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Renal Cysts and Nephrocalcinosis in a Patient Deficient in 11 beta-Hydroxylase Enzyme

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Summary	
Background:	Chronic hypokalemia is known to induce renal structural and functional abnormality. The former includes induction of renal cyst formation and interstitial fibrosis while the latter entails urine-concentrating defect. However, these hypokalemia-mediated changes occur in a handful of conditions including primary aldosteronism, distal renal tubular acidosis, Liddle's disease, apparent mineralocorticoid excess syndrome and Bartter's type 3 syndrome. Such a finding has never been described in an 11 beta-hydroxylase deficient individual.
Case Report:	We describe a case of a 15-year-old male, deficient in 11 beta-hydroxylase enzyme, presenting with hypertensive haemorrhage in basal ganglia and chronic hypokalemia-mediated nephrocalcinosis and renal cysts. To add to the uniqueness, our patient was discovered to harbour bilateral testicular adrenal rests as well.
Conclusions:	An early diagnosis could help prevent these sequelae and preserve long-term renal function and safeguard against ill-effects of hypertension. Besides, aetiology of nephrocalcinosis should be sought for and corrected.
MeSH Keywords:	Adrenal Hyperplasia, Congenital • Hypertension • Hypokalemia • Nephrocalcinosis
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Background

A deficiency of 11 beta-hydroxylase enzyme presents as hypertension with hypokalemia [1]. A chronic hypokalemic state may induce renal changes including cyst formation, nephrocalcinosis and urinary concentration defect [2]. In this case report, we describe a case of a 15-year-old male patient presenting with hypertensive haemorrhage in basal ganglia with renal cysts, nephrocalcinosis and bilateral testicular adrenal rests.

Case Report

A 15-year-old boy, born of third degree consanguineous marriage, fifth by birth order presented to our services with sudden-onset weakness in the left half of the body. On inspection, his built was sturdy and he measured 154 cm (less than 5th centile). He weighed 71 kilograms (156 pounds). His skin was hyperpigmented with excessive body hair and temporal recession of hairline. He had

macro-orchidism as well. Significant past history included holocranial headaches on and off since a few months.

On admission, he was afebrile. Blood pressure was 180/110 mmHg with no significant difference in the upper and lower limbs. There was no bruit in the renal area. Computed Tomography depicted a hyperdense lesion in the right basal ganglia suggestive of acute haemorrhage. A renal sonogram with doppler study was performed. It revealed medullary nephrocalcinosis with multiple bilateral renal cysts. The Doppler waveforms and velocities of renal arteries on either side were normal. The size of both kidneys was within normal limits but both the adrenal glands were bulky. A CT was performed that confirmed the findings of bilateral medullary nephrocalcinosis (Figures 1, 2) with multiple bilateral renal cysts (Figures 3, 4) and bulky adrenals. Besides, the spermatic cord was bulky on both sides with enlarged nodular testes. A testicular sonogram was performed which showed hyperechoic nodules located adjacent to the mediastinum testis (Figure 5). There was no



Figure 1. Non-contrast CT at the level of kidneys reveals a right renal cyst (arrow) with a speck of calcification on the medial aspect. Numerous such foci are visualised on the contralateral side.



Figure 2. Unenhanced CT shows medullary nephrocalcinosis in the right kidney with a cyst on the left (arrow).

distorsion of testicular contour. The epididymes were uninvolved. Color doppler interrogation revealed increased vascularity. The vessels were, however, undisplaced.

Laboratory parameters were Na^+ = 144 mmol/L (normal: 136–146 mmol/L), K^+ = 2.4 mmol/L (normal: 3.5–5 mmol/L), pH 7.5, creatinine 2 mg% (normal: 0.5–1.4 mg%). The plasma renin activity was 0.25 ng/mL/hr (normal: in supine position 1.31–3.59 ng/mL/hr), ACTH 1250 pg/mL (normal: 0–46 pg/mL), aldosterone 4.55 pg/mL (normal: in supine position 40–310 pg/mL), testosterone >15 ng/mL (normal: 4–11 ng/mL), 17 hydroxy progesterone 114 ng/mL (normal: 0.6–3.42 ng/mL), cortisol 4.3 microgm/dL (normal: 5–25 microgm/dL). Urinary calcium was normal. Serum markers for testicular tumor were negative. ECG revealed flattened 't' waves. Thus, a final diagnosis of congenital adrenal hyperplasia (deficient 11 beta-hydroxylase enzyme) with bilateral testicular adrenal rest tumor with acute hypertensive hemorrhage in the basal ganglia on the right side was established.



Figure 3. Gray-scale sonogram using a curvilinear transducer shows a left renal cyst (arrowhead). The pyramids are studded with numerous tiny hyperechoic foci suggestive of medullary nephrocalcinosis.



Figure 4. Non-contrast coronal CT with MIP reformation depicts nephrocalcinosis.

