Turkish Archives of Pediatrics

CASE REPORT
DOI: 10.14744/TurkPediatriArs.2020.38159

A rare cause of salt-wasting in early infancy: Transient pseudohypoaldosteronism

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What is already known on this topic?

- *Severe hyperkalemia and hyponatremia are life-threatening electrolyte disturbances and early treatment is essential. Salt-wasting suggests adrenal insufficiency, the most common cause of which is congenital adrenal hyperplasia.*
- *Pseudohypoaldosteronism (PHA) is not a well-known diagnosis and caused by renal tubular resistance to aldosterone, which mimics congenital adrenal hyperplasia. However, in hormonal studies, cortisol and 17-hydroxyprogesterone levels are normal, whereas aldosterone levels are extremely high.*

What this study adds on this topic?

- *Transient PHA in early infancy is associated with urinary tract malformations or urinary tract infections. Physicians should consider the diagnosis of PHA when an infant admits with urinary tract malformations/infection and electrolyte imbalance.*

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Received: : 28.11.2019
Accepted: 18.05.2020
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ABSTRACT

Three infants aged between 38 days and 43 days all presented with poor weight gain, hyponatremia, hyperkalemia, and were diagnosed as having urinary tract infections, which were accompanied by urinary tract malformations in our cases. Hydration and infection treatments were given. A few days after admission, hormonal studies revealed normal cortisol and 17-hydroxy progesterone levels and markedly high aldosterone levels, thus the patients were diagnosed as having transient pseudohypoaldosteronism. After the proper treatment was given, the transient pseudohypoaldosteronism resolved. In conclusion, when an infant with urinary tract infection or malformation has electrolyte abnormalities, pediatricians should consider the diagnosis of transient pseudohypoaldosteronism.

Keywords: Infant, pseudohypoaldosteronism, urinary tract infection, urinary tract malformation

Introduction

Severe hyponatremia and hyperkalemia, which are rarely observed in the first months of life, are known as life-threatening conditions. Congenital adrenal hyperplasia (CAH), abnormal mineralocorticoid production, pseudohypoaldosteronism (PHA), isolated aldosterone deficiency, and drugs should be considered in the differential diagnosis for these electrolyte imbalances in infancy (1). Pseudohypoaldosteronism is a rare condition that is classified as type 1 and type 2. Type 1 PHA is also divided into two groups as primary and secondary (transient) PHA. Primary PHA occurs as a result of mutations in the gene that encodes the type 1 epithelial sodium channels or mineralocorticoid receptors. Secondary (transient) PHA is usually caused by urinary tract infections (UTIs), which are mostly caused by structural anomalies of the urinary tract (2).

We present three infants whose primary symptom was poor weight gain who were diagnosed as having. Although PHA is a rare condition, it should be considered in the differential diagnosis of infants with hyponatremia and hyperkalemia. Urinary tract infections and urinary tract malformations (UTMs) should be evaluated as predisposing factors for PHA.

Case Presentations

Case 1

A 43-day-old male infant who was born at term presented with poor weight gain (4 g/day). On admission, his vital signs were within normal limits and a physical examination showed no hyperpigmentation or any other abnormal findings. The initial serum sodium was 118 mEq/L and serum potassium was 7.05 mEq/L. Urinalysis was positive for leukocytes. At this point, the differential diagnoses were adrenal insufficiency, CAH, and secondary PHA. After blood

Cite this article as: Ceylan D, Bayramoğlu E, Polat E, Erdeve ŞS, Çetinkaya S, Aycan Z. A rare cause of salt-wasting in early infancy: Transient pseudohypoaldosteronism. Turk Arch Pediatr 2021; 56(1): 75-7.

