Secondary pseudohypoaldosteronism caused by urinary tract infection associated with urinary tract anomalies: case reports

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Secondary pseudohypoaldosteronism type 1 develops due to transient aldosterone resistance in renal tubules and is characterized by renal sodium loss, hyponatremia, hyperkalemia and high plasma aldosterone levels. Although many reasons are described, urinary tract infections and/or urinary tract anomalies are the most common causes. Although the cause of the tubular resistance is not known exactly, renal scar development due to obstruction and reduced sensitivity of mineralocorticoid receptors due to cytokines such as transforming growth factor (TGF)-β are the possible mechanisms. It is seen especially within the first three months of life and the frequency decreases with age. The treatment is usually elimination of the underlying cause. In this article, we present four patients with several urinary tract anomalies and concomitant urinary tract infection who developed transient secondary pseudohypoaldosteronism.

Key words: urinary tract infection, urinary tract anomalies, secondary pseudohypoaldosteronism.

Pseudohypoaldosteronism type 1 (PHA-1) is a salt-losing syndrome that occurs as a result of the unresponsiveness of renal tubules to aldosterone. It is characterized by dehydration, inability to gain weight, hyponatremia, hyperkalemia, metabolic acidosis, and increased plasma aldosterone levels and plasma renin activity. Primary PHA-1 is a hereditary disease due to mutation of epithelial sodium channel or mineralocorticoid receptors, but secondary (transient) PHA-1 is usually associated with urinary tract anomalies and/or urinary tract infections (UTIs)[1,2]. Here, we present four infants with secondary PHA-1 due to urinary tract anomalies in association with UTIs.

Case Reports

Case 1

A four-month-old girl presented with dilatation of the left renal collecting system detected during the antenatal period and persisting in the postnatal examinations. Previous imaging studies revealed grade 1-2 ectasia on the left kidney by abdominal ultrasonography (USG), absence of vesicoureteral reflux (VUR) by voiding cystourethrography (VCUG) and non-obstructive dilatation of the left kidney and ureter by mercapto acetyl triglycine scintigraphy. Physical examination was normal. Dipstick examination revealed pyuria and presence of nitrite, while microscopic examination showed >100 white blood cells (WBC)/high-power field (hpf), and 10^5 col/ml *Escherichia coli* was recovered in the urine culture. The initial blood chemistry yielded normal liver and kidney functions, but hyponatremia and hyperkalemia were detected (Table I). Magnetic resonance (MR) urography showed hydronephrosis and megaureter on the left kidney. These findings suggested non-obstructive uropathy and secondary PHA-1 caused by UTI. Plasma renin activity (PRA) and plasma aldosterone level were highly elevated (Table I). After treatment of the UTI, serum sodium (137 mmol/L),

Table I. Clinical, Biochemical and Hormonal Features of the Patients

	Case 1	Case 2	Case 3	Case 4
Sodium (mmol/L)	129	131	130	123
Potassium (mmol/L)	5.7	6.3	6.2	7.2
Bicarbonate (mmol/L)	18	20	19.5	15.8
Plasma renin activity (ng/ml)[1]	150	126	3.9	145
Aldosterone (pg/ml)[2]	5000	1772	1400	>3000
Fractional Na excretion (%)	6.8	5.4	4.8	5.2
Urinary malformation	Hydronephrosis	PUV	VUR	VUR
Urinary tract infection	+	-	+	+

1 range 2.4-37 ng/ml
2 range 50-900 pg/ml
PUV: Posterior urethral valve. VUR: Vesicoureteral reflux.

potassium (4.4 mmol/L) and aldosterone (340 pg/ml) levels and PRA (3.8 ng/ml) were normalized. Thus, the patient was considered to have transient PHA-1 caused by UTI in association with non-obstructive urinary tract dilatation.

Case 2

A preterm male infant born at the 33rd week of gestation was admitted to the hospital due to posterior urethral valve (PUV) detected at the 24th week of gestation. A vesicoamniotic shunt had been placed at the 31st gestational week. The physical examination was normal. Abdominal USG showed bilateral pelvicaliceal and ureteral dilatation in addition to increased bladder wall thickness. PUV resection was performed on the postnatal 8th day. One week later, his biochemical tests showed serum creatinine of 1.76 mg/dl and blood urea nitrogen (BUN) of 13.6 mg/dl. Other laboratory tests disclosed low serum sodium, hyperkalemia, elevated fractional sodium excretion, and mildly decreased plasma HCO_3, and high PRA and plasma aldosterone levels (Table I). His urine culture was sterile. He was considered to have secondary PHA-1 caused by obstructive uropathy. He was treated first with intravenous (IV) saline and then oral sodium replacement was started. One month later, laboratory tests revealed serum sodium of 138 mmol/L, potassium of 5.6 mmol/L and aldosterone of 1555 pg/ml. At one year of age, he was detected to have UTI and persistence of elevated aldosterone level. Re-evaluation due to recurrent UTI and persistent hyperaldosteronism disclosed remnant PUV, and complete PUV resection was performed. As the patient was lost to follow-up, further assessment of serum aldosterone and electrolytes could not be performed.

