



Clinical Course and Follow-Up of Type 1 Pseudohypoaldosteronism

ORIGINAL
ARTICLE

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ABSTRACT

Objective: This study aimed to evaluate the management of primary pseudohypoaldosteronism type 1 (PHA1), which is a rare disease.

Materials and Methods: We retrospectively reviewed the hospital records of patients who were followed up with a diagnosis of primary PHA1.

Results: Of the eight patients diagnosed with primary PHA1, two had renal PHA1 and five had systemic PHA1. Five patients were initially administered steroids until a definite diagnosis was made. One patient was initially misdiagnosed with congenital adrenal hyperplasia due to “the high-dose hook effect”. In patients with systemic PHA1, the highest salt requirement was 32–53 mEq/kg/day, which gradually decreased in all patients. Salt supplementation could not be stopped in patients with systemic PHA1 except one patient. Four of the eight patients died.

Conclusion: After excluding the causes that may lead to secondary PHA in the initial evaluation of patients referred with a salt-depletion crisis, a differential diagnosis of congenital adrenal hyperplasia and PHA1 should be made. The hook effect and interference probabilities should be considered for evaluating hormone levels.

Keywords: Pseudohypoaldosteronism type 1, salt-depletion crisis, aldosterone, treatment

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INTRODUCTION

Aldosterone increases sodium (Na) and water reabsorption against potassium (K) discharge in the distal tubules in the kidney. Hyponatremia, hyperpotassemia, hypovolemia, and metabolic acidosis occur with a clinical presentation similar to that of pseudohypoaldosteronism (PHA), where there is a peripheral resistance to aldosterone activity or aldosterone deficiency (1). Aldosterone resistance may be due to primary or secondary causes. Primary PHA occurring due to genetic causes is classified into two different syndromes: type I PHA and type II PHA (2, 3).

Patients with PHA type I (PHA1) may have autosomal recessive or dominant inheritance. The autosomal dominant form, also called renal PHA1, is characterized by isolated aldosterone receptor resistance and causes renal salt-depletion. Apart from the kidney, aldosterone resistance is also seen in the sweat glands, distal colon, lungs, reproductive organs, and salivary glands in the form of autosomal recessive inheritance, which is known as systemic PHA1. Thus, it has a more severe clinical course than renal PHA1 and does not recover with time, similar to the renal type (4, 5).

PHA type II (PHA2) is also known as Gordon syndrome or familial hyperkalemic hypertension. It presents with salt retention instead of salt-depletion, mild hyperchloremic metabolic acidosis, hyperpotassemia, and hypertension. The plasma aldosterone level is normal or high, and plasma rennin activity (PRA) is low. It generally becomes symptomatic during adolescence (1, 4).

Although there are case reports on PHA1 in the literature, only few case series are available. In our study, we focused on the clinical management and long-term follow-up of patients with PHA1 who were followed up at our department of pediatrics.

MATERIALS and METHODS

Approval was obtained from the Ethics Committee, Faculty of Medicine, Erciyes University, before starting the study. We included eight patients who were followed up with a primary PHA1 diagnosis between October 1995 and October 2015 at Child Health and Diseases Department, Faculty of Medicine, Erciyes University. The clinical

features and laboratory results were retrospectively reviewed from the patients' records.

Clinical and laboratory findings and diagnoses for the patients were re-evaluated by two different pediatric endocrinologists. Among the patients who had primary PHA1, those who had high chloride levels in the sweat test (sweat chloride reference range: 33.9 ± 10.2 mEq/L) or high salivary Na level (saliva Na reference range: 33.1 ± 13.4 mEq/L) were evaluated as having systemic PHA1 and those who had normal sweat chloride level or normal salivary Na level were evaluated as having renal PHA1.

Salivary Na level was measured from the saliva collected from the sublingual area. All the serum hormone levels and serum and urine electrolytes were measured in accordance with the manufacturer's recommendations using commercial kits. Plasma samples for measurements of aldosterone levels and PRA were obtained in the supine position.

The study was reviewed and approved by the local ethics committee (28.08.2015–2015/378) and was conducted in accordance with the ethical standards of the Institutional National Research Committee and the Declaration of Helsinki (1964) and its later amendments.