Table 1. Characteristics and laboratory findings patients with transient pseudohypoaldosteronism

	Patient-1	Patient-2	Patient-3
Age at presentation	43 days	39 days	38 days
Gender	Male	Male	Male
Birth week and weight	39 weeks / 3525 g	41 weeks / 3400 g	38 weeks / 3400 g
Main complaint	Failure to thrive (4 g/day)	Failure to thrive (6 g/day)	Failure to thrive (5,2 g/day)
On admission;			
Sodium (mEq/L)	116	109	118
Potassium (mEq/L)	6,4	6,07	5,2
Cortisol (µg/dL)	23,3	16	12,8
17-OH progesterone (ng/mL)	1,63	3,15	0,58
Aldosterone (pg/mL)	>1600	>1600	3630
Urine microbe	Klebsiella pneumonia	Klebsialla pneumonia	Escherichia coli
Urinary Ultrasonography	Left hydroureteronephrosis	Right hydroureteronephrosis	Bilateral hydroureteronephrosis
Initial treatment	Hydrocortisone, Intravenous hydration, Antibiotics	Fludrocortisone Hydrocortisone Intravenous hydration Antibiotics	Antibiotics, Intravenous hydration Oral salt
Timeline of electrolyte recovery	6 days	4 days	4 days

samples were taken for hormonal studies, hydrocortisone, intravenous hydration, and antibiotics were started. Hormonal analyses showed that random cortisol 23 µg/dL, 17-hydroxyprogesterone 1.63 ng/mL, and aldosterone 1689.55 pg/mL (20-1100). These results were compatible with the diagnosis of PHA. Hydrocortisone was stopped after hormonal studies were evaluated. Also, urine culture was positive for *Klebsiella pneumoniae* (>10^5 cfu/mL) and urinary ultrasonography demonstrated left hydroureteronephrosis. The electrolyte imbalance improved on the 5th day of treatment. After the antibiotic regimen ended on the 10th day of admission, the patient was discharged with normal electrolyte levels.

Case 2

A 39-day-old male was admitted to the hospital for persistent poor weight gain (6 g/day). He was a full-term infant and had been breastfeeding. His physical examination was normal and no hyperpigmentation was detected. Serum sodium was 109 mEq/L and potassium was 6.07mEq/L. Urinalysis was positive for white and red blood cells. Fludrocortisone, hydrocortisone, and hydration were started for suspected adrenal insufficiency and antibiotics were started for urinary tract infection. A few days later, laboratory analyses revealed that 17-hydroxyprogesterone 3.1 ng/mL, aldosterone >1600 (20-1100) pg/mL and random cortisol 16 µg/dL. Also, the urine culture grew *Klebsiella pneumonia* (>10^5 cfu/mL). Urinary ultrasonography showed severe right hydroureteronephrosis. Even though laboratory results were leading to PHA, electrolyte imbalances were persistent and drug doses were adjusted to keep the electrolyte levels within the normal range. Patient was discharged with antibiotic prophylaxis, hydrocortisone, and fludrocortisone treatments. Hydrocortisone and fludrocortisone were discontinued gradually within the second month of treatment. After that, an adrenocorticotropic hormone (ACTH) stimulation test was performed to exclude CAH, which resulted as normal. At the age of 4 months, he underwent pyeloplasty.

Case 3

A 38-day-old male infant was referred to our facility with symptoms of poor feeding and failure to thrive. Urinalysis was positive for leukocytes and ultrasonography showed hydronephrosis. A weak sucking reflex was the only finding on physical examination and his weight gain was 5.2 g/day. Initial blood chemistry yielded sodium 120 mEq/L and potassium 6.14 mEq/L. Hydrocortisone was not started immediately because UTM and secondary UTI were recently diagnosed at an external facility. Antibiotics, intravenous hydration, and oral salt were started for the initial diagnosis of PHA. His blood aldosterone level was 3380 pg/mL (20-1100), electrolyte levels were within normal limits on day 4, and oral salt was discontinued on the 6th day of admission. A urine culture grew *Escherichia coli* (10^7 cfu/mL) and after the antibiotic regimen ended, the patient was discharged in a healthy condition.

Informed consents were obtained from all parents of the patients and the data were evaluated for the study.