Case 3

A three-month-old boy presented for evaluation of antenatally detected hydronephrosis. Although vesicoamniotic shunt had been placed for PUV antenatally, no PUV had been detected by cystoscopy at the postnatal 5th day, leading to the removal of the shunt. In the same period, VCUG revealed grade V VUR on the right and grade II VUR on the left. ^{99m}Tc-dimercaptosuccinic acid renal scintigraphy showed decreased uptake on the right. He also had a history of recurrent UTIs. Physical examination was normal except for anthropometric developmental delay. The laboratory evaluation yielded creatinine of 0.6 mg/dl, BUN of 9 mg/dl, low serum sodium and HCO_3, high serum potassium, aldosterone, and PRA, and presence of UTI (Table I). He was considered to have secondary PHA-1 caused by non-obstructive uropathy (VUR) and UTI. The blood chemistry values were normalized after treatment of the UTI.

Case 4

A 37-day-old girl presented for evaluation of meningomyelocele. Her history was characterized by the presence of meningomyelocele and flaccid paralysis of the lower extremities. Physical examination was marked by growth retardation, meningomyelocele sac in the sacral region and absence of deep tendon reflexes in the lower extremities. Laboratory test results were as follows: urine specific gravity 1005, pH 6.0, protein 0.3 g/L, 4-5 WBC/hpf; hemoglobin

12 g/dl, platelets 310,000/mm^3, leukocytes 29,000/mm^3, creatinine 0.5 mg/dl, BUN 40 mg/dl, low serum sodium and HCO_3, and high serum potassium, plasma aldosterone level and PRA (Table I). Her urine culture revealed 10^5 col/ml *Klebsiella pneumoniae*. Urinary system USG was normal and VCUG showed grade 1 reflux on the left. She was considered to have secondary PHA-1 associated with UTI. She was given antibiotics for UTI and IV sodium replacement for hyponatremia. After treatment of the UTI, serum sodium (136 mmol/L), potassium (3.6 mmol/L) and aldosterone (102 pg/ml) levels and PRA (3 ng/ml) normalized.

Discussion

Aldosterone is involved in sodium reabsorption and potassium secretion in the distal tubules. Disorders that affect renal tubules or the renin-angiotensin-aldosterone system may lead to electrolyte imbalance[3]. Secondary PHA-1 is due to the temporary aldosterone resistance and usually develops in association with UTI and/or urinary tract anomalies[4,5]. Systemic lupus erythematosus, sickle cell anemia, acute renal allograft rejection, and chronic allograft nephropathy are among the other causes[4]. In a recent literature review of 93 patients with secondary PHA-1, 84 patients had obstructive uropathy including PUV (n=16), ureteropelvic junction obstruction (n=12), ureterovesical junction obstruction (n=9), VUR (n=33), and other pathologies (n=14). Seventy-five (89%) of these 84 patients also had UTI, while nine had only obstructive uropathy. On the other hand, nine patients had only UTIs without obstructive uropathy[6]. All four of our patients had urinary tract anomalies including non-obstructive megaureter, PUV and VUR (n=2). Furthermore, three (75%) of them also had UTI.

The pathophysiology of secondary PHA-1 is still unknown. Aldosterone resistance in renal tubular cells is a possible mechanism[7]. The underlying cause of tubular resistance could be associated with decreased sensitivity of mineralocorticoid receptors due to cytokines like transforming growth factor (TGF)-β and parenchymal scarring secondary to obstruction[8].

The risk of developing secondary PHA-1 in infants younger than three months of age is higher due to tubular immaturity[7,9]. The prevalence is dramatically decreased after three months of age[4,5]. Ninety percent (81/90) of reported cases were under three months[6]. In a study of 60 cases with secondary PHA-1, all cases were less than seven months of age[8]. All of our patients were less than four months.

Pseudohypoaldosteronism type 1 (PHA-1) is characterized by renal sodium loss, hyponatremia, hyperkalemia, and increased renin and aldosterone levels. Because of hyponatremia and hyperkalemia, the differential diagnosis should include congenital adrenal hyperplasia, isolated aldosterone synthase deficiency and adrenal insufficiency[1,2]. On the other hand, as transient tubular mineralocorticoid resistance can develop in infants with urinary tract malformation or UTI, all children presenting with hyperkalemia and salt loss should be evaluated by renal USG and urine culture[2]. Determination of hormone levels and normalization of serum electrolytes after treatment of UTI and/or urinary malformation exclude these diseases and confirm the diagnosis of secondary PHA-1[1].

The treatment of PHA consists of 0.9% sodium chloride infusion, normalization of potassium levels, antibiotic therapy, and surgical intervention when indicated (relief of urinary obstruction)[10]. Furthermore, it has been reported that large amount of saline infusion might prevent the development of metabolic imbalance in small infants with urinary tract malformation and/or pyelonephritis[9]. On the other hand, as partial reduction of aldosterone sensitivity in the distal tubules may continue for a long time, monitoring of serum electrolytes for at least one year is recommended after surgical correction of urinary tract anomalies[7]. In three of our cases, the treatment of the UTI alone improved the clinical picture of PHA-1. In two of our patients, saline infusion was required. In one patient, high plasma aldosterone level persisted for more than one year after PUV resection. However, it was understood that this situation resulted from incomplete resection of the PUV.

In conclusion, serum electrolyte levels should be closely monitored in infants with urinary

malformation and/or UTI; infants with UTIs should be closely followed for the development of UTI and they should be treated promptly if an infection occurs. On the other hand, long-term follow-up of the serum electrolyte and aldosterone levels is required after the surgical treatment of urinary malformations in these patients.

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