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Case Report

A Case of Secondary Pseudohypoaldosteronism in a Neonate not Due to Urinary Tract Issues

Altınok Eİ and Özer Y. Secondary Pseudohypoaldosteronism in a Neonate without Urinary Issues

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What is already known on this topic?
Secondary pseudohypoaldosteronism (PHA) is typically associated with urinary tract infections (UTIs) and/or urinary tract anomalies (UTAs), especially in male infants under six months of age. In most cases, the salt-wasting symptoms improve with the treatment of the underlying infection or anomaly. The diagnosis requires exclusion of congenital adrenal hyperplasia (CAH) and other adrenal disorders.

What this study adds?
This case highlights that secondary PHA can occur in the absence of UTIs and UTAs, even in female infants. It emphasizes the importance of considering secondary PHA in the differential diagnosis of neonatal hyponatremia, hyperkalemia, and metabolic acidosis, regardless of gender or the presence of urinary tract pathology. The case contributes to the limited number of reports documenting idiopathic or nosocomial causes of secondary PHA.

Abstract
In this report, we present a case of a female infant diagnosed with secondary PHA who exhibited weight loss, hyponatremia, hyperkalemia, and metabolic acidosis without the presence of UTA or UTI. The patient was a female infant born at 35 weeks gestation who developed electrolyte abnormalities and was diagnosed with secondary pseudohypoaldosteronism (PHA). Initially managed for transient tachypnea of the newborn, she developed respiratory distress requiring mechanical ventilation. Subsequently, she exhibited persistent hyponatremia, hyperkalemia, and metabolic acidosis despite adequate fluid therapy, prompting consideration of adrenal insufficiency and congenital adrenal hyperplasia (CAH). Treatment with hydrocortisone and fludrocortisone was initiated empirically until hormonal analyses excluded CAH. Further evaluation excluded urinary tract anomalies and infections as underlying causes, implicating secondary PHA. The infant responded well to saline and electrolyte replacement therapy, with normalization of electrolyte levels and clinical improvement. Follow-up assessments demonstrated resolution of electrolyte imbalances, and the patient was discharged after 20 days without further complications. Secondary PHA, characterized by renal tubular resistance to aldosterone, typically presents with severe electrolyte disturbances in infancy. It can occur independently of urinary tract abnormalities or infections, highlighting the importance of considering this diagnosis in neonates and infants presenting with hyponatremia, hyperkalemia, and metabolic acidosis that do not respond to conventional therapies. Early recognition and appropriate management, including fluid-electrolyte correction and hormone replacement if indicated, are crucial to prevent life-threatening complications associated with salt-wasting syndromes in this vulnerable population.
Keywords: Secondary Pseudohypoaldosteronism, Newborn, Without Urinary Tract Anomalies And İnfections

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Introduction
Secondary pseudohypoaldosteronism (PHA) is a rare but potentially life-threatening condition in neonates and infants, typically caused by urinary tract infections (UTIs), urinary tract anomalies (UTAs), or transient tubular dysfunction. It is characterized by aldosterone resistance at the renal tubular level, despite elevated levels of plasma renin and aldosterone, leading to hyponatremia, hyperkalemia, and metabolic acidosis. Although congenital adrenal hyperplasia (CAH) is the most common cause of salt-wasting in the neonatal period, secondary PHA should be considered in patients who do not respond to standard fluid and electrolyte management and whose hormonal findings indicate mineralocorticoid resistance (1,2).
The exact pathophysiology of secondary PHA is not fully understood. Immature renal tubular responsiveness to aldosterone in early infancy, intrarenal inflammation due to infections, and increased intrarenal pressure related to anomalies such as vesicoureteral reflux are considered contributing factors (3). However, in rare cases, secondary PHA may develop without UTI or UTA, which can pose a diagnostic challenge. Early recognition of this condition is critical, as delayed or incorrect diagnosis may lead to inappropriate interventions and potentially fatal electrolyte disturbances. Misdiagnosis as CAH is a common concern, given the overlap in biochemical presentation. Unlike CAH, however, secondary PHA is typically transient and resolves with treatment of the underlying cause, most often infection or obstruction. Awareness of this entity and its atypical presentations is essential to avoid unnecessary hormonal therapies and to ensure prompt, supportive management (
In this report, we present a case of a female infant diagnosed with secondary PHA who exhibited weight loss, hyponatremia, hyperkalemia, and metabolic acidosis without the presence of UTA or UTI. Informed consent and approval were obtained from the patient's relative.

