Congenital Adrenal Hyperplasia with 11–Beta Hydroxylase Deficiency with Testicular Adrenal Rest Tumour

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Abstract

Congenital adrenal hyperplasia refers to the non-malignant enlargement of adrenal gland tissue as a result of deficiency of one of several enzymes involved in adrenal hormone synthesis, secondary to a genetic mutation. 11 - Beta hydroxylase is one such enzyme, and its deficiency is a rare cause of Congenital Adrenal Hyperplasia. We describe the case of an 18-year old man who presented to us with an acute right ganglio-capsular bleed, hypertension and bilateral scrotal swelling. Investigations revealed hypokalemia, and normal renal and cardiac functions. Furthermore, sex hormone levels were found to be markedly raised, and Renin to Aldosterone ratio was also deranged. CT imaging of the adrenals confirmed hyperplasia, and ultrasound of the testes confirmed Testicular Adrenal Rest tumour, a rare finding. His condition improved significantly with treatment, and he is currently undergoing physical and occupational rehabilitation. Our case highlights the importance of evaluation of hypertension in young patients and a high degree of suspicion for rarer causes.

Introduction

Hypertension is one of the commonest health problems faced, and it can manifest in myriad ways, like renal failure, cardiac failure, or as in the case of our patient, intra cerebral haemorrhage. Hypertension in the young is an emerging disease, and its magnitude is rising at an alarming rate. It is of importance to note that if the underlying aetiology for young hypertension can be found, specific and effective treatment can be given, perhaps even cure. Congenital Adrenal Hyperplasia of 11β-Hydroxylase Deficiency subtype is one such condition, and may rarely present as intra-cerebral haemorrhage due to hypertension. A timely diagnosis leads to a very good prognosis.

Case Report

An 18 year old male labourer presented to us with sudden onset headache and weakness of left side of his body, associated with asymmetry of face. There was no history of trauma, fever, altered sensorium, chest pain, palpitations or any other history of heart disease in the past. Patient denied addictions and high risk sexual behaviour. Patient was a known hypertensive since the age of eight years, but by his own account had stopped taking all medications since the past 2 months. On enquiry, he recalled an episode of quadriplegia at the age of 7 years which recovered within 2 days after taking some treatment with a local practitioner, but he was never evaluated further for this.

On further enquiry, he also gave history of an early increase in testicular size, along with development of pubic and axillary hair from the age of 7-8 years, suggestive of precocious puberty. He gave no history suggesting any similar or major medical illness in any family member.

On examination, his pulse was normal, and blood pressure measured 180/120 mmHg in all the limbs. His height and weight was 148 cms and 55 kg respectively with a BMI of 25.11 kg/m². He had androgenic alopecia, and features of precocious puberty with well grown beard and moustache. He had palpable bilateral soft scrotal masses, without any local warmth or tenderness. On fundus examination, grade two hypertensive retinopathy was noted. Neurological examination showed normal higher mental function, left sided hemiplegia with exaggerated deep tendon reflexes and extensor plantar response on the left side.

CT Brain revealed an acute large 45×39 mm right ganglio-capsular hemorrhage with moderate mass effect, without intra ventricular extension or midline shift.

Routine investigations were normal except for hypokalemia (serum K - 2.5 meq/L). ECG was suggestive of left ventricular hypertrophy with strain pattern. 2 D ECHO confirmed LVH, with an Ejection Fraction of 60%. Renal Doppler did not show any evidence of renal artery stenosis and ultrasound of the kidneys showed right kidney 10.8×5.2 cm, left kidney 9.6×4.4 cm with bright echotexture, medullary nephrocalcinosis. Thyroid function tests were in normal range (Free T3- 2.9 pg/mL, Free T4- 0.8 ng/ml , TSH- 3.6 mIU/mL). Urinary Vanillylmandelic acid (VMA) Level was done to rule out Pheochromocytoma which was within normal limits (2.5 mg/d) with a reference range: <6 mg/d (Table 1).

We evaluated our patient for causes of young hypertension with hypokalemia and scrotal swelling, with renal and adrenal pathology being foremost in our suspicion, with a possibility of a testicular malignancy also kept as a differential. With a normal renal doppler, in-range creatinine levels, and absence of any raised tumour marker level, effectively ruling out the other possibilities. We investigated for adrenal causes, and found serum Aldosterone-renin ratio (ARR) to be significantly low. CT adrenals (Figure 1) revealed bilateral bulky adrenals with normal configuration and no evidence of any mass, suggesting a congenital adrenal hyperplasia. Further endocrine work up revealed high ACTH of >1250 pg/ml (NR : 0-46pg/ml), low basal cortisol of 5.96 microgram/dl (NR : 0-25 microgram/dl), high Serum testosterone levels

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of >15 ng/ml (4-11 ng/ml), and High 17 hydroxy-progesterone level of 114 ng/ml (NR: 0.60-3.42 ng/ml). 11 Deoxycorticosterone (DOC) could not be done due to non availability of test. Based on these findings, the diagnosis of congenital adrenal hyperplasia with 11β-Hydroxylase deficiency was confirmed. For the testicular swelling, ultrasound of scrotum was performed, which revealed normal shaped testes, but with bilateral heterogenous enlargement with highly increased vascularity and increased venous drainage, suggestive of bilateral testicular adrenal rest tumors (TART) (Figure 2).