The patient was started on spironolactone 100 mg twice a day, losartan 50 mg twice a day, nifedipine 30 mg four times a day, clonidine 0.1 mg three times a day, hydrocortisone 100 mg three times a day, prednisolone 5 mg twice a day. Later prednisolone was replaced by 0.5 mg dexamethasone. Besides, he was advised physiotherapy.

The patient is currently on dexamethasone 0.5 mg at night, spironolactone 25 mg twice a day, nicorandil 20 mg four times a day. On 1 year follow-up, our patient is doing well.

Discussion

Congenital Adrenal Hyperplasia (CAH) is a disorder of steroid synthesis pathway [3]. Deficiency of any enzyme in this cascade prevents feedback inhibition of corticotropin by the final product. This increase in corticotropin levels manifests as hyperplasia of native adrenal gland or ectopic adrenal tissue [3]. The enzyme most commonly deficient

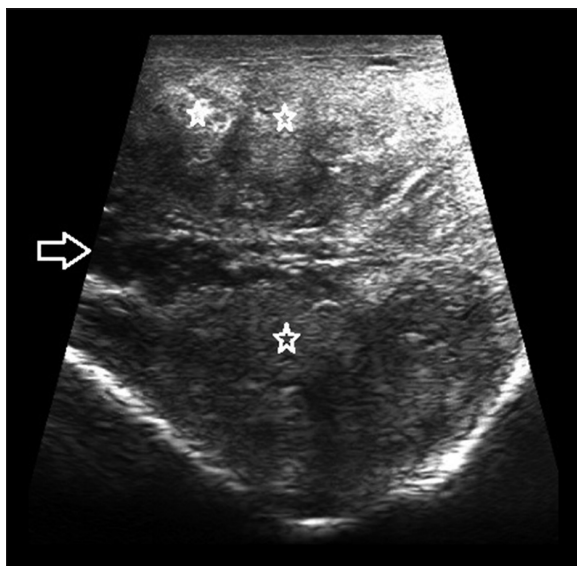


Figure 5. Gray-scale sonogram using 7.5 MHz transducer depicts enlarged testis. There are multiple heterogeneous, predominantly hyperechoic nodules (asterisk) situated along the mediastinum testis (arrow).

is 21 alpha-hydroxylase. Other less commonly encountered ones are 17 alpha-hydroxylase/17, 20-lyase, 11 beta-hydroxylase, 3 beta-hydroxy steroid dehydrogenase [1].

A deficiency of 11 beta-hydroxylase results in hypertensive variant of CAH [1]. Plasma levels of 11-deoxycortisol and deoxycortisone are elevated. Clinically, the patient presents with hypertension and symptoms of androgen excess [1]. Skin pigmentation may be seen. Hypokalemic alkalosis occasionally occurs (as seen in our patient) [1].

Induction of renal cyst formation in the presence of chronic hypokalemia has been sparsely described. Torres et al. described formation of renal cysts in primary aldosteronism [2], while Igarashi reported presence of renal cysts in 70.6%

of patients with distal renal tubular acidosis [2]. Other diseases with chronic hypokalemia-induced renal cysts include Liddle's disease [2], apparent mineralocorticoid excess syndrome [4] and Bartter type 3 syndrome [2].

The pathogenesis of formation of renal cysts in chronic hypokalaemic state is multifactorial. A reduction in extracellular potassium (K^+) ion concentration is a potent stimulus for hypertrophy and hyperplasia of the epithelial cells in the collecting duct [2]. Such a growth pattern will cause luminal obstruction and tubular dilation. Besides, hypokalemia can cause an increase in ammonium ion (NH_4^+) levels. Such an increase in intra-renal NH_4^+ can promote cyst formation by a number of mechanisms viz. stimulating DNA, RNA and protein synthesis [2]. Finally, complement activation due to increased NH_4^+ can cause interstitial nephritis. The healing thence occurs by scarring and dystrophic calcification [4]. This calcification can plug in tubules and cause cyst formation [2]. Moudgil et al. proposed nephrocalcinosis to be a consequence of dystrophic calcification [4].

Our patient exhibited unusual features of nephrocalcinosis with renal cysts with features of 11 beta-hydroxylase deficiency. The renal changes were probably a result of long-standing hypokalemia. Such a presentation has never been reported earlier. Nephrocalcinosis was postulated to be an end result of interstitial nephritis due to chronically low potassium levels. The common causes of nephrocalcinosis due to hypercalcaemia, hypercalciuria and renal tubular acidosis were not seen. Additionally, he had enlarged ectopic adrenal tissue in both testes. Finally, the presentation of our patient with hypertensive bleed was again unique.

Conclusions

Our case emphasizes the importance of comprehensive evaluation so as to lead to an early diagnosis. An early diagnosis may help prevent these sequelae and preserve long-term renal function and safeguard against ill-effects of hypertension.

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