

Congenital adrenal hyperplasia due to 11 β hydroxylase deficiency masquerading as testicular tumours and myopathy in children

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Introduction

Deficiency of 11 β hydroxylase in the pathway of adrenal steroidogenesis causes a hypertensive form of congenital adrenal hyperplasia (CAH). The following descriptions are of two children presenting with this rare form of CAH.

Case 1

A 10 year and 2 month old boy was transferred to Lady Ridgeway Hospital (LRH) in March 2007 for further evaluation. He was the youngest of 7 children born to unrelated parents. He had always been dark complexioned. There was no history suggestive of an adrenal crisis during the neonatal period, infancy or childhood. An increase in his height had been noted around 8 years of age followed by appearance of secondary sexual characteristics one year later. He was taller than his 13 year old brother who was prepubertal. His parents did not think this abnormal and had not sought medical advice. A month prior to admission he had developed a headache which progressively worsened and when taken to the local hospital hypertension was detected. He was also suspected to have testicular tumours and was transferred to LRH for further assessment.

He was a dark complexioned tall boy with a height of 149 cm (97th percentile) and weighed 41.7 kg (90th percentile). He was hoarse and very muscular with facial and body hair. His behaviour was appropriate to the chronological age but not to the pubertal stage. There was cardiomegaly with an ejection systolic murmur and a blood pressure (BP) of 180/110 mm Hg.

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Funduscopy was normal. Genital examination showed a 9 cm phallus, stage III pubic hair and bilateral 15 ml testes which were hard, irregular and non tender. The initial serum sodium and potassium were 132/2.7mmol/l respectively which gradually improved to 142/3.0mmol/l on oral potassium chloride supplements. The serum 17 hydroxyprogesterone (17 OHP) and serum testosterone were markedly elevated at 93nmol/l (<10) and 8.1ng/ml (1.0–3.2). His serum creatinine was normal. The tumour markers were normal: α FP 0.84ng/ml (0–10) and β hCG 0.27mu/l (0–4). Midnight gonadotrophins were prepubertal. Plasma renin activity could not be done. His bone age was 16 years at a chronological age of 10 years and 2 months. Echocardiography showed a bicuspid aortic valve with congenital aortic stenosis and mild aortic regurgitation with evidence of left ventricular hypertrophy.

Ultrasonography showed slightly prominent adrenal glands and bilateral hypoechoic testes with heterogeneous echo pattern without calcification or mass lesions compatible with adrenal rests in the testes (Figure 1).

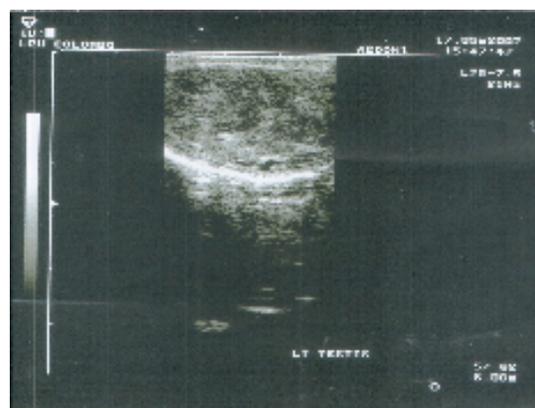


Figure 1 Testis with testicular adrenal rest tissue

A clinical diagnosis of long standing untreated CAH due to 11 β hydroxylase (11 β -OH) deficiency, with bilateral testicular adrenal rest tissue, was made. This was based on the presence of hypertension, hypokalaemia, markedly increased 17 OHP and

testosterone levels with an advanced bone age and no evidence of central precocious puberty. A filter paper sample of urine, sent to Melbourne, Australia for estimation of the metabolites of adrenal steroids, confirmed the clinical diagnosis. Testicular malignancies were unlikely as both testes were involved, tumour markers were negative and ultrasonographic features were more suggestive of testicular adrenal rest tissues (TART) rather than malignancy.

He was started on hydrocortisone. Two months later the 17 OHP was gradually decreasing and his serum potassium had normalized without medication, his pigmentation was less and the size of the testes had reduced. His BP was controlled on nifedipine. Ultrasonographically the testicular sizes were smaller but the echo-texture was the same.

Two of his brothers were healthy with normal blood pressures. When last reviewed in August 2008 at 11 years and 7 months of age, he was fairer and well with no complaints but his height had only increased by 0.8 cm over 17 months. His BP was under control and the testicular sizes had reduced to 10 ml and were normal in consistency. He was started on dexamethasone for the CAH as his bone age was 17 years and the growth velocity was minimal.

Case 2

A 4 year old boy was sent to LRH in November 2007 for further evaluation of hypertension and weakness of the body. He was the younger of 2 boys of a consanguineous marriage. There were no concerns during the neonatal period or infancy. He had always been darker and taller than his 7 year old brother and was the tallest at his preschool. Around the age of 2 years and 6 months his mother had noticed pubic hair and increase in the penile length but had been reassured by a medical practitioner. From 3 years of age he had polyuria and polydipsia. Around the same age he had developed weakness of the body with difficulty in walking which had gradually progressed and when he couldn't raise his head, he was taken to the local hospital. He had also complained of a headache on the day prior to admission. Hypertension, a low serum potassium and evidence of puberty had been noted and he was transferred for further assessment.