Patient was treated with cerebral decongestants, anti-hypertensives including Losartan, Nifedipine and Spironolactone, and physiotherapy. For definitive management, patient was started on low dose Dexamethasone (0.5 mg) OD to provide cortisol supplement to normalize ACTH which in turn removes the drive for oversecretion of Deoxycorticosterone, which causes the uncontrolled hypertension, and tab. Spironolactone (25 mg) BD, a mineralocorticoid receptor antagonist to block mineralocorticoid effects of Deoxycorticosterone. Patient improved with this regimen, and blood pressure was well maintained. He was discharged on a regimen of Tab. Spironolactone (25 mg) BD, Tab. Nifedipine (10 mg) QID, and Tab. Dexamethasone (0.5 mg) OD.

At one month follow up, his scrotal swelling due to the Testicular Adrenal Rest Tumour (TART) had regressed completely, and his endocrine and metabolic parameters such as Serum ACTH, 17-OH-progesterone, serum potassium levels had come to near normal values. Patient resumed his daily routine activities after one month after discharge, with gradual and sustained improvement in power. At three month follow up, patient’s 17-Hydroxyprogesterone was 2.14 ng/ml (NR: 0.6-3.42), Testosterone was 4.88 ng/ml (NR: 4-11).

**Discussion**

Congenital Adrenal Hyperplasia (CAH) comprises group of autosomal recessivedisorders caused by deficient adrenal corticosteroid biosynthesis.1 It results from defects in one of the steroidogenic enzymes involved in cortisol biosynthesis or in the electron-providing factor, P450 oxidoreductase (POR), (Figure 3).

Four major Enzymes deficiencies are clinically important:

1. **21-Hydroxylase Deficiency** – Most common, with Glucocorticoid (GC) and Mineralocorticoid (MC) deficiency.

2. **11β-Hydroxylase Deficiency** – with GC deficiency and MC excess
3. 17α-Hydroxylase Deficiency – with GC deficiency and MC excess, and additional androgen deficiency

4. 3β-Hydroxysteroid Dehydrogenase Deficiency – with GC and MC deficiency, and androgen excess. 11β-hydroxylase deficiencies accounts for 7% of all cases of CAH. Incidence is 1 in 100,000 live births.2

Mutations in the 11β-hydroxylase (CYP11B1) gene, located on chromosome 8q24.3, results in loss of enzyme activity and a block in the conversion of 11-deoxycortisol to cortisol.3 Loss of negative cortisol feedback results in excess ACTH production, with enhanced ACTH-mediated adrenal androgen excess, resulting in virilisation and ambiguous genitalia in females, and precocious puberty in males. Our patient had features of precocious puberty in the form of pubic and axillary hair since 7 years of age. Patient had Hypertension, which was the principal differentiating factor from 21-hydroxylase deficiency, which is considered to be due to overproduction of Deoxycorticosterone (DOC), and resulting mineralocorticoid excess. Our patient had presented with intracranial hemorrhage with underlying hypertension, and associated with hypokalemia.

Treatment is with replacement glucocorticoid therapy; with suppression of Deoxycorticosterone (DOC) secretion.4,5 Antihypertensive treatment should be commenced at an early stage to avoid excessive glucocorticoid exposure. Patients with 11β-hydroxylase deficiency cannot mount a sufficient stress response and should receive appropriate stress doses of glucocorticoids as for other patients with adrenal insufficiency. Biochemical monitoring should include testosterone, androstenedione and 17-Hydroxyprogesterone levels.

Testicular adrenal rest tumors (TART) are benign tumors, resembling adrenocortical tissue, usually seen bilaterally, within the rete testes.6 While they are not malignant, in long standing cases, these tumors may cause irreversible testicular damage, and are an important cause of infertility in young males with CAH. However, regression of the tumor is noted with steroid replacement therapy.7

Our patient fulfilled the clinical as well as laboratory criteria for the diagnosis and responded to steroid and mineralocorticoid receptor antagonist treatment.

Conclusion

Our case showcases the importance of early diagnosis, counseling and management of a young patient presenting with Hypertension. Our patient was treated successfully with steroids, anti-hypertensive medications, and is currently undergoing occupational rehabilitation.

References