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ORIGINAL ARTICLE PEDIATRICS

Analysis of patients presenting with serum electrolyte imbalance in terms of the differential diagnosis of pseudohypoaldosteronism

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ABSTRACT

OBJECTIVE: The aim of this study was to contribute to the differential diagnosis of transient pseudohypoaldosteronism (t-PHA).

METHODS: Twenty-nine infants, younger than 24 weeks, and with high aldosterone levels were included in the study. The patients were divided into two groups as t-PHA and other diagnoses group. Of 29 patients, 18 were in the t-PHA group and 11 were in other diagnoses group.

RESULTS: The means aldosterone, plasma renin activities (PRA), adrenocorticotropic hormone (ACTH), cortisol, and 17-hydroxyprogesterone (17-OHP) of those with t-PHA were 138±92.8 ng/dL, 8.39±10.57 ng/mL/h, 26.86±19.56 ng/L, 19.44±21.84 µg/dL, and 7.66±10.71 ng/mL, respectively. In other diagnoses group, the mean level of aldosterone, PRA, ACTH, cortisol, and 17-OHP levels was 100.9±70 ng/dL, 5.49±8.41 ng/mL/h, 408.28±491.9 ng/L, 19.99±14.43 µg/dL, and 11.99±12.21 ng/mL, respectively. In the t-PHA group, the number of patients with high PRA was eight (50%), while the number of patients with high levels was two (18.1%) in other diagnoses group. In the t-PHA group, although the average serum K levels were the same in both groups, serum aldosterone/K ratios were higher.

CONCLUSION: When an infant younger than 24 weeks, with urinary tract infection and/or urinary tract malformation has electrolyte abnormalities, pediatricians should primarily consider the diagnosis of t-PHA. Thus, many unnecessary investigations and inappropriate treatments can be avoided.

Keywords: Hyperkalemia; hyponatremia; pseudohypoaldosteronism; urinary tract infection; urinary tract malformation.

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Aldosterone is mineralocorticoid hormone regulating sodium (Na) absorption and potassium (K) secretion at renal tubules. Any disturbance in the aldosterone secretion or mechanism of action results in serum electrolyte imbalance. In early infancy, the kidneys cannot respond adequately to aldosterone due to the immaturity of the tubules, even if aldosterone levels are normal or increased. Therefore, patients may exhibit signs and symptoms of hypoaldosteronism called transient pseudohypoaldosteronism (PHA) [1]. PHA is divided into two subgroups as Type 1 and Type 2. PHA Type 1 (PHA-1) is the salt-losing type and develops as the result of inadequate response of the renal tubules to aldosterone. PHA type 2 (PHA-2) is a rare familial renal tubular defect characterized by hypertension and hyperkalemic metabolic acidosis although low levels of renin and aldos-

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terone. PHA-2 is caused by mutations that play a role in the regulation of blood pressure. The children with PHA-2 also have elevated levels of serum chloride (Cl). PHA-2 is usually detected in the childhood period or during the investigation of hypertension in adolescents.

Infants having PHA-1, as a result of unresponsiveness of tubules to aldosterone, despite they also have elevated plasma aldosterone levels and plasma renin activity, present with anorexia, inability to gain weight, dehydration, hyponatremia, and hyperkalemia. PHA-1 also is subdivided as primary (Genetic) and secondary (Transient) PHA-1. While the genetic type of PHA-1 is persistent and caused by the mutation of the epithelial sodium channel or mineralocorticoid receptors, the transient type of PHA-1 transient-pseudohypoaldosteronism (t-PHA) is temporary and mostly encountered in infants.