Given the retrospective and observational nature of this study, informed consent from the parents of each neonate was not considered necessary by our local ethics committee.

Statistical analysis

The variables were investigated using visual and analytical methods (Shapiro–Wilk test) to determine whether or not they were normally distributed. While examining the associations between normally distributed variables, the correlation coefficients and their significance were calculated using the Pearson test and were expressed as “r.” $p < 0.05$ was considered as statistically significant for all the tests.

RESULTS

The clinical and laboratory characteristics of eight patients who were diagnosed with primary PHA are summarized in Table 1. There was a negative correlation between plasma sodium and aldosterone levels in seven patients with primary PHA at admission ($r = -0.73$, $p = 0.03$) (Figure 1).

Hydrocortisone and fludrocortisone treatment was initially started in four patients with CAH prediagnosis. Hospitalization duration and treatments received during hospitalization, discharge, and last follow-up are summarized in Table 2.

Table 1. Clinical, laboratory, and imaging characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Gender	male	male	male	male	male	female	female	male
Age at presentation	7 days	29 days	9 days	10 days	7 days	31 days	7 days	45 days
Symptoms at presentation	diarrhea, weight loss, sucking weakness, vomiting,	diarrhea, vomiting, weight loss	diarrhea, sucking weakness, rash, ocular discharge	sucking weakness, rash	icterus, sucking weakness	weight loss	rash, ocular discharge, weight loss	womiting, poor growth, ocular discharge
S sodium (mEq/L)	135	110	130	116	127	123	129	103
S potassium (mEq/L)	7	6.8	6.9	10.1	9.7	6.7	6.6	7.1
S BUN (mg/dL)	37	42	39	32	28	6	22	20.6
S creatinine (mg/dL)	0.7	1.6	0.9	0.7	0.9	0.2	0.4	0.4
S aldosterone (pg/mL)	941	13000	5662	6980	4400	1591	>6000	(0.01)x 6490
PRA (ng/mL/hour)	NA	33	435	495	41	21	>100	166
S 17-OHP (ng/mL)	2.6	3.4	1.02	4.1	2.43	13.7	1.9	3.5
Cortisol (µg/dL)	NA	NA	2.05	15.2	8.4	18.73	30	26
U sodium/potassium (mEq/L)/(mEq/L)	87/NA	FeNa % 7.9	111/0.7	31/12	82/5.7	58/NA	31/NA	66/8.5
Saliva sodium/Sweat chlorine (mEq/L)/(mEq/L)	NA/30	NA	140/158	133/150	125/NA	35/NA	157/NA	51/55
Blood gas analysis Ph/HCO ₃ (mEq/L)	7.18/9.7	7.34/11.2	7.30/18.2	7.19/16	7.25/19	7.16/10,7	7.33/18.7	7.28/14.7
Renal/surrenal ultrasonography	normal	normal	normal	normal	normal	normal	normal	normal

S serum, U urine, BUN blood urea nitrogen, PRA plasma renin activity, 17-OHP 17-hydroxiprogesterone, NA not available, x due to hook effect
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), saliva sodium reference range: (33.1 ± 13.4 mEq/L), sweat chlorine reference range: (33.9 ± 10.2 mEq/L)

Table 2. The treatment during hospitalization and at the time of discharge of the patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Initial treatment	NaCl Indomethacin P.sulfonate Fludrocortisone	NaCl Indomethacin P.sulfonate	Fludrocortisone+ Hydrocortisone+ Dialysis NaCl P.sulfonate Indomethacin	Fludrocortisone+ NaCl P.sulfonate	Dialysis Hydrocortisone+ Fludrocortisone+ NaCl P.sulfonate	Fludrocortisone NaCl	Hydrocortisone+ Fludrocortisone NaCl	Fludrocortisone+ Hydrocortisone+ NaCl P.sulfonate
Highest salt requirement (mEq/kg/d)	18	12	40	48	53	15	50	32
Duration of first hospitalisation	5 months (exitus)	8 months (exitus)	8 months	10 months	2.5 months	7 days	3 months	2.5 months
Treatment at the discharge			NaCl (16.3 mEq/kg/d) NaHCO ₃ (4.6 mEq/kg/d) indomethacin (3x4 mg) P.sulfonate (2x1.5 g)	NaCl (14 mEq/kg/d) P.sulfonate (4x1 g) Phenobarbital	NaCl (20 mEq/kg/d) P.sulfonate (3x1g) Phenobarbital	NaCl (4.5 mEq/kg/d)	NaCl (27 mEq/kg/d) NaHCO ₃ (4 mEq/kg/d) P.sulfonate (4x3 g)	NaCl (16 mEq/kg/d) P.sulfonate (3x1 g) Fludrocortisone (1x0.1 mg)
Age and treatment at the last follow-up			12 years of age NaCl (2 mEq/kg/d) NaHCO ₃ (0.5 mEq/kg/d)	exitus when 13 months age	8 years of age NaHCO ₃ NaCl (13 mEq/kg/d)	5 years of age No treatment	exitus when 8 months age	8 years of age P.sulfonate (1x1 g)