Case Presentation
A 35-week gestational age female infant weighing 2450 grams was born via cesarean section due to fetal distress as the third living child of a 33-year-old mother's healthy pregnancy. Initially monitored at an external center with a preliminary diagnosis of transient tachypnea of the newborn, the infant was referred to our hospital on the third postnatal day after being intubated. Physical examination revealed tachypnea, subcostal, and intercostal retractions. Heart rate was 136 beats per minute, respiratory rate was 70 breaths per minute, and blood pressure was 82/43 mmHg (95th percentile BP value: 90/49 mmHg). Body weight was measured at 2400 grams. There was no hyperpigmentation, and the infant had a female phenotype appearance. Hemogram and blood biochemistry were normal. The ongoing treatment with ampicillin and gentamicin was continued. The patient, who had respiratory acidosis (pH: 7.27, pCO2: 63 mmHg, HCO3: 18 mEq/L), was followed on mechanical ventilation for five days and then extubated. On the ninth day, the infant's body temperature rose to 38.5°C, and cutis marmorata

appearance was observed. Routine blood tests were repeated. Hemogram and renal function tests were normal, but the patient had elevated CRP (24 mg/L, NR: 0-5), hyponatremia (sodium: 131 mEq/L, NR: 135-145), hyperkalemia (potassium: 6.3 mEq/L, NR: 3.5-6), and metabolic acidosis (pH: 7.22, pCO2: 40 mmHg, HCO3: 13 mEq/L). Urine analysis showed no pyuria. Cultures were taken, and antibiotics were changed to ampicillin and cefotaxime. On postnatal day 7, weight loss (16%) was noted in the infant with adequate urine output. After a saline bolus infusion (10 ml/kg), hydration was maintained with saline infusion. On the eleventh day, despite ongoing hydration and antibiotic therapy, the patient's hyponatremia (Na: 127 mEq/L) and hyperkalemia (K: 6.7 mEq/L) deepened. Renal and pelvic ultrasound were normal. Urine culture showed no growth. On the twelfth day, hyponatremia (Na: 121 mEq/L) and hyperkalemia (K: 7.1 mEq/L) persisted despite adequate fluid therapy. Adrenal insufficiency and CAH were considered, and hydrocortisone, fludrocortisone, and oral salt were initiated until serum cortisol, 17-OHP, and aldosterone levels were available. The patient's clinical status and electrolyte imbalances due to salt loss improved during follow-up. Ten days later, results showed ACTH: 25 pg/mL (NR: 10-60), cortisol: 21 ng/dL (NR: 7-29), plasma renin activity (PRA): 32 ng/mL/hour (NR: 1.4-7.8), and aldosterone level: >200 ng/dL (NR: 17-154). Neonatal CAH screening, conducted simultaneously, was normal. Significant laboratory results of the case are presented in Table 1.

(Place Table 1 near here)

Following hormone assessments, hydrocortisone and fludrocortisone were discontinued. No electrolyte imbalances or abnormal clinical findings were observed in subsequent follow-ups. The patient, who was enterally fed and had no electrolyte disturbances, was discharged on postnatal day 27. Follow-up evaluations showed normal aldosterone (4.29 ng/dL) and PRA (0.25 ng/mL/hour). The patient, now 6 months old, continues to be monitored. The changes in plasma renin activity and aldosterone levels during follow-up are shown in Figure 1.

(Place Figure 1 near here)

Discussion

Our case highlights secondary pseudohypoaldosteronism (PHA) as an important but rare cause of salt-wasting syndrome in neonates. The diagnosis is made when hyponatremia, hyperkalemia, and metabolic acidosis are accompanied by high plasma renin activity and aldosterone levels, and other conditions such as congenital adrenal hyperplasia (CAH) are excluded. In our patient, appropriate fluid and sodium replacement, along with temporary mineralocorticoid therapy, were promptly initiated (5). CAH was excluded based on the normal phenotype, pelvic ultrasound, and ACTH-cortisol results. Normalization of renin and aldosterone levels during follow-up confirmed the diagnosis of secondary PHA.