Various hypotheses have been proposed to explain the pathophysiology of t-PHA. Obstruction due to urinary system anomaly increases the synthesis of a number of cytokines such as transforming growth factor beta-1, tumor necrosis factor-alpha, interleukin-1, interleukin-6, and vasoactive compounds [2]. It is speculated that these cytokinins alter the aldosterone receptors. In a study by Kuhnle et al. [3], it was revealed that the number of aldosterone receptors decreased in the acute phase of obstructive uropathy, and the receptors returned to normal after the surgical correction. Hence, the reduced aldosterone effect due to down regulation of receptor sites can elucidate the elevated level of aldosterone. It is also speculated that bacterial endotoxins can damage aldosterone receptors. Endotoxins increase the production of prostaglandin, thromboxane, interleukin-1, leukotriene, and endothelin [2]. Endotoxins give rise to natriuresis, either direct effect or through cytokines [4]. The renal effects of cytokines that are produced by the combined action of urinary tract infection (UTI) and endotoxins result in vasoconstriction, reduce glomerular filtration rate, and increase the natriuresis. Most of the studies reported in the literature are cases of t-PHA secondary to UTI accompanied by urinary tract malformation (UTM). However, it is debatable which one is more decisive.

t-PHA often has often non-specific signs and symptoms such as refusal to feed, poor weight gain, vomiting, diarrhea, and dehydration. However, rapidly deterioration of general condition, peripheral circulation collapses, and sometimes, life-threatening electrolyte imbalance (hyperpotassemia) may occur [2]. Therefore, the differential diagnosis in infants with t-PHA is important for deciding the type of treatment. The differential diagnosis should be made from other conditions that cause electrolyte disturbances such as congenital adrenal hyperplasia (CAH), adrenal insufficiency, and isolated aldosterone deficiency. The aim of this study is to contribute to the differential diagnosis and treatment of t-PHA. To the best of our knowledge, our series is one of the largest in the literature.

Highlight key points

- In early infancy, the kidneys cannot respond adequately to aldosterone due to the immaturity of the tubules, even if aldosterone levels are normal or increased. Therefore, patients may exhibit signs and symptoms of hypoaldosteronism called transient pseudo-hypoaldosteronism
- The differential diagnosis should be made from other conditions that cause electrolyte disturbances such as congenital adrenal hyperplasia, adrenal insufficiency and isolated aldosterone deficiency.
- When an infant younger than 24 weeks, with UTI and/or UTM has electrolyte abnormalities, pediatricians should primarily consider the diagnosis of t-PHA.

MATERIALS AND METHODS

Twenty-nine infants younger than 24 weeks and with high aldosterone levels were included in the study. The patients were divided into two groups as t-PHA and other diagnoses group (CAH, adrenal insufficiency, and isolated aldosterone deficiency). The cases who took drugs that cause aldosterone resistance or disrupt the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors, mineralocorticoid blockers, were excluded from the study. In addition, other rare causes of secondary PHA1 such as tubulointerstitial nephritis, lupus nephritis, nephropathy associated with sickle cell anemia, renal allograft rejection, nephropathy following medullary necrosis in neonatal period, and unilateral renal vein thrombosis in young infants constituted other exclusion criteria. Obstructive uropathy was defined as the structural change in the urinary tract impeding the normal flow of urine, including ureteropelvic junction obstruction, ureterovesical junction obstruction, and posterior urethral valves.

Aldosterone levels were measured by Siemens Advia Centaur® XP immunoassay system using chemiluminescence method, while plasma renin activities (PRA) were determined by radioimmunoassay an Ang I RIA KIT

(Beckman Coulter, Immunotech, Prague, Czech Republic). The normal range for aldosterone level was accepted as 3–16 ng/dL in the supine position and 7–30 ng/dL in standing. The normal range for PRA was accepted as 0.51–2.64 ng/dL in the supine position and 0.98–4.18 ng/dL while standing. The levels of cortisol, adrenocorticotropic hormone (ACTH), and 17-hydroxyprogesterone (17-OHP) were measured by the commercial radioimmunoassay in a venous blood sample drawn while the patient was in the supine position.

When the serum K concentration in the non-hemolyzed blood sample was >5.5 mEq/dL, hyperpotassemia, when the serum Na concentration was <130 mEq/dL, hyponatremia was accepted. The serum aldosterone/K ratio and the urine K/Na ratio were calculated to evaluate the tubular response to aldosterone. UTI was defined as a positive urine culture leading to the isolation of a single pathogen at a concentration of 105 colony-forming units/mL in a sample obtained by urethral catheterization. The study was approved by the local ethics committee of the institution with the registration number E-86737044-806.01.03 and date October 15, 2021. The study was conducted in compliance with the principles included the Declaration of Helsinki.

