Congenital adrenal hyperplasia 11β-hydroxylase deficiency: two cases managed with bilateral adrenalectomy

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ABSTRACT

This series describes two patients with congenital adrenal hyperplasia due to 11β-hydroxylase deficiency. The first patient, a ten-year-old with XX genotype, reared as a male, presented with resistant hypokalaemia and hypertension. The second patient, a 23-year-old with XY genotype, presented with bilateral adrenal masses and resistant hypertension. Both the patients were offered bilateral adrenalectomy. These two patients are described with a discussion on the role of bilateral adrenalectomy in the management of difficult cases of congenital adrenal hyperplasia. The association of myelolipoma and testicular rests with this condition is also discussed.

Keywords: 11β-hydroxylase deficiency, adrenal hyperplasia, adrenalectomy, congenital adrenal hyperplasia, myelolipoma, resistant hypertension, testicular rests

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a family of inherited disorders of steroidogenesis in which enzymatic defects result in impaired synthesis of cortisol by the adrenal cortex. Steroid 11β-hydroxylase deficiency is the second most common cause of CAH, accounting for less than 5% of cases.[1] Steroid 11β-hydroxylase deficiency is characterised by the overproduction of adrenal androgens and deoxycorticosterone, leading to virilisation of the female foetus, pseudoprecocious puberty in male infants and hypertension with or without hypokalaemia in both genders. We describe two patients with 11β-hydroxylase deficiency managed with bilateral adrenalectomy, discuss the role of this procedure in the management of 11β-hydroxylase deficiency, and conduct a literature review of previously described cases. We also describe the association of adrenal myelolipoma and testicular rests with 11β-hydroxylase deficiency.

CASE REPORTS

Case 1

This patient was born in 1986, reared as a male, presented at the age of five years with pubic hair development, was informed to be of "female gender" and detected to be hypertensive. The parents could not accept raising this child as a female and the child was lost to follow-up until he presented to us at the age of ten years with acne and breast development. The younger sister had postnatal virilisation, was on treatment with steroids and was being reared as a female. She was hypertensive and hypokalaemic. The patient was 139 cm tall (95th percentile), with bilateral breast enlargement (B2), heavily pigmented and virilised. Pubic hair was Tanner IV, with a phallus length of 6.5 cm, chordee and penoscrotal hypospadias. The labioscrotal folds were empty. Blood pressure was 170/110 mmHg with grade 3 hypertensive retinopathy. 17-hydroxyprogesterone was 10 (normal < 1) ng/ml and 11-deoxycortisol levels were 10 (normal range 0.2–0.6) µg/dL. Karyotype analysis showed 46 XX. Mullerian structures were visualised in the pelvis by ultrasonography (US). A diagnosis of 11β-hydroxylase deficiency was made in view of hypertension with virilisation in a 46 XX individual, with pathognomonic biochemical features. The patient was started on prednisolone at a dose of 4 mg/m^2 with antihypertensives.

At the age of 13 years, he was admitted with hypokalaemic paralysis following episodes of vomiting, after which he was started on potassium replacement. At 14 years of age, the patient underwent release of chordee and urethroplasty. The intraoperative period was managed with a stress dose of hydrocortisone and was uneventful. In the postoperative period, the patient had a left hemiparesis, with computed tomography (CT) showing a right middle cerebral artery territory infarct. The potassium requirement continued to increase (approximately 200 meq/day = 6.5 meq/kg), despite ensuring compliance. The testosterone level was 3.8 ng/ml. The suppressive steroid was changed to dexamethasone 0.75 mg daily and antihypertensives were stepped up to the maximum doses of atenolol, nifedipine, spironolactone and prazosin.

At 16 years of age, the patient underwent bilateral laparoscopic adrenalectomy and hysterectomy. Both resected specimens showed adrenal cortical hyperplasia. The cells were arranged in a lobular pattern. Individual cells have eosinophilic cytoplasm and few cells have nucleomegaly. Focal collections of mononuclear cells are seen between lobules. In the postoperative period, he had three episodes of transient ischaemic attacks involving the right middle cerebral artery territory, followed by the

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gradual recovery of neurodeficits. Magnetic resonance angiogram showed occlusion of the right middle cerebral artery. Postoperative testosterone was 0.1 ng/ml. The patient was discharged on replacement doses of prednisolone, fludrocortisone, aspirin, clopidogrel and 25 mg of atenolol. After six months follow-up, he was normokalaemic without supplementation of potassium but required antihypertensives in a smaller dose of 25 mg of atenolol and 5 mg of amlodipine. The neurological deficits have been resolved and he is currently on testosterone replacement.