In secondary PHA (Type 3), the etiology often involves obstructive uropathy, VUR, or UTA, which can occur in conjunction with or independently of UTIs (6). However, in contrast to most cases in the literature, our patient did not have any urinary tract infection or anomaly. This is a distinguishing feature, as secondary PHA is predominantly reported in association with such conditions

The literature suggests that secondary PHA is more frequent in males. A 2019 review of 116 patients showed that 90% had UTIs, most of whom were male and under 6 months of age (7). Kocaoğlu et al. (8) reported that 38.5% of their 18 secondary PHA patients were female. Günay et al. (9) found that 87.5% (7/8) of their patients were male, with 62.5%. Despite all eight patients having UTIs, two did not have an underlying UTA. Our case is particularly noteworthy as it involves a female neonate.

After addressing the salt-wasting crisis urgently, the underlying cause should be corrected. The exact pathogenesis of secondary PHA is not fully understood. Early infancy is a risk factor due to the immature proximal tubular function, which is insufficient to respond to increased aldosterone levels for sodium reabsorption. A study by Melzi et al. (10) showed that 34% of 50 infants aged 15 days to 15 months with UTIs had PHA, all under 3 months. Delforge et al. (9) reported that 92.2% of their cases were under 6 months. On the other hand, it is thought that interstitial inflammation or bacterial toxins may lead to tubular unresponsiveness to aldosterone, primarily or through the synthesis and release of inflammatory mediators such as interleukin 1, thromboxane, and natriuretic peptide. Furthermore, urinary obstruction or vesicoureteral reflux in children may increase intrarenal pressure, resulting in downregulation of aldosterone receptors (11). Increased intrarenal pressure has also been shown to increase the synthesis of cytokines such as TNF alpha and TGF beta 1. In summary, high intrarenal pressure and inflammation are implicated in the pathogenesis.

The elevated C-reactive protein level in our patient suggests the co-occurrence of neonatal sepsis, indicating that the secondary PHA might have developed as a result of this septic process. Since the patient was already receiving antibiotic treatment (ampicillin + gentamicin), no specific infectious agent was isolated. Therefore, it is not accurate to entirely exclude a potential relationship between secondary PHA and sepsis. However, in a neonate without urinary tract anomalies and already under antibiotic therapy, the occurrence of a urinary tract infection at such an early stage is reported to be quite rare. Thus, although the possibility of urosepsis is considered clinically, the lack of strong supporting evidence reduces its likelihood. It is important to emphasize that the diagnostic evaluation should extend beyond urinary tract infections and consider other potential causes.

When compared to these studies, our case stands out as it involves a female neonate with neither UTI nor UTA, yet developed secondary PHA. This supports the hypothesis that additional mechanisms such as transient tubular immaturity, prematurity-related susceptibility, or hospital-acquired inflammation may play a role in the pathogenesis. Kumar et al. (12) reported a case of PHA associated with congenital hydrometrocolpos in the absence of any urinary tract pathology, supporting the notion that alternative etiologies exist.

Premature infants have immature renal tubular function, particularly in the proximal tubules, which may impair sodium reabsorption despite elevated aldosterone levels (13). This functional immaturity can mimic aldosterone resistance and contribute to secondary PHA without any structural urinary tract anomalies. In our case, the absence of UTI or UTA alongside prematurity strongly suggests that tubular immaturity was a key contributing factor. Recognizing this mechanism is critical for timely diagnosis and appropriate management, especially in premature neonates.

Furthermore, the early onset of symptoms in our case and the rapid normalization of renin and aldosterone levels after fluid-electrolyte management also emphasize the transient and potentially reversible nature of such non-urinary causes.

Clinically, secondary PHA most commonly presents with gastrointestinal symptoms such as vomiting, decreased feeding, abdominal distension, and diarrhea. Severe electrolyte disturbances may also lead to acute renal failure and sudden cardiac arrest. Cases of secondary PHA associated with pneumothorax and cholecystolithiasis have been reported. Our patient was diagnosed with a salt-wasting crisis (14).