Statistical Analysis

The statistical analyses were performed using the statistical package for social sciences for Windows, release 22.0 (SPSS, Chicago, IL, USA). While the normality of data was tested using the Kolmogorov–Smirnov test, the Mann–Whitney U-test or t-test was used to compare the mean values. The results were accounted for as mean±standard deviation for data with normal distribution or median interquartile range for data without normal distribution, and the statistical significance was accepted as $p<0.05$.

RESULTS

Study participants consisted of 29 infants younger than 24 weeks. Of 29 patients, 18 were in the t-PHA group and 11 were in the other diagnoses group. Seven (38.9%) of 18 patients diagnosed with t-PHA were girl and 11 (61.1%) were boys. The mean age was 6.5±7 weeks (min 1, max 24) in this group. The means aldosterone, PRA, ACTH, cortisol, and 17-OHP of those with t-PHA were 138±92.8 ng/dL, 8.39±10.57 ng/mL/h, 26.86±19.56 ng/L,19.44±21.84 µg/dL, and 7.66±10.71 ng/mL, respectively (Table 1). Furthermore, the average glucose, Na, K, Cl, blood gas HCO_3, serum aldosterone/K ratio, fractional sodium excretion (FeNa), and urine Na/K ratio are given in Table 1.

Table 1. Comparison of hormonal and biochemical averages of t-PHA and other diagnosis groups

	t-PHA group	Other diagnoses group	p
Aldosterone (ng/dL)	138±92.8	100.9±70	>0.05
PRA (ng/mL/h)	8.39±10.57	5.49±8.41	>0.05
ACTH (ng/L)	26.86±19.56	408.28±491.9	**<0.05**
Cortisol (µg/dL)	19.44±21.84	19.99±14.43	>0.05
17-OHP (ng/mL)	7.66±10.71	11.99±12.21	>0.05
Glucose (mg/dL)	83.5±20.6	85.5±13.9	>0.05
Na (mEq/L)	129.9±9.8	123.6±9.4	>0.05
K (mEq/L)	5.8±1.3	5.8±1.3	>0.05
Cl (mEq/dL)	96±9.1	89.8±17.9	>0.05
HCO_3 (mmol/L)	18.23±4.98	19.56±10.09	>0.05
Serum aldosterone /K ratio	26.32±18.37	19.63±18.44	>0.05
Urine Na (mEq/L)	38±42.2	36.4±5.3	>0.05
Urine K (mEq/L)	16.7±6.1	27.4±28	**<0.05**
FeNa	1.57±1.94	2.64±2.37	>0.05
Urine Na/K ratio	1.52±1.53	0.83±0.98	>0.05

ACTH: Adrenocorticotropic hormone; Cl: Chloride; FeNa: Fractional excretion of sodium; HCO_3: Bicarbonate; K: Potassium; Na: Sodium; PRA: Plasma renin activity; 17-OHP: 17-hydroxyprogesterone; t-PHA: Transient type of pseudohypoaldosteronism-1; Urine K: Potassium in urine; Urine Na: Sodium in urine.

In the t-PHA group, the number of patients with normal PRA level was 6 (37.5%), the number of patients with high level was 8 (50%), and the number of patients with low level was 2 (12.5%) (Table 2). Considering the levels of ACTH, while the number of patients with normal ACTH levels was 8 (88.9%), the number of patients with high ACTH levels was only one (11.1%). Given the levels of cortisol, however, the number of patients with normal cortisol levels 6 (60%), the number of patients with high levels was 3 (30%), and the number of patients with low levels was 1 (10%). While the number of patients with normal 17-OHP levels was only one (11.1%), the number of those with high 17-OHP levels was eight (88.9%). There were no patients in this group with low 17-OHP levels.