*empirical treatment before PHA diagnosis, P.sulfonat: polystyrene sulfonate

Patient 1: The patient was evaluated as having renal PHA1. The patient was treated with a high salt supplementation of 18 mEq/kg/day and indomethacin during hospitalization. The most important problems during follow-up were frequent attacks of salt-depletion crises and infection. The patient was followed up without discharge for 5 months and died due to sepsis at the age of 5 months.

Patient 2: The patient was referred to our clinic with dehydration at the age of 29 days. The serum electrolyte levels were normalized with 100 mg/kg/day oral salt supplementation in addition to intravenous 10 mEq/kg/day Na and indomethacin treatment. It was impossible to distinguish between the renal and systemic types because the sweat test was not available. The patient was discharged at the age of 4 months. Due to severe dehydration and metabolic acidosis, the patient was rehospitalized 13 days later. The patient was hospitalized and observed for 3 months and had sepsis twice. After being rehospitalized due to a salt-depletion crisis and infection at the age of 8 months, the patient died due to sepsis.

Patient 3: The patient had a widespread rash and viscous ocular discharge. Na was found to be 109 mEq/L and K was 9 mEq/L in the blood sample taken after rehydration (on the second day after referral). Peritoneal dialysis was started due to hyperpotassemia. The patient was evaluated as having systemic PHA1. Ocular discharge and dermatitis on the skin continued. Attacks of infection frequently occurred. The patient was discharged at the age of 8 months. However, 2 weeks later, the patient was admitted to the intensive care unit due to pneumonia and salt-depletion. Peritoneal dialysis was restarted due to resistant hyperpotassemia. Conjunctivitis in the eyes and extensive hyperemic maculopapular skin rashes continued during follow-up visits. Salt supplementation was changed according to the laboratory results during the follow-ups. In the most recent follow-up, the patient was 12 years old with height and weight < 3rd percentile. The treatment was continued with NaHCO₃ (1 g/day) and NaCl (3 mEq/kg/day) on his last visit.

Patient 4: This patient needed IV Na up to 48 mEq/kg/day at the follow-up. Salt-depletion crisis developed at times despite Na supplementation. The patient was constantly observed with electrocardiography monitoring during hospitalization, and the serum electrolyte levels were measured 1–3 times/day since hyperpotassemia frequently occurred. Fludrocortisone was started due to hyponatremia and very high urine Na loss despite high Na supplementation at the

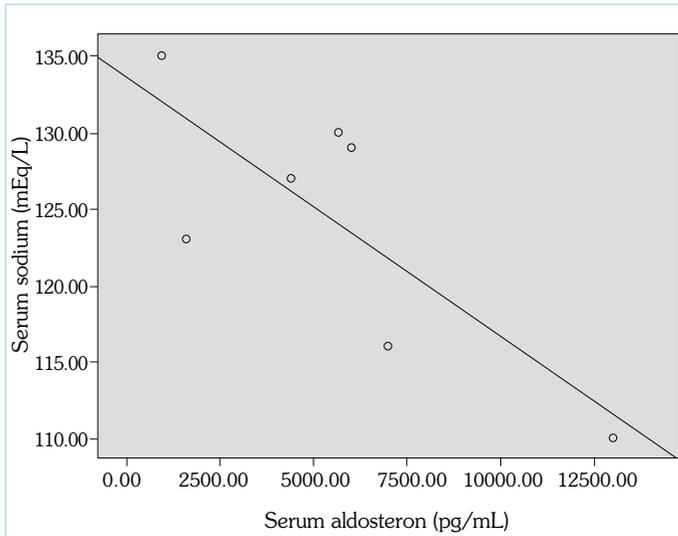


Figure 1. Plasma sodium and aldosterone levels in all patients with primary pseudohypoaldosteronism.

