CASE SERIES

A potential serious complication in infants with congenital obstructive uropathy: Secondary pseudohypoaldosteronism

Sabriye Korkut,[1] Leyla Akin,[2] Nihal Hatipoglu,[3] Ahmet Özdemir,[4] Zübeyde Gündüz,[5] Ismail Dursun,[6] Levent Korkmaz,[7] Selim Kurtoglu[8]

Abstract

Patients who have secondary pseudohypoaldosteronism (PHA) in addition to hyponatraemia, hyperpotassaemia and high serum aldosterone levels for the age were included in this retrospective study.Among eight patients, seven patients were diagnosed with PHA secondary to obstructive uropathy (OUP), whereas one patient had PHA secondary to ileostomy. Six patients with OUP had simultaneous urinary tract infection (UTI) and in all except one patient, secondary PHA recovered with only UTI treatment before applying surgical correction. All the patients were younger than 3 months age. In three patients with PUV diagnosis, salt wasting recurred in an UTI episode under 3 months of age.

Keywords: Obstructive uropathy,salt wasting, Ileostomy, Secondary pseudohypoaldosteronism, Urinary tract infection, Prune Belly syndrome.

Introduction

Salt wasting crisis is a life threatening emergency which is characterized by hyponatraemia and hyperpotassaemia in the presence of dehydration. Among the most common causes of salt wasting crisis are congenital adrenal hyperplasia(CAH), isolated aldosterone deficiency, and peripheral resistance to aldosterone.[1]

Pseudohypoaldosteronism (PHA) is a disease characterized by renal tubular unresponsiveness to aldosterone. Genetically caused primary (type 1 and type 2) and transient secondary forms exist.[1] Secondary PHA is a transient aldosterone resistance condition mostly occurring in relation with urinary tract infection and/or malformations and its laboratory characteristics are similar to primary PHA1. Many kinds of congenital obstructive uropathies (OUP) (ureteropelvic junction obstruction, ureterovesical junction obstruction, posterior urethral valves, ureterocele) may cause PHA. More rarely, it has been reported that systemic lupus erythematosus, sickle cell nephropathy and, in adults, colon/ileum resection, ileostomy and renal allograft rejection may be the cause of secondary PHA.[2-4] Some drugs may also cause mineralocorticoid resistance.[1,2]

Secondary PHA cases and very few case series have been reported in the literature.[2,5-7] In this article, we report 8 infants including a different clinical presentation which has not as yet been reported in the literatüre and their follow-ups.

Case Series

The study was approved by Erciyes University Faculty of Medicine Ethics Committee.

Hyponatraemia, hyperpotassaemia and high serum aldosterone levels were present in all cases. All patients had OUP except for patient 8. All patients had UTI at diagnosis, except for patients 4 and 8. Patient 2 and 3 were initially treated with hydrocortisone and fludrocortisone due to an initial suspicion of CAH.

The clinical, laboratory and imaging characteristics are summarized in Table-1 and applied treatments are summarized in Table-2.

Patient 1: Serum electrolyte levels normalized on the eighth day of hospitalization. After that, additional salt supplementation was not required. On the postnatal 50th day, the patient was discharged. Although urinary infection relapsed at the follow-up visit, but salt wasting did not. Growth was normal when the patient was seven years old.

Patient 2: The patient was discharged 17 days after being admitted in the unit. Salt supplementation was discontinued in the sixth month. In the final follow-up at 18 months age, growth was within normal limits.

Patient 3: 20mEq/day NaCl was given in gradually decreasing amounts and was completely stopped at the end of a week. The patient was discharged after 11 days of hospitalization. In the final follow-up visit, the patient was one year old, weight was < 3 percentile, height was

[1,4,7,8]Department of Neonatology, [2,3]Department of Pediatric Endocrinology, [5,6]Department of Pediatric Nephrology, Erciyes University Medical Faculty, Turkey.