In conclusion, failure to thrive and weight loss in the neonatal and infant periods may signal underlying serious conditions. If the clinical picture includes hyponatremia, hyperkalemia, and metabolic acidosis, secondary PHA should be considered in the differential diagnosis. In such cases, the presence of UTA and UTI should be investigated, but it should be noted that secondary PHA can develop without UTA and UTI. Our case contributes to the limited body of evidence supporting this possibility. We believe this perspective may be especially relevant to neonatologists who frequently manage complex salt-wasting syndromes in the NICU setting.

References

1.Ellison DH. Pseudohypoaldosteronism Type II. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. *GeneReviews®*. Seattle (WA): University of Washington, Seattle; November 10, 2011.

2.Memoli E, Lava SAG, Bianchetti MG, Vianello F, Agostoni C, Milani GP. Prevalence, diagnosis, and management of secondary pseudohypoaldosteronism. *Pediatr Nephrol*. 2020;35(4):713-714. doi:10.1007/s00467-019-04419-z

3.Krishnappa V, Ross JH, Kenagy DN, Raina R. Secondary or Transient Pseudohypoaldosteronism Associated With Urinary Tract Anomaly and Urinary Infection: A Case Report. Urol Case Rep. 2016;8:61-62. doi:10.1016/j.eucr.2016.07.001

4.Betti C, Lavagno C, Bianchetti MG, Kottanattu L, Lava SAG, Schera F, Lacalamita MC, Milani GP. Transient secondary pseudo-hypoaldosteronism in infants with urinary tract infections: systematic literature review. Eur J Pediatr. 2024;183(10):4205-4214. doi:10.1007/s00431-024-05676-3
5.Ranjith G, Uthup S, Satish B, Jain N. Salt wasting disorder in the newborn. Indian J Pediatr. 2006;73:95-96.
6.Klingenberg C, Hagen IJ. Transient pseudohypoaldosteronism in infants with vesicoureteral reflux. Tidsskr Nor Laegeforen.2006;126:315-317
7.Kocaoglu C, Akturk S. Analysis of patients presenting with serum electrolyte imbalance in terms of the differential diagnosis of pseudohypoaldosteronism. North Clin Istanb. 2023 Nov 6;10(6):754-760. doi: 10.14744/nci.2022.70105. PMID: 38328721; PMCID: PMC10846578.
8.Delforge X, Kongolo G, Cauliez A, Braun K, Haraux E, Buisson P. Transient pseudohypoaldosteronism: a potentially severe condition affecting infants with urinary tract malformation. J Pediatr Urol. 2019;15(3):265.e1-265.e7. doi: 10.1016/j.jpurol.2019.03.002. Epub 2019 Mar 9. PMID: 30962012.
9.Günay F, Şıklar Z, Berberoğlu M. Difficulties in the diagnosis and management of eight infants with secondary pseudohypoaldosteronism. Turk J Pediatr. 2022;64(3):490-499. doi: 10.24953/turkjped.2021.1443. PMID: 35899562.
10.Melzi ML, Guez S, Sersale G, Terzi F, Secco E, Marra G, Tirelli AS, Assael BM. Acute pyelonephritis as a cause of hyponatremia/hyperkalemia in young infants with urinary tract malformations. Pediatr Infect Dis J. 1995;14:56-59.
11.Rodríguez-Soriano J, Vallo A, Oliveros R, Castillo G. Transient pseudohypoaldosteronism secondary to obstructive uropathy in infancy. J Pediatr.1983;103: 375-380.
12. Kumar S, McDermott H, Kamupira S, Agwu JC. Rare case of pseudohypoaldosteronism in a neonate secondary to congenital hydrometrocolpos. BMJ Case Rep. 2020;28;13(6):e234813. doi: 10.1136/bcr-2020-234813. PMID: 32595115; PMCID: PMC7323414.
13. Martinerie L, Pussard E, Yousef N, Cosson C, Lema, I, Husseini K, Mur S, Lombès, M, & Boileau P. Aldosterone-signaling defect exacerbates sodium wasting in very preterm neonates: The Premaldo Study, The Journal of Clinical Endocrinology & Metabolism, 2015;100(11):4074–4081, https://doi.org/10.1210/jc.2015-2272
14.Watanabe T, Yamazaki A. Pneumothorax and transient pseudohypoaldosteronism in an infant with hydronephrosis. Pediatr Nephrol Berl Ger.2013;18:62-64https://doi.org/10.1007/s00467-002-1005-0.