The negative correlation between serum sodium and aldosterone levels in the seven patients with primary PHA. ($r=-0.78$, $p=0.03$)

age of 20 days. IV fluid was stopped at the age of 47 days. Since the patient had not tolerated the salty formula, an orogastric catheter was used for feeding at times. Sepsis and pneumonia attacks frequently occurred during the follow-up. Although the salt loss was more significant with the infection present, salt-depletion crisis was also present when there was no infection. The patient had a sudden cardiac arrest due to hyperpotassemia at the age of 88 days and cardiopulmonary resuscitation was applied. After that, neurological deterioration was observed. Widespread cortical atrophy was present in the cranial magnetic resonance imaging performed at the age of 4 months. Fludrocortisone treatment was stopped at the age of 4 months. Growth was insufficient despite calories being increased in the formula. The patient was discharged with 14 mEq/kg/day Na supplement at the age of 10 months. However, the patient was admitted to the emergency service a week later due to fever. Serum Na was 181 mEq/L and urine Na was 334 mEq/L. Urinary tract infection was present. The patient was rehospitalized with pneumonia and infective endocarditis diagnosis at the age of twelve months. The body weight and height were <3rd percentile. The patient was fed with an orogastric catheter since the patient could not tolerate the salty diet. Two days after being discharged (13 months old), the patient was admitted to the emergency service due to salt-depletion crisis and died after cardiac arrest.

Patient 5: The patient was evaluated as having systemic PHA1 due to high salivary Na levels. Intravenous NaCl was increased up to 53 mEq/kg/day. Peritoneal dialysis was applied due to hyperpotassemia. The patient was discharged at the age of 12 months. The patient was rehospitalized twice due to salt-depletion crisis at the age of 1 and 4 years. Inpatient treatment was provided four times due to lower respiratory tract infection. The patient was 8 years old at the last follow-up; the body weight was <3rd percentile, height was between 3rd and 10th percentiles, serum Na level was 137 mEq/L, serum K level was 5.02 mEq/l, serum aldosterone level was 1505 pg/ml, PRA level was 4.44, and urine Na level was 178 mEq/L. The patient had normal success at school.

Patient 6: The patient was followed up in the newborn unit for 18 days due to prematurity. The serum Na level was 127 mEq/L, serum K level was 6.4 mEq/L, urine Na level was 75 mEq/L, pH was 7.16, and HCO₃ was 10.7 mEq/L on the postnatal 8th day. The patient was examined with CAH prediagnosis. Rehospitalization was required at the follow-up visit when the patient was 31 days old since the serum Na level was 123 mEq/L and serum K level was 6.7 mEq/L. The urine Na level was 58 mEq/L and serum aldosterone level was 1591 pg/ml. Cortisol and 17-OHP levels were normal. Since the salivary Na level was 35 mEq/L (primary diagnosis, PHA1), the patient was evaluated as having renal PHA. The family was screened, and the aldosterone level of the father was found to be high, serum electrolyte levels were normal, and it was learned that the patient had not been diagnosed previously. The patient, who had intravenous 15 mEq/kg/day NaCl supplementation at the beginning, was discharged on the 7th day of hospitalization with the suggestion to add salt (5 mEq/kg/day) to the formula. Salt supplementation was stopped at the age of 5 months. Patient growth was normal during the last follow-up at 5 years of age and was at the same level as the patient's twin. No treatment is currently being administered. The patient is now 8 years old; in the last follow-up, the serum level Na was 139 mEq/l, serum K level was 5.02 mEq/l, and serum aldosterone level was 2006 pg/ml.