Correspondence: Sabriye Korkut. Email: sabriyeyaman@hotmail.com

Table-1: Characteristics of the study population.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Gender	M	F	F	M	M	M	M	F
Age at presentation (days)	33	29	72	2	2	22	40	27
Symptoms at presentation	Fever Bloody urine Sucking weakness	Sucking weakness Weight loss	Sucking weakness Failure to thrive	Prenatal diagnosis of multicystic kidney Prematurity	Prenatal diagnosis of PUV	Fever Sucking weakness	Fever Sucking weakness	Sucking weakness, failure to thrive
S sodium (mEq/L)	119	113	113	118	129	118	114	128
S potassium (mEq/L)	6.2	10.2	7.6	8.6	6.4	6.2	8.1	6,5
S BUN (mg/dL)	35	136	52	37	19	74	28	9
S creatinine (mg/dL)	1.3	3.7	1.5	2.9	1.6	3.2	0.8	0.7
S aldosterone (pg/mL)	2250	11610	6200	2680	1253x	3095	3500	4396
PRA (ng/mL/saat)	NA	NA	16.5x	38.05	5.8x	2.1x	45.9	33.2
U Na/K (mEq/L)	60/8.7	NA	20/2.4	93/NA	46/8.2	39/0.8	20/8.1	2/10.8
Urine microscopy and/or culture at admission	Pyuria polymicrobial	Pyuria C.albicans	Pyuria	Sterile	Pyuria E.coli	Pyuria Klebsiella/E.coli	Pyuria E.coli	Sterile
Urinary USG and/or VCUG	Right pelviectasis, left dublicated collecting system, PUV	Left grade 4 VUR	Right grade 4 VUR	Bilaterally grade 5 VUR, right multicistyc kidney, patent urachus, megacystis	PUV	PUV	PUV	Normal

M : Male. F: Female. S: Serum. U: Urine. BUN: Blood Urea Nitrogen. PRA: Plasma Renin Activity. VUR: Vesicoureteral Reflux. PUV: Posterior Urethral Valve.
NA: Not Available. USG: Ultrasonography. VCUG: Voiding Cystourethrography.
x It was obtained after 7-10 days from the beginning of salt supplementation,
Aldosterone reference range : 7th day (50-1750 pg/mL), 1-11 months (50-900 pg/mL), PRA reference range : 0-3 age (<16.6 ng/mL/hour).

25-50 percentile.

Patient 4: In the prenatal 27th week, bilateral multicystic kidney, megaureter and patent urachus were detected. The patient was evaluated as having Prune Belly syndrome (PBS). Salt wasting was observed starting from the second day. It was not impossible to stop the salt supplementation, and the patient died due to renal failure and sepsis on the 18th day.

Patient 5: On the 34th day postnatal, the patient was discharged. When the patient was 3 months old, salt supplementation was gradually decreased. PUV ablation was applied when the patient was 2 years old. On the final visit the patient was five years old and growth was within normal limits.

Patient 6: Serum electrolytes were normalized on the 8th day of the follow-up. The patient was discharged when 44 days old. The patient was re-hospitalized due to urinary tract infection (E.coli) and hyponatraemia at 62 days age. After treatment of infection, serum electrolytes normalized and salt supplementation was discontinued. The patient was five years old at the final follow-up visit, weight and height were <3rd percentile.

Patient 7: No additional sodium supplementation was initially required. On the 16th day of the follow-up, pyuria, hiponatraemia, hyperkalaemia, and metabolic acidosis were detected during hospitalization. Electrolyte abnormality recovered 24 hours later with treatment and salt suplementation was stopped. Growth was normal at 6 months old.

Patient 8: On the postnatal 10th day, an operation was performed due to necrotizing enterocolitis. An ileostomy was performed by removing the last 30 cms of the ileum. In the control a week after discharge (on postnatal 27th day), hyponatraemia and hyperpotassaemia were detected. Serum electrolyte levels were normalized on

Table-2: Treatment modalities during hospitalization and at the time of discharge.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Treatment during hospitalization	IV/oral salt Antibiotic PUV ablation	Hydrocortisone* Fludrocortisone* Hyperkalaemia treatment IV/oral salt Antibiotic	Hydrocortisone* Fludrocortisone* IV/oral salt, Antibiotic	IV salt, Hyperkalaemia treatment	IV/oral salt Antibiotic Vezicostomy	IV/oral tuz Antibiotic Ureterostomi	IV salt Hiperkalaemia treatment Antibiotic	IV/oral salt
Treatment at the time of discharge	Antibiotic	Oral salt (4x250 mg NaCl) Antibiotic	Antibiotic	exitus	Oral salt (4x250 mg NaCl) Antibiotic	Oral salt (2x250 mg NaCl) Antibiotic	Antibiotic	Oral salt (4x250 mg NaCl)
Duration of salt supplementation	3 days	6 months	7 days	exitus	3 months	55 days	3 days	1 months

IV: Intravenous. PUV: Posterior Urethral Valve.
* It was administered until hormone level results are acquired.

the third day of treatment. The ileostomy was closed and on the 13th day of hospitalization, the patient was discharged. At the age of one month, salt supplementation was completely stopped. Growth was normal at the age of four years.