In this group, while the number of patients with UTM was eight (44.4%), the number of patients without any anomaly was 10 (55.6%). Five of the eight patients with

TABLE 2. Comparison of frequencies of t-PHA and other diagnosis groups

	t-PHA group (%)	Other diagnoses group (%)
PRA normal	6 (37.5)	4 (36.4)
PRA high	8 (50)	2 (18.1)
PRA low	2 (12.5)	5 (45.5)
ACTH normal	8 (88.9)	4 (36.4)
ACTH high	1 (11.1)	7 (63.60
Cortisol normal	6 (60)	5 (50)
Cortisol high	3 (30)	4 (40)
Cortisol low	1 (10)	1 (10)
17-OHP normal	1 (11.1)	1 (9.1)
17-OHP high	8 (88.9)	9 (81.8)
17-OHP low	0 (0)	1 (9.1)

PRA: Plasma renin activity; ACTH: Adrenocorticotropic hormone; 17-OHP: 17-hydroxyprogesterone; t-PHA: Transient type of pseudohypoaldosteronism-1.

anomaly were male. The number of those with UTI was five (27.8%), while the number of those without UTI was 11 (72.2). Four of the five patients with UTI were male. In addition, the number of patients with acidosis was five (27.8%) and the number of those without acidosis was 13 (72.2%) in this group. The mean recovery time of electrolyte imbalance of 16 patients in t-PHA group was 2.2±1.4 days. One of the remaining two patients was diagnosed at 8 weeks of age, and both hormonal and clinical improvement was achieved at week 26. The other patient was diagnosed at 12 weeks of age, and clinical improvement was delayed until 52 weeks, while hormonal regulation takes place in 3 weeks, and both patients had no UTM.

There were 11 patients in the other diagnoses group, and the distribution of patients in this group was as follows: Eight patients with CAH, one patient with primary PHA-1, one patient with adrenal insufficiency, and one patient with Typ-IV renal tubular acidosis. Of these patients, seven (63.6%) were boys, two (18.2%) were girls, and two (18.2%) were ambiguous genitalia. The mean age was 11.1±12.6 weeks (min 1, max 24 weeks) in this group.

In other diagnoses group, the mean level of aldosterone, PRA, ACTH, cortisol, and 17-OHP levels was 100.9±70 ng/dL, 5.49±8.41 ng/mL/h, 408.28±491.9 ng/L, 19.99±14.43 μg/dL, and 11.99±12.21 ng/mL, respectively (Table 1). Furthermore, the average glucose, Na, K, Cl, blood gas HCO_3, serum aldosterone/K ratio, FeNa, and urine Na/K ratio of this group were given in Table 1.

In this group, the number of patients with normal PRA was four (36.4%), the number of patients with high levels was two (18.1%), and the number of patients with low levels was five (45.5%) (Table 2). Considering ACTH levels, while the number of patients with normal ACTH levels was four (36.4%), the number of patients with high ACTH levels was seven (63.6%). In terms of cortisol, the number of patients with normal cortisol levels was five (50%), the number of patients with high levels was four (40%), and the number of patients with low levels was one (10%). In this group, while the number of patients with normal/ low 17-OHP levels was only one (9.1%)/one (9.1%), the number of patients with high 17-OHP levels was nine (81.8%).

In other diagnoses group, there were patients with neither UTM nor UTI. While the number of patients with acidosis was four (36.4%), the number of those without acidosis was seven (63.6%). The mean recovery time of electrolyte imbalance was 7.3±4.1 day in other diagnoses group.

There was no difference between the mean age of both groups. While there was no difference between the aldosterone, PRA, cortisol, and 17-OHP averages of both groups, only the ACTH averages were statistically different (Table 1). While there were no cases of ambiguous genitalia in t-PHA group, two patients with ambiguous genitalia were detected in other diagnoses group, and the male gender was seen to be more preponderant in both groups.

DISCUSSION

Severe hyponatremia and hyperkalemia may be a life-threatening condition, especially in the 1st months of infancy [2]. Therefore, differential diagnosis is critical in infants presenting with electrolyte imbalance, as this situation may be caused by serious endocrine pathologies as well as by relatively mild pathologies such as t-PHA. In most of t-PHA cases in the literature, the electrolyte imbalance and metabolic acidosis have been reported to be normalized within 1–7 days with appropriate treatment [5, 6]. However, in some patients, salt supplementation may be necessary for weeks or months due to the ongoing loss of renal Na [6, 7]. In the literature, there are also publications emphasizing that full recovery can last for up to 2 years depending on the completion of tubular maturation [1]. In a series of eight cases published by Bogdanović et al. [2] it was reported that the clinical status and biochemical parameters had

improved within 24–48 h in most of patients after intravenous administration of fluids and bicarbonate supplementation. In the series of three cases of Ceylan et al. [5], the timeline of electrolyte recovery was reported to be between 4 and 6 days. In our study, the mean recovery time of the electrolyte imbalance was 2.2±1.4 day in t-PHA group, while this time was 7.3±4.1 day in other diagnoses group. In this context, we consider that it would be prudent to take other diagnoses into account in persistent cases despite appropriate treatment.