Patient 7: The patient was referred to our hospital on the postnatal 7th day since conjunctivitis did not recover. There were pinhead-sized papules on the hyperemic ground on the skin (especially on the face), white-colored viscous ocular discharge, and macerations around the eye. Due to CAH prediagnosis, steroid treatment was also started. At the beginning, salt supplementation up to IV 50 mEq/kg/day was required. She was diagnosed with systemic PHA1 due to high salivary Na levels. Hydrocortisone and fludrocortisone were stopped. Treatment was continued with oral NaCl, polystyrene sulfonate, and NaHCO₃. Electrolyte and blood gas were followed up daily since the serum electrolyte levels can have sudden and severe changes. Convulsions were observed twice. The external auditory canal was obstructed due to Na crystals and was cleaned at intervals. The eyes were constantly cleaned due to hyperviscous secretions below the lashes, and synthetic tears were used. Skin lesions were persistent and skin care was done constantly. Gastrostomy was performed since the oral intake was not satisfactory as the salty formula was rejected. The gastrostomy was used partially for feeding and completely for oral salt treatment. The patient was discharged at the age of 3 months. Due to two episodes of pneumonia, at the age of 5 and 6 months, the patient was hospitalized. Salt supplementation was decreased (17 mEq/kg/day), and NaHCO₃ and polystyrene sulfonate were continued. The patient's body weight was <3rd percentile and the height was between the 3rd and 10th percentiles. The patient was admitted to the emergency service at the age of 8 months with salt-depletion crisis. The serum Na level was 119 mEq/kg/day and K level was 9.1 mEq/kg/day. The patient died on the same day in the intensive care unit due to cardiac arrest.

Patient 8: Hydrocortisone was started at the first referral with CAH prediagnosis. The serum 17-OHP level was normal, and the serum aldosterone level was found to be very low (0.01 pg/ml). Fludrocortisone treatment was started, considering the aldosterone synthesis deficiency, and hydrocortisone treatment was gradually decreased.

The serum aldosterone level was rechecked considering the hook effect on recurrent examinations and was found to be 6490 pg/ml. The patient, whose chloride level was high in the sweat test, was regarded as having systemic PHA1. There was viscous ocular discharge since birth. In the clinical follow-up, the patient was given NaCl-containing IV fluid treatment up to 32 mEq/kg/day and polystyrene sulfonate treatment. After being followed up for 76 days, the patient was discharged. The sweat test was repeated at the age of 15 months and the chloride level was 58 mEq/L. Rashes were observed only on the cheeks when the patient was 2 years old, and the ocular discharge had decreased significantly. There were no rashes or ocular discharge at the follow-up at 3 years of age. The patient was eight years old at the time of the most recent visit and had a body weight between the 75th and 90th percentiles and height in the 50th percentile. The serum Na level was 140 mEq/L, serum K level was 4.43 mEq/L, aldosterone level was 1941 pg/ml, and PRA level was 1.71 ng/ml/hour. The patient has normal success at school.

DISCUSSION

Eight patients were included in our case study. Out of the eight patients diagnosed with primary PHA1, two were evaluated as having renal PHA1 and five as having systemic PHA1. It was impossible to distinguish between the renal and systemic types from the records of Patient 2 because the sweat test was not available.

All the cases in our study group were referred to our clinic with a salt-depletion crisis. The most common cause for salt-depletion in newborns is CAH (6). The evaluation of 17-OHP and aldosterone levels is a top priority in the distinctive diagnosis of CAH and PHA1. Further, sexual differentiation disorders and hyperpigmentation are observed together with salt-depletion presentation in CAH cases.

However, two facts that may cause an error in the laboratory studies for a PHA1 and CAH distinctive diagnosis should be considered. The first of these is the high-dose hook effect. This effect is a very high amount of antigen causing lower detection of antigen by weakening the antigen-antibody binding in an immunoassay system. Due to the hook effect caused by very high aldosterone levels in Patient 8, the aldosterone level was found to be very low and caused a misdiagnosis. The first eight-month progress of Patient 8, who is 8 years old now, was also reported by Akin et al. (7). The second point that may cause an error is the possibility of measuring higher aldosterone levels in severe sepsis cases and CAH cases due to the interference of other hormones and precursors. The extraction and purification of serum samples should be done to prevent this (8). Based on this fact, it is understood that CAH and PHA1 distinction should not be made based on high aldosterone levels alone in cases involving a salt-depletion crisis, and it should be investigated whether extraction and purification were performed in serum samples with high aldosterone levels, and 17-OHP levels should definitely be examined. Again, the detection of an increase in surrenal dimensions with ultrasonography (USG) in these patients may be helpful for a distinctive diagnosis by suggesting the possibility of CAH diagnosis.