Discussion

Among the eight patients in our case series, patients 1,2,3,5,6 and 7 were diagnosed with PHA secondary to OUP together with UTI. In all except one patient, secondary PHA recovered with UTI treatment before applying surgical correction. Patient 4 was diagnosed with PHA secondary to OUP without UTI and patient 8 was diagnosed with PHA secondary to ileostomy.

Severe hyponatraemia, hyperkalaemia, hyperreninaemia and, paradoxially, significant high plasma aldosterone concentration are present in pseudohypoaldosteronism and urinary sodium loss is significant. Urinary sodium level may be affected by serum sodium level and the amount of salt supplementation. Therefore urine Na/K rate may reflect aldosterone tubular effectiveness better. The normal urine Na/K rate is nearly 2 in children. In PHA cases, this rate was found to have increased in a way to reflect tubular unresponsiveness to aldosterone.[8] In our study, apart from patient 8 whose urine sodium was low and patient 2 whose urine electrolyte records couldn't be reached, the urine Na/K rates of all patients were found to have increased. Although the clinical and laboratory characteristics of primary type 1 PHA and secondary PHA are similar, their management and prognosis are very different. Therefore, in patients diagnosed with PHA, the differentiation of primary/secondary PHA should be made initially. Secondary PHA is often associated with urinary system infection and/or malformations. In infants with OUP, UTI may not always be present during sodium deflection. However, in these patients it is known that a UTI episode precipitates salt loss significantly. Therefore, in order to be able to make secondary/primary differentiation in a patient with a PHA1 picture, evaluation with urine culture and urinary USG are very important.[2] There has not as yet been any report on whether obstructive uropathologies being bilateral or unilateral can affect PHA development risk. In this study, unilateral VUR in patient 2 and 3 and PUV in patients 1, 5, 6 and 7 were detected.

The mechanism underlying tubular unresponsiveness to aldosterone in obstructive uropathy is not definitely known. During the course of urethral obstruction, inflammatory changes developing in the renal parenchyma may cause tubular interstitial fibrosis in different degrees and decrease in the number of nephrons.[9] In our study, in the other 6 patients with OUP, except for patient 4 (died when 18 days old), UTI was present when salt loss was found. The point we would like to emphasize is that salt wasting recovers only with UTI treatment before surgical correction. Except for patient 5 who underwent a vesicostomy, salt wasting recovered in the other patients of our patient group before surgical correction.

In a patient with PHA, impaired renal function may be a warning for PHA secondary to obstructive uropathy. However, it should not be forgotten that prolonged dehydration in the first evaluation in primary PHA1 may also result in impaired renal functions. In our study, the other six OUP patients, apart from patient 7, had impaired renal function.

PBS is observed in 1/40000 live births, the most important

factor determining prognosis is the severity of urinary system involvement.Renal parenchyma damage develops due to infection or obstruction and contributes to the development of aldosterone resistance in the renal tubules. PBS cases in which salt wasting developed have been reported in the literatüre.[10] Patient 4 was diagnosed with PBS. Renal failure and salt wasting developed on the first few postnatal days and she died when 18 days old due to renal failure and sepsis.

Cases in which OUP and/or urinary tract infection(UTI) was related with transient mineralocorticoid resistance have been reported in the literature in infants aged younger than 7 months age.[2,8] In terms of prevalence of secondary PHA occurring due to renal causes, there is in fact, a severe decrease after postnatal third month. This situation has been explained by renal immaturity which facilitate the aldosterone resistance in newborn and early infancy.[2] Breast feeding with mother's milk which has low sodium content makes newborns more sensitive to sodium deficiency. Melzi et al. investigated 50 15 day-15 month old pyelonephritis cases with and without OUP and reported that all of the patients with salt wasting picture were younger than 3 months age and it occurred together with OUP. In infants over 3 months with and without OUP, salt wasting did not occur in pyelonephritis attacks.[8] All of our patients were younger than 3 months age, as in the literature. Except for patient 4, the other six patients with OUP had an urinary tract infection during salt wasting. Salt wasting became more significant with recurrent urinary tract infection in patient 6. In patients 5, 6 and 7 with PUV diagnosis, salt wasting recurred in an UTI attack which occurred at under 3 months of age. Although they had an UTI attack in later follow-ups, salt wasting did not develop.

