶ The complete absence of gonads in our patient seems therefore to be a feature not previously recorded and at present unexplained.

The present case illustrates the importance of ensuring that steroid metabolism is normal in

patients presenting with primary amenorrhoea and sexual infantilism. Even the simple measurement of plasma cortisol was sufficient to indicate that a major disorder of steroid synthesis was present. The omission of this step may lead to an erroneous diagnosis with the consequence of considerable delay before proper treatment is instituted.

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