Primary PHA1 generally presents with growth retardation (failure to thrive) accompanied by severe urinary Na depletion, severe hy-

ponatremia, hyperkalemia, acidosis, hyporeninemia, and paradoxically, significantly high plasma aldosterone level during infancy. The glomerular filtration rate and adrenal functions are normal (6, 9). The Na/K ratio, which is nearly 2 in children, is increased in PHA1 cases (10). The referral age of patients in our study group was between 7 and 45 days, and the most common referral causes were poor nutrition and weight loss. The kidney functions of all patients were normal. A high BUN level present in some patients during the first referral was due to prerenal deficiency and recovered after fluid resuscitation. High urine Na level and/or high urine Na/K ratio were present in all the patients. Patient 8 was not included in the correlation analysis because the serum aldosterone levels were not available at admission. There was a negative correlation between plasma sodium and aldosterone levels in the remaining seven patients with primary PHA at admission. In the follow-up, it was observed that urinary Na levels were increased in all the patients after salt supplementation.

The distinction between primary and secondary PHA should be made initially in patients who are diagnosed with PHA1. Thus, evaluation with urine culture and urinary USG is of prime importance in a patient with PHA presentation (11, 12). In this way, unnecessary and expensive hormone tests can be prevented in secondary PHA cases.

The distinction between renal and systemic PHA1 can be made clinically or through genetic examination (13). We made this distinction based on sweat test and salivary Na level results in our study. The clinical characteristics of the patients also supported this distinction. Temporary salt supplementation requirement in the renal and systemic distinction can be used in the favor of renal PHA1. In the systemic type, salt supplementation needs to be continued lifelong (13). Except for Patient 8 in our study, it was not possible to stop salt supplementation in patients who had systemic PHA1. The presence of rashes and viscous ocular discharge supported our systemic PHA1 diagnosis in Patient 8. The chloride level was high in the repeated sweat test, but it was lower than that in the other systemic PHA1 cases. Further, the Na supplementation requirement was not continuous, and this situation was in line with the clinical features of the renal type. This difference could have been explained with the genotype-phenotype relationship, but it was not possible to make a genetic analysis. We accept the inability to make a genetic examination and discuss the genotype-phenotype relationship as a limitation of our study.

It is also noteworthy that there is a possibility of viscous discharge from the eyes and skin rashes as specific examination findings in systemic PHA1 cases. Miliaria rubra occurring due to the obstruction of sweat glands with salt may be observed on the skin (14). The Meibomian glands providing special lipid compounds to prevent drying are present in the tarsal plate in the eye. Since epithelial Na channels are inactive in systemic PHA1 cases, formations resembling a series of teeth appearing near the eyelid with the accumulation of salt and sebum in the Meibomian glands and can be evaluated as conjunctivitis (15, 16). Patients 3, 4, 7, and 8 had discharge from the eyes and/or skin rash at the time of referral. The cause for hospital referral was discharge from the eyes on the postnatal 7th day in Patient 7, where the discharge from the eyes and skin rash were best documented. White, viscous, and continuous discharge below the lashes,

irritation-related redness around the eyes, and the appearance of miliaria rubra on the body and arms were present in the examination. We have previously reported the progress of Patient 7 for the first month (16). Patient 7 died at the age of 8 months old, and there was no decline in the skin rashes and eye discharge until that time. Complaints of skin rashes were still present in the control visit of Patient 3 at the age of 8 years. The patient had no complaints related to skin rashes in the final control made at 12 years of age. There was a decline in the eye discharge and skin rash complaints of Patient 8 at the age of 3.5 years. Knowledge about these skin and eye findings may contribute to an earlier diagnosis and renal and systemic distinction in these cases.

Systemic PHA is characterized by poor growth (10). Although the growth percentiles are lower, renal PHA cases demonstrate normal psychomotor growth (17). The growth percentiles of Patient 6, whom we evaluated as having renal PHA, were normal and the same as those of the patient's twin. While there was growth retardation in four out of the five patients we evaluated as systemic PHA1 cases, the growth of one patient was normal.