The typical laboratory features of t-PHA 1 are high aldosterone and high PRA levels. In our study, as expected, both high aldosterone and high PRA levels were detected. However, the averages of both aldosterone and PRA were higher in the t-PHA group than other diagnoses groups. In addition, the proportion of those with high PRA was approximate three-fold higher in the t-PHA group (50% vs. 18.1%). t-PHA may sometimes result in metabolic acidosis, as well as hyponatremia and hyperkalemia [5]. In our study, the rate of patients with acidosis was higher (27.8% in PHA group vs. 36.4% in other diagnoses group). Therefore, we think that it would be more plausible to consider t-PHA in situation accompanied by metabolic acidosis when making a differential diagnosis in cases with elevated aldosterone and PRA.

Other laboratory findings in t-PHA are high excretion of urine Na and low excretion of urine K given that serum Na and K levels. Furthermore, in our study, inappropriately with low serum Na levels and high serum K levels, urine Na mean was high, urine K mean was low in both group. However, while the mean of urine Na levels was similar in both groups, the mean of urine K levels was higher in t-PHA group. In addition, higher serum aldosterone/K ratio, higher urine Na/K ratio, and higher FeNa level were detected in t-PHA group compared to the other diagnoses group. Therefore, we suggest that it would be appropriate to measure excretion of urine N and K, urine Na/K ratio, serum aldosterone/K ratio, and FeNa calculation in the differential diagnosis.

UTM and UTIs are the most common factors contributing to t-PHA although its mechanism has yet to be elucidated [8, 9]. t-PHA has been described most frequently in young infants in association with UTI and/or UTM such as ureterohydronephrosis, ureterocele, ureteropelvic junction obstruction, and posterior urethral valves [10]. This situation could be explained by the renal interstitial inflammation present in acute pyelonephritis and the immaturity of the renal tubules. In addition, it can be hypothesized that the younger the infants, the more frequently is electrolyte disorders occur and is overt. Although transient tubular resistance to aldosterone could be seen in older children with UTI such as pyelonephritis, it not usually cause to electrolyte imbalance as severe as seen in infancy [11]. In our study, while the rate of patients with urinary anomalies was 44.4% in t-PHA group, there were no patients with urinary anomalies in other diagnoses group. But there were two patients with ambiguous genitalia. On the other hand, while the rate of patients with UTI was 27.8% in t-PHA group, there were no patients with either UTM or UTI in other diagnoses group. Although the pathophysiology of t-PHA is controversial, salt loss has been shown to correlate with age [7]. This correlation is explained by tubular immaturity. Albeit all patients in our study were <24 weeks of age, the fact that the mean age of the patients in t-PHA group was almost half that of the patients in the other diagnoses group has supported this hypothesis. In the study by Melzi et al. [12], all t-PHA cases were younger than 3 months of age, despite the presence of UTM. Our study was in agreement with that of Melzi et al. [12] However, in some reports, it has been reported that the cases are clustered under 7 months of age [13].

Serum electrolyte disturbance detected in t-PHA may be similar to those seen in CAH, adrenal insufficiency, and isolated aldosterone deficiency. Hence, these entities should be considered in the differential diagnosis of t-PHA. Unlike CAH, in the t-PHA situation, the patient's clinical status will not improve with the administration of corticosteroids, but with fluid electrolyte resuscitation and bicarbonate supplementation [14]. Normal ACTH, cortisol, and 17-OHP levels may rule out the diagnosis of CAH [2]. In our study, in accordance with the literature, while the ACTH average was normal in the t-PHA group, it was significantly higher in other diagnoses group. In addition, while the proportion of patients with high ACTH levels in the t-PHA group was only 11%, the proportion of patients with high ACTH levels in the other diagnoses group was 63.6%. However, while the mean of cortisol was similar in both groups, the mean of 17-OHP was higher in other diagnoses group, even though it was not statistically significant. On the other hand, the mean PRA was detected to be higher in t-PHA group. Moreover, while the high PRA was more common in the t-PHA group, low PRA was more frequent in the other diagnoses group. One of the striking