On examination at LRH, his height and weight of 120.5 cm and 23.4 kg respectively were well above the 97th percentiles. There was no facial or body hair. The BP was 150/100 mm Hg and he had a systolic murmur. Funduscopy was normal. The muscle

weakness had improved with the treatment given at the local hospital. He had a 8 cm phallus and bilateral 3 ml testes with stage III pubic hair.

The serum sodium and potassium on admission to LRH were 146.2/2.25mmol/l which gradually normalized to 138.8/3.19mmol/l on oral potassium chloride supplements. The bone age was advanced at 12 years. The initial 17 OHP was more than 57.6nmol/l (0.21–5.1). Midnight gonadotrophins were prepubertal. USS showed both adrenal glands to be enlarged, compatible with adrenal hyperplasia. Both testes were normal with no adrenal rests or testicular mass lesions. Kidneys were normal. Echocardiography showed mild concentric left ventricular hypertrophy with good chamber function.

A diagnosis of CAH due to 11 β -OH deficiency was made on the basis of pigmentation, hypertension, markedly elevated 17 OHP with severe hypokalaemia and high serum sodium levels, most of which except hypertension, normalized after treatment with hydrocortisone. Confirmatory test of estimation of metabolites of adrenal steroids on a urine sample could not be done on this boy. His brother was fair complexioned and prepubertal with the height on the 50th percentile and normal blood pressure.

In August 2008, 9 months after presentation, his height velocity had reduced and BP was under control on nifedipine. Right and left testes were 6 ml and 8 ml respectively and not lobular. Serum electrolytes were normal. USS showed prominent adrenal glands and normal testes with no evidence of adrenal rest tissue.

Discussion

There are 2 genes *CYP11B1* and *CYP11B2* located on chromosome 8 which encode two 11 β hydroxylase isoenzymes, 11 β hydroxylase and aldosterone synthetase respectively. 11 β hydroxylase catalyses the conversion of 11-deoxycorticosterone (DOC) to corticosterone and 11-deoxycortisol to cortisol. *CYP11B1* is expressed in the zona fasciculata and is controlled by adrenocorticotrophic hormone (ACTH). Conversion of DOC to corticosterone and then to aldosterone is dependant on aldosterone synthetase which is encoded by *CYP11B2* expressed in the zona glomerulosa under the control of angiotensin II and potassium^{1,2,3,4}.

11 β hydroxylase deficiency due to mutations of these genes has an autosomal recessive inheritance with an incidence of 1 in 100,000 live births in the Caucasian population. This accounts for 5–8% of all causes of

adrenal steroidogenic defects and is the second commonest cause of congenital adrenal hyperplasia (CAH)^{4,5}. Deficiency of cortisol results in increased secretion of ACTH which causes accumulation of steroid precursors. Shunting of these precursors into the pathway for androgen biosynthesis causes ambiguous genitalia in a baby girl with subsequent progressive virilization. Baby boys will have normal genitalia with precocious iso-sexual development. In both sexes if untreated there is progressive virilization with rapid somatic growth and skeletal maturation with premature epiphyseal closure resulting in short adult stature^{1,2,3,4}.

Elevated serum levels of 11-deoxycorticosterone (DOC) & its metabolites with mineralocorticoid activity induces hypokalaemia with metabolic alkalosis and low plasma renin levels, and hypertension due to salt and water retention and volume expansion^{1,4,6}. If untreated or non compliant with treatment, boys are at risk of developing hyperplasia of adrenal rests in the testes that produce bilateral, less commonly unilateral, testicular tumour-like masses or testicular adrenal rest tissue (TART) that may respond to glucocorticoid suppression¹.

Hypertension is seen in approximately two thirds of these patients and is detected during the first few years of life. Left ventricular hypertrophy and hypertensive retinopathy have been reported in one third of patients and in the minority, hypokalaemia and muscle weakness were seen^{1,3,4,6}.

Hypertension was symptomatic in one of our patients and hypokalaemia masquerading as a myopathy was the prominent feature in the other.

Adequate glucocorticoid replacement therapy prevents further virilization by suppressing ACTH and excessive adrenal androgen production. This also prevents the formation of adrenal rests and enhances fertility in the adult male but may not always control the hypertension^{1,3,4}.

Long term follow up with ultrasonography has shown these TART lesions to remain the same in size, grow larger or smaller or even regress completely⁷. These changes do not always correlate with clinical control based on 17-hydroxyprogesterone levels⁷.

In our patient, after 17 months of treatment with hydrocortisone, the testicular sizes had reduced progressively and were normal in consistency. The adrenal glands were normal on ultrasonography at the last examination in August 2008 and the testes were smaller.

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