Table 1 The Patient's Significant Laboratory Results

Test	Result	Range
Blood		
Alanine transaminase	35 U/L	0–50 U/L
Aspartate transaminase	55 U/L	20–60 U/L
Glucose	84 mg/dl	60-100 mg/dl
Creatinine	0.6 mg/dl	0.2–0.6 mg/dl
Blood urea nitrogen	23 mg/	8–28 mg/dl
Sodium	131 mEq/L	135-145 mEq/L
Potassium	6 mEq/L	3.5-6 mEq/L
Chloride	105 mmol/L	96–111 mmol/L
Calcium	10 mg/L	8.0–10.7 mg/L
Phosphate	mg/L	4.8–8.1 mg/L
C-Reactive Protein (CRP)	24 mg/L	0-5 mg/L
Blood gas (capillary)		
pH	7.42	7.34-7.43
Pco2	40	35-45 mmHg
HCO_3^-	13	19–24 mEq/L
Serum anion gap	14	8–16 mEq/L
Urine		
Sodium (Na^+)	20 mmol/L	
Hormones (blood)		
17-α-Hydroxyprogesteron	1.1 nmol/L	< 2.5 nmol/L
ACTH	25 pg/ml	10-60 pg/ml
Cortisol	21 µg/dl	7-29 µg/dl
plasma renin activity (PRA)	32 ng/ml/hour	1.4-7.8 ng/ml/hour
Aldosterone	>200 ng/dl	17-154 ng/dl

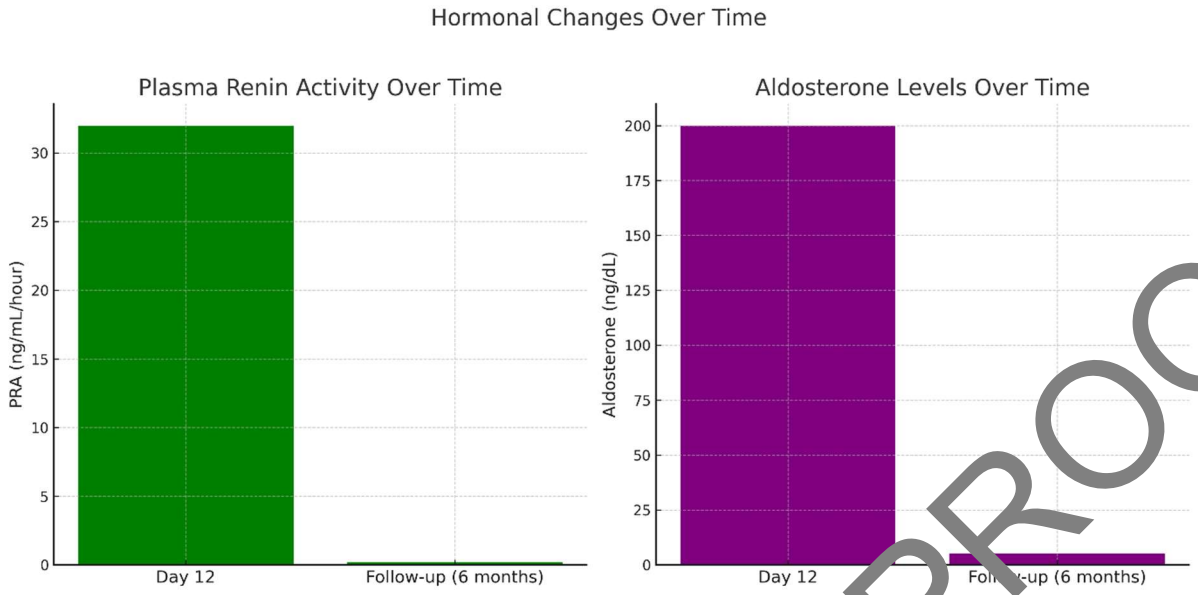

Figure 1. The change in the patient's plasma renin activity and aldosterone levels over time.