In ileostomized patients in whom a small intestine resection was applied, it is well known that too much stomal water and sodium losses result in secondary hyperaldosteronism.[11,12] Case reports in which PHA developed instead of hyperaldosteronism after ileum and colon resection in adults are present in the literatüre.[3,4,13] To the best of our knowledge, patient 8 is the first case in the literature in whom PHA was demonstrated after ileal resection and ileostomy in a newborn with diagnosis of necrotizing enterocolitis. In the referral of patient 8, 17 days after the operation, hyponatraemia, hyperpotassaemia and high aldosterone levels were present. These findings supported PHA but low urine Na level was in line with common hyperaldoteronism condition after ileostomy losses. Vantygham et al. suggested the idea that hyperkalaemia occurred in these patients because aldosterone could not provide potassium discharge due to a significant decrease in renal tubular sodium.[3] However as they stated, the urinary sodium and potassium concentration of the patient they reported (25 and 100 mmol/L, respectively) were not in line with this hypothesis. The fact that urinary sodium was too low in our case seems to support the hypothesis suggested by Vantygham et al. Despite the high aldosterone level in patient 8, our hypothesis on hyperpotassaemia is based on the flow related regulation of potassium secretion. In the aldosterone-sensitive distal tubules, the apical membrane potassium channels (BK and ROMK channels) maximize potassium excretion when too much potassium is absorbed from the diet but in the case of intravascular volume depletion (as in patient 8), the channels limit potassium excretion despite high aldosterone.[14]

The main treatment in secondary PHA is medical and/or surgical treatment of the underlying disease. Initially, in addition to treating hyperkalaemia and acidosis, replacement of salt wasting and rehdyration are also required. The amount of sodium needed is related to the severity of the symptoms and normalization of plasma potasium concentration and plasma renin level. Salt loss is supplemented by giving NaCl, HaHCO3 and 3-20 mEq/kg/day sodium by giving NaCI or NaHCO3 in secondary PHA.[1] Fluid and electrolyte resuscitation was applied to all of our cases after referral to hospital. In our case group, salt supplementation was made with IV/oral NaCl of at least 3 mEq/kg/day and with at most 32 mEq/kg/day. NaHCO3 was preferred for sodium supplementation in patients with metabolic acidosis.

In secondary PHA, there are no clear data on the duration of salt supplementation requirement. After medical or surgical treatment of primary disease in these patients, the aldosterone response becomes normal and laboratory findings recover in a few days.[3,15] However in some infants, partial tubular resistance to aldosterone may continue for three years after early correction of congenital urinary tract obstruction but major risks occur in the first year.[4] An interesting point is the fact that aldosterone response normalized with UTI treatment before the application of surgical correction in all of our OUP patients except for patient 5 in our case group. When sodium wasting decreased in our patients whose serum sodium level became normal, the salt supplementation need was reconsidered and was cut by gradually decreasing it. Salt supplementation was cut before discharge in three patients (patients 1,3,7). Belot et al. reported long salt supplementation of nearly 11 and 12 months in patients in whom PHA developed secondary to pyelonephritis.[15] The longest salt supplementation of our

cases lasted 6 months (patient 2).

All patients with hyperpotassaemia underwent electrocardiography monitoring. Only 3 patients (patients 2,4,6) initially received antipotassium treatment for 1-2 days.

In newborns referred with salt wasting crisis, replacement treatment with fludrocortisone and hydrocortisone may be given until differential diagnosis from congenital adrenal hyperplasia is made.[1] When patient 2 and 3 were referred with salt wasting, they initially underwent hydrocortisone and fludrocortisone treatment until the hormone tests results were obtained. CAH is the first prediagnosis which comes to mind in a newborn presenting with salt wasting crisis as in this case, and commonly CAH treatment is administered until hormone level results are acquired.[3,10]

However we would like to point out that steroid use is not safe in patients with infection. For example, Candida albicans was reproduced in the urine culture taken during hospitalization from patient 2 who was initially given steroid treatment for 4 days. If the steroid treatment had been continued, it could have resulted in sepsis and death. In such cases, aldosterone level should also be requested together with 17 hydroxyprogesterone level for CAH screening and diagnosis delays should be prevented. CAH may present with enlarged and cerebriform adrenal gland. Therefore, in addition to renal USG, adrenal gland USG can help in the differentiation of CAH and OUPs.

Conclusion

PHA should be considered in the differential diagnosis in patients referred with salt wasting crisis in the newborn and early infancy period. In the initial evaluation of patients referred with salt wasting crisis, the aim should be to exclude the reasons which might be responsible for secondary PHA. Therefore, urine analysis and renal/adrenal gland ultrasonography should be considered first. On the other hand, infants known to have OUP should be closely observed for salt wasting in the presence of urinary tract infection, especially in the early infancy period.

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