PHA1 treatment includes the replacement of salt-depletion and rehydration in addition to the treatment of hyperkalemia and acidosis in the acute phase of the disease. Fludrocortisone and hydrocortisone replacement treatments can be given until a differential diagnosis from CAH is made. Salt replacement should be continued (17, 18). Fluid-electrolyte resuscitation was applied at the beginning in all our cases. Five patients were initially treated with fludrocortisone and/or hydrocortisone. Based on this, the aldosterone level should also be measured along with the 17-OHP level, which is required for CAH screening in an infant with salt-depletion crisis; hence, diagnosis delays should be prevented.

Salt-depletion is addressed by giving NaCl and NaHCO₃ with 3–20 mEq/kg/day Na in renal PHA1, and a rapid clinical and biochemical recovery is observed. The amount of Na needed is related to the severity of the symptoms and the normalization of plasma K concentrations and plasma renin levels (17, 18). The end of salt requirement in the renal type can be explained by the maturation of the salt retention ability of the kidney (13). Salt supplementation can be ended around 18–24 months of age in most patients. Children over this age are generally asymptomatic due to normal salt intake in the diet (17, 18). The highest salt requirements for Patients 1 and 6, who had renal PHA, were 18 mEq/kg/day and 15 mEq/kg/day, respectively. Patient 1 died at the age of 5 months, but the salt requirement continued until that point. The salt requirement for Patient 6 ended at the age of 5 months.

In contrast to renal PHA1, the normalization of fluid and electrolyte balance is particularly important in systemic PHA1. The treatment type and dose are specific for every patient. Generally, a high dose of Na that may require tube feeding is used (20–50 mEq/kg/day), and diet manipulations and ion exchange resin are required to decrease the K levels. Corticoid and indomethacin treatments can rarely provide additional benefit (19). Symptomatic treatment is required for respiratory tract diseases and skin phenotypes. Salt supplementation (8–20 g NaCl/day) and treatment containing salt and ion exchange resin is obligatory as a lifelong requirement (2, 20). The highest salt requirement in the systemic type was 32–53 mEq/

kg/day in our study. The salt requirement gradually decreased in patients. It was continuous in all patients with systemic PHA, except for Patient 8. Peritoneal dialysis was applied in Patients 3 and 5 due to persistent hyperpotassemia.

CONCLUSION

PHA1 is present in the differential diagnosis for patients referring to the hospital with a salt-depletion crisis for newborn and in the early infancy period. It is characterized by high PRA and serum aldosterone levels accompanied by severe hyponatremia, hyperpotassemia, and metabolic acidosis. After excluding the causes that may lead to secondary PHA in the initial evaluation of patients referred with a salt-depletion crisis, primary examinations for PHA and CAH should be taken together, and the hook effect and interference conditions should be considered in the evaluation stage of hormone levels. To be able to predict the clinical course and treatment duration in primary PHA, a renal or systemic distinction should be made and genetic tests should be employed for related mutations.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University Medical Faculty Ethics Institution (28.08.2015–2015/378).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Arai K, Chrousos G. Aldosterone deficiency and resistance. Endotext Last update: 04 July 2013
2. Riepe FG. Pseudohypoaldosteronism. *Endocr Dev* 2013; 24: 86-95. [\[CrossRef\]](#)
3. Tajima T, Morikawa S, Nakamura A. Clinical features and molecular basis of pseudohypoaldosteronism type 1. *Clin Pediatr Endocrinol* 2017; 26(3): 109-17. [\[CrossRef\]](#)
4. Casas-Alba D, Vila Cots J, Monfort Carretero L, Martorell Sampol L, Zennaro MC, Jeunemaitre X, et al. Pseudohypoaldosteronism types I and II: little more than a name in common. *J Pediatr Endocrinol Metab* 2017; 30(5): 597-601. [\[CrossRef\]](#)
5. Zennaro MC, Hubert EL, Fernandes-Rosa FL. Aldosterone resistance: structural and functional considerations and new perspectives. *Mol Cell Endocrinol* 2012; 350(2): 206-15. [\[CrossRef\]](#)
6. Amin N, Alvi NS, Barth JH, Field HP, Finlay E, Tverman K, et al. Pseudohypoaldosteronism type 1: clinical features and management in infancy. *Endocrinol Diabetes Metab Case Rep* 2013; 2013: 130010. [\[CrossRef\]](#)
7. Akın L, Kurtoglu S, Kendirci M, Akın MA, Hartmann MF, Wudy SA. Hook effect: A pitfall leading to misdiagnosis of hypoaldosteronism in an infant with pseudohypoaldosteronism. *Horm Res Paediatr* 2010; 74(1): 72-5. [\[CrossRef\]](#)