Case 2

A 23-year-old unmarried male patient was referred for evaluation of recently-detected accelerated hypertension, target organ dysfunction (left ventricular hypertrophy, grade 4 hypertensive retinopathy and renal dysfunction) and a left adrenal mass. Biochemical assessment for pheochromocytoma was negative. Imaging showed a left adrenal mass 10 cm × 10 cm × 8 cm with fat density. The patient underwent open left adrenalectomy. Histopathology was suggestive of myelolipoma. Postoperatively, his blood pressure remained high, requiring maximal doses of atenolol and amlodipine.

He was lost to follow-up and presented five years later with uncontrolled hypertension and diminution of vision. Detailed history revealed that he was born of a consanguineous marriage, was the shortest in his family and had developed pubic hair at around three years of age. He was pigmented, short (< 5th percentile) and with a stocky built. Testicular volume was 20 ml bilaterally with a firm, irregular feel. Basal 17-hydroxyprogesterone was 16 (normal < 1) ng/ml and 11-deoxycortisol was 6.9 (0.2–0.6) µg/dL. CT showed a right hypodense adrenal mass measuring 6.5 cm × 3.7 cm × 2.8 cm, and the left adrenal was bulky. US of the scrotum revealed altered echotexture and calcification, with hypovascular regions and a rim of hypervascularity. Open bilateral adrenalectomy with complete excision of remnants of the left adrenal was done. Histopathology showed bilateral adrenal cortical hyperplasia. Nodules composed of predominantly adipose tissue with separated islands of haemopoietic cells consistent with myelolipoma were seen in the resected specimen. The patient refused a biopsy of the testicular masses. He was started on prednisolone 5 mg and fludrocortisone 50 µg once daily with antihypertensives. Follow-up after five months showed a reduction in the size of testicular rests, as well as a reduction in blood pressure and pigmentation.

DISCUSSION

The decision to undertake bilateral laparoscopic adrenalectomy in the first patient was prompted by his uncontrolled hypertension, requiring high doses of multiple antihypertensives, and hypokalaemia requiring large doses of potassium replacement despite adequate compliance. The response of the patient to adrenalectomy was quite gratifying. In the second patient, despite his pigmentation and short stature with bilateral adrenal masses, the diagnosis of CAH evaded the treating physicians. Adrenalectomy was undertaken based on the belief that it would smoothen the blood pressure control. This was confirmed on follow-up. This case also demonstrated the association of adrenal myelolipomas and testicular rests in association with untreated CAH.

Steroids form the cornerstone of the management of CAH. They replace the deficient corticosteroids, suppress the adrenocorticotropic hormone (ACTH) drive and reduce the adrenal androgen secretion. In 11β-hydroxylase deficiency, they reduce the ACTH drive and hence the overproduction of deoxycorticosterone. Medical treatment for females with 21-hydroxylase deficiency has long been a point of frustration for both clinicians and patients alike. The dose of glucocorticoids required to suppress hyperandrogenaemia is often supraphysiological and can result in iatrogenic Cushing's syndrome.[2] Shortened final height as a result of accelerated bone maturation due to androgens and epiphyseal damage due to glucocorticoids are the ultimate effect. A meta-analysis of data from 561 patients with classic CAH found a mean final height of –1.4 SD.[3]

Van Wyk and Ritzen have suggested that certain patients with CAH would benefit from bilateral adrenalectomy because children with Addison's disease present with fewer problems in management.[2] He reviewed 18 patients of CAH described in the literature who underwent adrenalectomy for various reasons. The reasons for adrenalectomy in CAH 21-hydroxylase deficiency were unsuppressed hyperandrogenism, Cushingoid appearance, impaired glucose tolerance due to steroid dosages and patient preference. These patients included 16 patients with 21-hydroxylase deficiency (two simple virilising, one late onset and 13 salt-wasting) and two patients with 11β-hydroxylase deficiency. Three of these patients were part of a prospective study to compare prophylactic adrenalectomy in the most severely affected children with conventional treatment. A total follow-up of 90 patient-years was available and showed that adrenalectomy is a safe procedure in CAH patients with a good quality of life and health benefits. Glucocorticoid therapy could be maintained at replacement doses in a majority of patients, lower than the suppressive doses. There was resolution of the Cushingoid features with loss of fat mass. The adverse effects noticed in postoperative follow-up were adrenal crisis, hypoglycaemia and activation of ectopic adrenal rests. There were no deaths.[2]

