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CASE STUDY

Congenital Hyperreninemic Hypoaldosteronism: A Case Report

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ABSTRACT

Congenital hypoaldosteronism due to an isolated aldosterone biosynthesis defect is rare. We report a neonate for consanguineous parents who developed refractory hypotension, persistent hyponatremia and hyperkalemia. Investigations revealed normal serum 17-hydroxy progesterone, ACTH and cortisol. An inappropriately normal serum aldosterone level and normal serum 18 hydroxy corticosterone levels with a low 18-hydroxy corticosterone: aldosterone ratio was suggestive of corticosterone methyl oxidase type I deficiency. Patient was started on fludrocortisone replacement therapy with a subsequent normalization of electrolytes and blood pressure. Molecular analysis reveals no mutation in *CYP11B2*. This patient may have a form of familial hyperreninemic hypoaldosteronism distinct from aldosterone synthase deficiency and the affected gene(s) remain to be determined. Further homozygosity mapping is needed to ascertain the precise nature of the mutation.

KEYWORDS

Congenital, Hyperreninemic, Hypoaldosteronism, Preterm, Mutation, *CYP11B2*, Hypotension

INTRODUCTION

Defective aldosterone biosynthesis causes hypovolemia, hyponatremia, and hyperkalaemia and may be caused by congenital adrenal hyperplasia due to 21 hydroxylase (*CYP21*) deficiency affecting the cortisol biosynthesis or as a result of aldosterone synthase (cortisone methyloxidase, *CYP11B2*) deficiency. Disorders of isolated aldosterone biosynthesis are important in the differential diagnosis of salt wasting syndromes of infancy and childhood. Usually hyperreninemic hypoaldosteronism has been ascribed to the mutations in *CYP11B2*. We present a neonate with isolated hypo aldosteronism (corticosterone methyl oxidase Type I deficiency).

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Case Report

A preterm (34 weeks) baby boy was delivered through emergency cesarean section due to abruptio placenta for second degree consanguineous parents. Perinatal CTG showed early decelerations. Appearance, pulse, Grimace, Activity, respiration (Apgar) score was 7 at 1 minute and 8 at 5 minute. Birth weight 1.52 kg, length 42 cm and head circumference was 29.5 cm. He was admitted to NICU due to prematurity and hyaline membrane disease. Patient required CPAP for few days then shifted to nasal canula then room air. At age of two weeks, he had severe hypotension which required maximum doses of dopamine, dobutamine and epinephrine to maintain his mean blood pressure within normal range. One day after, his serum sodium and bicarbonate level start to drop while serum potassium rise gradually over few days. No documented hypoglycemia. There was no hyper-pigmentation and the external genitalia were

normal. His stretched penile length was 2 cm and both testicles were palpable in the scrotum. Initial hematological and biochemical values are shown in Table 1.

Table 1: Hematological and biochemical changes at two weeks after birth and at one year

Factors	At the Age of two weeks	At the Age of one year
Hb	15.4 gm/dL	11.3 gm/dL
WBC	14.1 cu.cm	8.7/ cu.cm
Platelets	727/cu.cm	358/ cu.cm
Na	122 meq/L	139 meq/L
K	7.9 meq/L	4.3 meq/L
Cl	92 meq/L	89 meq/L
Urea	17 mmol/L	4.2 mmol/L
Creatinine	68 micromol/L	41 micromol/L
HCO_3	14 meq/L	21 meq/L
Ca^{++}	2.21 meq/L	2.19 meq/L
Mg	0.93 meq/L	1.1 meq/L
PO_4	1.4 meq/L	1.1 meq/L
Serum cortisol	1049 nmol/L	782 nmol/L
ACTH	8.1 pmol/L	4.4 pmol/L
17 OH progesterone	3.2 ng/mL (< 5)	2.6 ng/ml
Corticosterone	39 ng/L (5-132)	-
18 OH cortecosterone	158 ng/Dl (5- 200)	-
Aldosterone	304 pgmol/L (139-3660)	83 pgmol/L
PRA	2720 pmol/L (0.14-1.9)	0.51 pmol/L

Blood, urine and cerebrospinal fluid cultures were negative. Tandem MS, urine metabolic screen, blood ammonia and serum lactate were normal. Chest *X*-ray and echocardiogram were normal. Ultra sonogram of the kidneys showed normal size for both kidneys with increased cortical echogenicity bilaterally (Figure 1). Both adrenal glands were visible with no hemorrhage. Hypernatremia, hyperkalemia and low serum bicarbonate were treated with intravenous calcium gluconate, sodium bicarbonate, oral sodium polystyrene and sodium chloride.