8. Ağlıadoğlu SY, Ayca Z, Kendirci HNP, Erkek N, Baş VN. Does pseudohypoaldosteronism mask the diagnosis of congenital adrenal hyperplasia? *J Clin Res Pediatr Endocrinol* 2011; 3(4): 219-21. [\[CrossRef\]](#)
9. Hatta Y, Nakamura A, Hara S, Kamijo T, Iwata J, Hamajima T et al. Clinical and molecular analysis of six Japanese patients with a renal form of pseudohypoaldosteronism type 1. *Endocrine Journal* 2013; 60(3): 299-304 [\[CrossRef\]](#)
10. Hanukoglu A, Edelheit O, Shriki Y, Gizewska M, Dascal N, Hanukoglu I. Renin-aldosterone response, urinary Na/K ratio and growth in pseudohypoaldosteronism patients with mutations in epithelial sodium channel (ENaC) subunit genes. *J Steroid Biochem Mol Biol* 2008; 111(3-5): 268-74. [\[CrossRef\]](#)
11. Abraham MB, Larkins N, Choong CS, Shetty VB. Transient pseudohypoaldosteronism in infancy secondary to urinary tract infection. *J Paediatr Child Health* 2017; 53(5): 458-63 [\[CrossRef\]](#)
12. Pai B, Shaw N, Högl W. Salt-losing crisis in infants-not always of adrenal origin. *Eur J Pediatr* 2012; 171(2): 317-21. [\[CrossRef\]](#)
13. Amin N, Alvi NS, Barth JH, Field HP, Finlay E, Tyerman K, et al. Pseudohypoaldosteronism type 1: clinical features and management in infancy. *Endocrinol Diabetes Metab Case Rep* 2013; 2013: 130010. [\[CrossRef\]](#)
14. Hanukoglu I, Boggula VR, Vaknine H, Sharma S, Kleyman T, Hanukoglu A. Expression of epithelial sodium channel (ENaC) and CFTR in the human epidermis and epidermal appendages. *Histochem Cell Biol* 2017; 147(6): 733-48. [\[CrossRef\]](#)
15. Akcakus M, Koklu E, Poyrazoglu H, Kurtoglu S. Newborn with pseudohypoaldosteronism and miliaria rubra. *Int J Dermatol* 2006; 45(12): 1432-4. [\[CrossRef\]](#)
16. Korkut S, Gökalp E, Özdemir A, Kurtoğlu S, Demirtaş Ş, Gül Ü, Baştuğ O. Dermal and ophtalmic findings in pseudohypoaldosteronism. *J Clin Res Pediatr Endocrinol* 2015; 7(2): 147-50. [\[CrossRef\]](#)
17. Zennaro MC, Hubert EL, Fernandes-Rosa FL. Aldosterone resistance: Structural and functional considerations and new perspectives. *Mol Cell Endocrinol* 2012; 350(2): 206-15. [\[CrossRef\]](#)
18. Loomba-Albrecht LA, Nagel M, Bremer AA. Pseudohypoaldosteronism type 1 due to a novel mutation in the mineralocorticoid receptor gene. *Horm Res Paediatr* 2010; 73(6): 482-6. [\[CrossRef\]](#)
19. Attia NA, Marzouk YI. Pseudohypoaldosteronism in a neonate presenting as life-threatening hyperkalemia. *Case Rep Endocrinol* 2016; 2016: 6384697.
20. Hanukoglu A, Hanukoglu I. Clinical improvement in patients with autosomal recessive pseudohypoaldosteronism and the necessity for salt supplementation. *Clin Exp Nephrol* 2010; 14(5): 518-9. [\[CrossRef\]](#)