Our two cases add to the previously described two cases in the literature where bilateral laparoscopic adrenalectomy was undertaken in patients with 11β-

hydroxylase deficiency.[1,4] Nasir et al reported a 14-year old girl with hirsutism, acne and premature pubic hair development starting at four years of age with delayed puberty and marked clitoromegaly. She was normokalaemic and normotensive. Bilateral laparoscopic adrenalectomy resulted in regression of acne, hirsutism and virilisation and normalisation of androgen levels.[1] The second case was a 44-year-old with XX karyotype, reared as a male, presented with uncontrolled hypertension with left ventricular hypertrophy, hypokalaemia and central retinal vein occlusion with poor compliance to a steroid regime. Following bilateral laparoscopic adrenalectomy, the patient normalised his blood pressure and potassium values.[4]

The basis of bilateral adrenalectomy in patients with 11β-hydroxylase deficiency is to remove the adrenal tissue that produces excess metabolites like deoxycorticosterone, which causes a low-renin hypertension. In our patient, hypokalaemia was resolved following adrenalectomy. Hypertensive renal disease due to longstanding hypertension may be a reason for the residual hypertension in both our patients. However, the problems associated with adrenalectomy should not be ignored. Hyperpigmentation and elevated ACTH values were observed in more than half the patients operated on so far.[2] Significant elevation of the steroid precursors was reported in eight out of 18 patients who underwent bilateral laparoscopic adrenalectomy. Ectopic adrenal rests can be present in the broad ligament and celiac plexus in females and the testes and spermatic cord in males, and can lead to steroidogenesis and virilisation.[2] Furthermore, the possibility of an ACTH-secreting pituitary tumour also exists.[5] With the advent of laparoscopic surgery, adrenalectomy has become a safe procedure. However, routine adrenelectomy is not recommended in CAH patients, especially those with 11β-hydroxylase deficiency. 11β-hydroxylase deficiency patients are not usually prone to adrenal crisis. Adrenalectomy converts them into adrenal insufficient patients prone to a potentially lethal adrenal crisis.[4] This fact should be carefully considered before embarking on bilateral laparoscopic adrenalectomy, especially in habitually noncompliant patients.

Myelolipoma is an uncommon benign tumour of the adrenal glands, composed of mature adipose tissue and haemopoietic elements resembling bone marrow. It has been associated with various forms of CAH like 21-hydroxylase deficiency and 17α-hydroxylase deficiency, but not with 11β-hydroxylase deficiency.[6] The rarity of the association with 11β-hydroxylase deficiency is possibly related to the early identification of these patients due to coexistent hypertension. Myelipoma is believed to be of metaplastic origin, due to chronic stimulation by ACTH and androgens.[6] Males with inadequately-treated CAH are known to develop testicular tumours that frequently are bilateral in adult life. They have been termed as testicular tumours of adrenogenital syndrome (TTAGS). A single case report describes a combination similar to our second patient – adrenal myelolipoma with testicular rests, in a patient with 21-hydroxylase deficiency.[7] This combination highlights the possible pathogenetic role of persistently-elevated ACTH levels in these dual "tumours". Patients with bilateral testicular adrenal rests in association with 11β-hydroxylase deficiency have been reviewed previously.[8] Testes-sparing surgery should be considered in patients with bilateral steroid unresponsive testicular rests.

In conclusion, these two cases highlight the unusual clinical and management problems to do with this uncommon disease. Laparoscopic bilateral adrenalectomy is a safe and effective procedure in patients with CAH presenting with resistant hypertension, hypokalaemia and steroid-unresponsive androgen excess. The benefits of this procedure should be fully discussed and compliance ensured before subjecting the patient to the hitherto experimental modality of treatment. Testicular rests in patients with poorly-treated CAH can impair fertility. Adrenal myelipomas in patients with CAH are usually on asymptomatic and left alone. The symptomatic ones should be surgically managed.

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