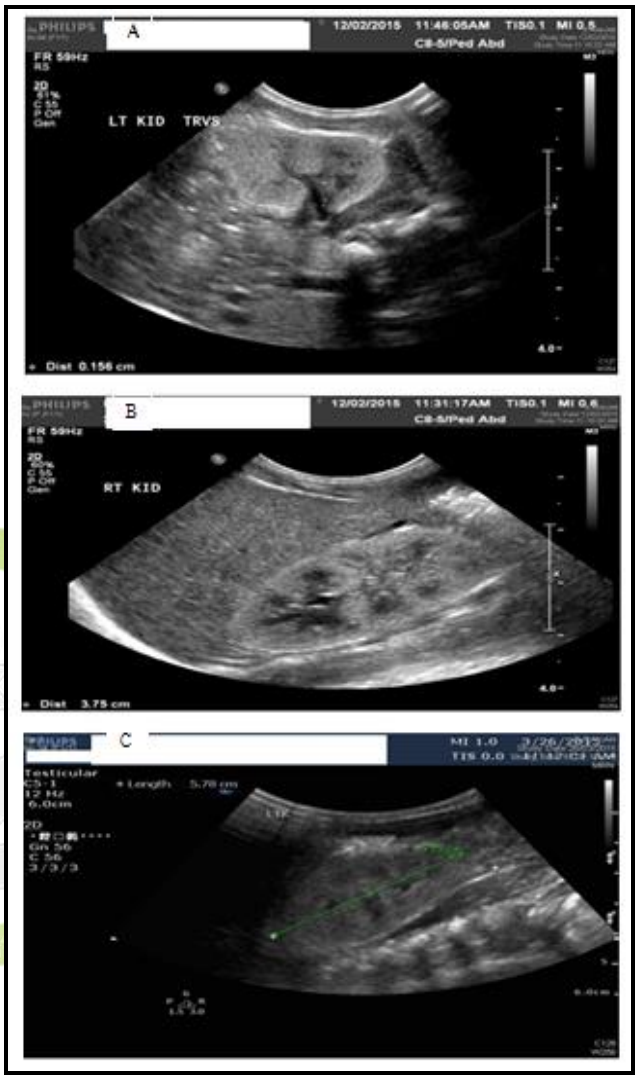

Figure 1: Shows A: Left kidney, B: right kidney, C: testis

At that time of hypotension, a blood sample for serum cortisol, ACTH, 17 OH progesterone, PRA and aldosterone was withdrawn and patient was started on hydrocortisone. The cortisol level came to be 1049nmol/L, ACTH 8.1pmol/L (1.1-13.2) and 17 OH progesterone 3.2 ng/ml (< 5.2). In view of the normal serum cortisol, 17 hyroxy-progestrone and ACTH, congenital hypoaldosteronism, familial hyperreninemic hypoaldosteronism and pseudohypo aldosteronism were considered. So, hydrocortisone was discontinued and

fludrocortisone 100 mcg was started in addition to oral sodium polystyrene and sodium chloride.

On the next day, the inotropes were tapered gradually over few days till completely discontinued and the patient maintained his blood pressure within normal range. During follow-up, serum sodium improved (135–141) mEq/L, potassium varied between 4.8 and 6.7 mEq/L with bicarbonate around 20 mEq/L. Few weeks later, the aldosterone level came to be 304 pmol/L (139 - 3660) and PRA 2720 pmol/L (0.14 -1.9) as shown in Table 1. Results showed very high PRA while aldosterone inappropriately normal. So, patient was labeled as congenital hypoaldosteronism.