Discussion

Aldosterone is the primary mineralocorticoid hormone that regulates sodium absorption and potassium secretion at distal renal tubules (3). Especially in early infancy, immature renal tubules may not respond to aldosterone adequately and even though aldosterone levels are markedly increased, patients may show signs and symptoms of hypoaldosteronism, which is called transient PHA (4). This rare condition results in hyponatremia, hyperkalemia, metabolic acidosis, and also causes a wide variety of symptoms such as poor feeding/weight gain, to life-threatening ventricular fibrillations (5). Despite the unclear mechanism, UTMs and UTIs in infancy are the most common and best-known contributing factors for transient PHA (6-10). Watanabe (7) reported 60 patients with transient PHA who were aged younger than 7 months. Eighty percent of these patients had UTMs and UTIs, 11.7% had UTMs without UTIs, and 8.3% had only UTIs. Bogdanovic et al. (8) reported 93 patients with transient PHA between 1983 to 2009. They were aged between 1 week and 7 months and 90% of the patients were aged under 3 months. Urinary tract malformation was detected in 84 (90.3%) of 93 patients and 89% had UTIs. Only 9.7% of patients had isolated UTIs. Hence, rapid treatment of UTIs and

follow-up for UTMs is essential for patients with transient PHA. The most common organisms seen in isolated UTIs are *Escherichia coli* (62.5%), *Klebsiella spp.* (12.5%), *Enterococcus fecalis* (16.7%,) and *coagulase-negative staphylococci* 8.3% (11). If a patient is immunocompromised or has a UTM, *Staphylococcus aureus, Staphylococcus epidermidis, Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus viridans, and Streptococcus agalactiae* may also be responsible for UTIs (12). Furthermore, when we searched for the etiology of the UTIs in patients with transient PHA, we found that the most common organism was *Escherichia coli* (1, 3, 8, 11, 13, 14). *Klebsiella pneumoniae, Staphylococcus aureus, Enterobacter spp., Klebsiella oxytoca* were other microorganisms that grew in urine cultures (1, 8, 9, 13).

Congenital adrenal hyperplasia is one of the most common inherited disorder, presenting with hyperkalemia, hyponatremia, severe metabolic acidosis, nonspecific symptoms of vomiting, dehydration, and poor feeding at ages 1 to 3 weeks (15). Therefore, physicians should collect blood samples for 17-hydroxy progesterone and cortisol to exclude this diagnosis. However, hormonal studies may take several days in many laboratories. It is vital to start intravenous fluid treatment immediately because of the life-threatening symptoms of electrolyte abnormalities (5). Even though CAH has a similar clinical and biochemical presentation to PHA, clinical condition, the patients' age, and specific physical examination findings may help to exclude CAH, which usually presents with vomiting and severe dehydration in the first two weeks of life. Also, ambiguous genitalia, macrogenitalia, and hyperpigmentation can be detected on physical examination. Moreover, it is essential to consider different causes other than CAH in infants older than one month with electrolyte imbalances and nonspecific symptoms. It is necessary to consider other defects in aldosterone synthesis or the effect of aldosterone in patients with a salt-wasting crisis who have external genitalia with normal female appearance because 46,XX infants with CAH often present with virilization (15).

All of our patients presented with mild nonspecific symptoms such as poor weight gain, hyponatremia, and hyperkalemia in early infancy after the neonatal period. Congenital adrenal hyperplasia was excluded with normal 17-OH progesterone levels. Patient 1 and 2's urine cultures were positive for *Klebsiella pneumoniae* and patient 3 had *Escherichia coli.* Ultrasonography demonstrated different types of UTMs and high aldosterone levels supported the diagnosis of PHA (Table 1). After proper hydration and infection treatments were given, transient PHA was resolved without complication.

In conclusion, we emphasize that in cases of failure to gain weight in early infancy, urinary tract infections and electrolyte disturbances should be investigated. Salt-wasting and hyperkalemia with a presentation at relatively later days of age and with no signs of CAH, physicians should suspect a defect in the mineralocorticoid effect, thus renal causes should also be considered as well as adrenal insufficiency.

Informed Consent: Written informed consent was obtained from parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.C., Ş.S.E.; Design – D.C., E.B.; Supervision – Ş.S.E., E.B.; Data Collection and/or Processing – E.P., S.Ç.; Literature Review – Z.A., E.P.; Writing – D.C., S.Ç.; Critical Review – Ş.S.E., Z.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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