findings of our study was that the mean aldosterone was also higher in t-PHA group. In conclusion, high levels of PRA and aldosterone together, normal ACTH, and lower 17-OHP levels lead to the diagnosis of t-PHA, while lower PRA and aldosterone levels together, high ACTH and higher 17-OHP levels suggest the CAH. In addition, the high serum aldosterone/K and the low urine K/Na values support the diagnosis.

The male gender predominance reported in previous studies may be attributed to both a greater predominance of UTI in boys than girls in this age group and a higher prevalence of obstructive malformations (posterior urethral valve, etc.) in boys [2]. In our study, although there was a slight male predominance in both groups, there was no difference between the groups in terms of gender distribution. However, it was noteworthy that there were two cases with ambiguous genitalia in the other diagnoses group. In addition, in t-PHA group, the higher incidence of both UTM and UTI in males, was consistent with previous reports.

In a study of 114 cases by Lee et al. [15] consisting of 47 patients with acute pyelonephritis, 42 patients with lower UTI and 25 control subjects; the mean uNa level was reported as 14 mEq/L, 23 mEq/L, and 35 mEq/L, respectively. In the same study, the mean uNa of 47 patients with high aldosterone levels was 15 mEq/L, and the mean uNa of 67 patients with low aldosterone levels was 23 mEq/L. The authors explained this situation with "the activation of local intrarenal renin–angiotensin–aldosterone system." This interpretation contradicts the hyponatremia that occurs despite the high aldosterone level in pyelonephritis cases seen in early infancy. This contradiction can only be explained by aldosterone resistance in early infancy because the age of the subjects ranged from 4 to 11 months in the low aldosterone group and 4–7 months in the high aldosterone group in the study of Lee et al. [15] Considering that our subjects were young infants at <24 months of age, the observation of high urine Na and high FENa levels supported this hypothesis, despite low serum Na and high serum aldosterone levels.

The limitation of this study was low number of cases, to our knowledge, although our study is one of the largest series published in the literature. This situation restrained us from making clearer comments. For example, although urine Na/K ratio and FeNa values of the two groups were different in our study, we could not interpret them because they were not statistically significant. Serum glucose, Na, K, clore, HCO_3, and urine Na levels were not different between groups. Therefore, they do not appear to be useful in the differential diagnosis of t-PHA.

Our findings indicated that early infancy is the main predisposing factor for t-PHA to occur, and UTI and UTM are facilitating factors for t-PHA's development. Therefore, we recommend monitoring serum electrolytes in infants younger than 24 weeks of age and with UTM and/or UTI regarding the early diagnosis of t-PHA. If necessary, the diagnosis of t-PHA should be confirmed by advanced hormonal studies. In spite of t-PHA having a similar clinical and biochemical presentation to various clinical entities, the patients' age and specific physical examination findings may help rule out the other diagnoses, especially CAH. Early response to the treatment should be interpreted in favor of t-PHA, but detection of anomalies such as ambiguous genitalia, macrogenitalia, hyperpigmentation, and virilization may suggest a serious underlying endocrine disorder. If necessary, physicians should analyze for ACTH, cortisol, PRA, and 17-OHP to make differential diagnosis, as well as analysis of aldosterone. Our study showed that high aldosterone, high PRA, and normal ACTH or relatively low 17-OHP levels suggest t-PHA. However, at the same time, our study showed that cortisol level is not a useful indicator in differential diagnosis. In addition, we consider that measuring urine K and serum aldosterone/K ratio will be helpful in the differential diagnosis.

Conclusion

When an infant younger than 24 weeks, with UTI and/or UTM, has electrolyte abnormalities, pediatricians should primarily consider the diagnosis of t-PHA. Thus, many unnecessary investigations and inappropriate treatments can be avoided.

Ethics Committee Approval: The Konya Provincial Health Directorate Ethics Committee granted approval for this study (date: 15.10.2021, number: E-86737044-806.01.03).

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