DISCUSSION

The terminal steps in synthesis of aldosterone includes 11 beta-hydroxylation of 11-deoxycorticosterone to form corticosterone, hydroxylation at position C-18 to form 18-hydroxycorticosterone (18-OHB) and finally oxidation at position C-18 to form aldosterone. Aldosterone synthase is a mitochondrial cytochrome P450enzyme, CYP11B2. It is encoded by the *CYP11B2* gene located on chromosome 8, band q 24.3, approximately 40 kb away from the 93%-identical *CYP11B1* gene encoding the steroid 11-Beta hydroxylase enzyme required for cortisol biosynthesis[1,2]. Most reported patients with presumed aldosteronesynthase deficiency carry mutations in *CYP11B2*[3,4]. Inborn errors of isolated aldosterone biosynthesis have been classified as corticosterone methyl oxidase (COM) type I and II. CMO-I is characterized by decreased production of 18-OHB, an elevated ratio of corticosterone to 18-OHB and a low plasma ratio of 18-OHB to aldosterone.

CMO-II is characterized by overproduction of 18-OHB, a decreased ratio of corticosterone to 18-OHB and an elevated plasma ratio of 18-OHB to aldosterone. Plasma renin activity and corticosterone are elevated in both cases while aldosterone is decreased[5]. The clinical picture in both is similar. CAH, pseudohypoaldosteronism and familial hyporeninemic hypoaldosteronism present with similar clinical and biochemical features. Diagnosis is through multisteroid analysis[5]. Fludrocortisone is the mainstay of treatment and it has been shown to normalize plasma renin activity (PRA), 18-OHB and aldosterone levels and improve linear growth in patients with CMO-II[6,7]. Severity of the disease decreases with age[5].

Kathleen et al., 2001(8), have studied five patients in four unrelated kindreds with hyper reninemichypo aldosteronism in whom they were unable to find such mutations. All presented in infancy with failure to thrive, hyponatremia, hyperkalemia, markedly elevated plasma renin activity and low or inappropriately normal aldosterone levels. All had normal cortisol levels and no signs or symptoms of congenital adrenal hyperplasia. All responded to fludrocortisone treatment. There were no mutations detected in exonsor splice junctions of *CYP11B2*. Linkage of the disorder to *CYP11B2* was studied in two unrelated consanguineous patients and in an affected sib pair. The consanguineous patients were each heterozygous for at least one of three polymorphic microsatellite markers near *CYP11B2*, excluding linkage to *CYP11B2* (linkage of the disease to *CYP11B2*could not be excluded in the affected sib pair). Genes involved in the regulation of aldosterone biosynthesis, including those encoding angiotensinogen, angiotensin converting enzyme and the AT1 angiotensin II receptor were similarly excluded from linkage. These results demonstrate the existence of an inherited form of hyperreninemic hypoaldosteronism, which they have termed familial hyperreninemic hypoaldosteronism-2 (FHHA2), distinct from aldosterone synthase deficiency (thus termed FHHA1)[8].

Our patient presented with severe hypotension, hyponatremia and hyperkalemia. We therefore, investigated further and began by ruling out the commonest cause of salt-wasting in neonates which is congenital adrenal hyperplasia. Serum cortisol, ACTH and 17 OH-progesterone were within normal limits. Hence, serum aldosterone and PRA were measured in order to differentiate between pseudohypo aldosteronism and isolated aldosterone deficiency. An inappropriately normal aldosterone level and high PRA were

seen despite concurrent hyperkalemia and hyponatremia. So, the *CYP11B2* defect was therefore considered and simultaneous aldosterone, Corticosterone and 18-OHB levels were estimated to differentiate between COM-I and COM-II.

18-OHB/aldosterone ratio was 1.44 which confirm COM-I. Peter *et al*., 1996[9] studied 16 infants with congenital hypoaldosteronism and concluded that decreased aldosterone with low 18-OHB and 18-OHB/ aldosterone <10 was confirmatory of CMO-I deficiency. Genetic analysis has shown no mutation in C*YP11B2* gene. In classical CMO I deficiency, the serum aldosterone is undetectable[8].

CONCLUSION

Our patient had severe hypotension and hyperkalemia while *CYP11B2* mutation was not detected. So, he may have a form of hyperreninemic hypoaldosteronism distinct from aldosterone synthase deficiency and the affected gene(s) remain to be determined. Further homozygosity mapping is needed to ascertain the precise nature of the mutation.

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