

CASE REPORT

A case of secondary pseudohypoaldosteronism that presented as poor weight gain

Keisuke Goshima | Hiroshi Tamura  | Yuko Hidaka | Keishiro Furuie | Shohei Kuraoka

Department of Pediatrics, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

Correspondence

Hiroshi Tamura, Department of Pediatrics, Faculty of Life Sciences, Kumamoto University, Kumamoto, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan.
Email: bohml905ht@kuh.kumamoto-u.ac.jp

Key clinical message

Pseudohypoaldosteronism (PHA) carries a good prognosis if treated early and appropriately, but some cases can have life-threatening events. We underscored the need to consider secondary PHA as one of the differential diagnoses of hyponatremia and hyperkalemia in infancy.

Abstract

Pseudohypoaldosteronism (PHA) type 1 has two classifications; the primary type, caused by genetic abnormalities that develop during neonatal and infancy periods, and the secondary type, caused by urinary tract malformation and urinary tract infection. Secondary PHA, if treated early and appropriately, has a good prognosis; however, some cases can present life-threatening events. Therefore, early diagnosis is crucial. We present a case of early infancy secondary PHA presented with marked hyponatremia and poor weight gain. The patient's growth and development improved with secondary PHA treatment. Here, we demonstrated the value of prompt action against infection and electrolyte imbalance and the importance of imaging for diagnosis, and underscore the need to consider secondary PHA as a differential diagnosis of hyponatremia and hyperkalemia in infancy. However further studies, including basic research, to elucidate the diseases pathology is warranted.

KEYWORDS

children, poor weight gain, pseudohypoaldosteronism, urinary tract infection, urinary tract malformation

INTRODUCTION

Pseudohypoaldosteronism (PHA) has no abnormalities in aldosterone secretion and kidney spherical function; however, causes sodium reabsorption disorders due to a decrease in response to mineral corticoids in distal tubes.

It is a rare hereditary disease that presents symptomatic and metabolic acidosis, and is divided into Type I with recognizable salt loss and Type II with hypertension and no salt loss.¹ PHA type 1 is common in boys during early infant and presents hyponatremia, hyperkalemia, metabolic acidosis, and hypersecretion of aldosterone. PHA

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type 1 has two classifications: primary type, caused by genetic abnormalities that develop during neonatal and infancy periods and secondary type, caused by urinary tract malformation (UTM) and urinary tract infection (UTI).^{2,3} Although PHA is considered to have a good prognosis if treated early and appropriately, some cases can have life-threatening events, such as cardiac arrest.⁴ We reported a case of secondary PHA presenting with marked hyponatremia and a chief complaint of poor weight gain.

CASE HISTORY/EXAMINATION

A 9-month-old boy with an unremarkable birth history presented with failure to thrive.

He was delivered at 39 weeks and 3 days, with a birth weight at 3360 g. There were no abnormalities on tandem mass screening. Cervical determination was not possible at 4 months, but he was able to roll over at 5 months and could sit up at 9 months. His poor weight gain was noted at 3 months of age. At 7 months after birth, he was noted to be vomiting once a day. The patient had been followed-up for poor weight gain of unknown cause.

METHODS

Nine months after birth, he was admitted at another hospital because for frequent vomiting and persisted poor weight gain. Physical measurements were height 70 cm (−0.7 standard deviation (SD)) and weight 7300 g (−1.6 SD) and vital signs were body temperature 37.5°C, blood pressure 76/40 mmHg, pulse 148/min, and respiratory rate 42/min.

The patient's anterior fontanels had caved in. He took gasping breaths; however, chest auscultation revealed no riles. His heartbeat was normal and had no abnormalities in the abdomen. His muscle tone had decreased and the extremities were cyanotic.

Edema was not observed on the external surface, and a decrease in skin turgor was observed. He had no vulvar abnormalities or pigmentation.

Investigation revealed serum levels of sodium at 103 mmol/L (normal 137–147 mmol/L), and potassium at 5.88 mmol/L (normal 3.70–4.90 mmol/L). He had nonanionic gap metabolic acidosis and transtubular potassium gradient of 3.67 (normal 8–9), which indicated reduced urinary potassium excretion. The urine sodium was <20 mmol/L. Correction of hyponatremia and dehydration treatment were started with physiological saline infusion. Infusion of 130 mEq/L of saline partially corrected the hyponatremia. Urinalysis revealed leukocytes and nitrites. Extended-spectrum beta-lactamase (ESBL)

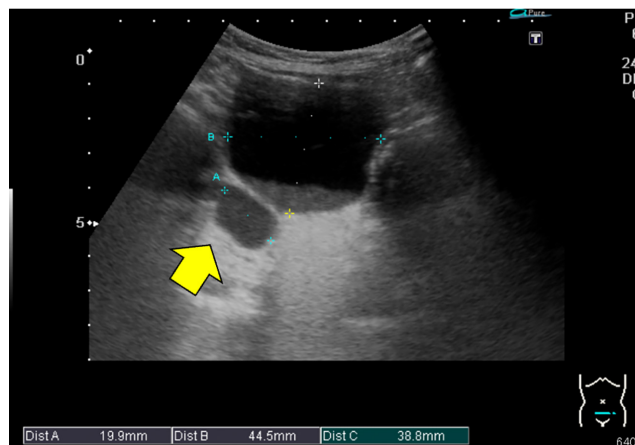


FIGURE 1 Abdominal ultrasound. Arrow: A luminal structure was observed on the right dorsal side of the bladder.

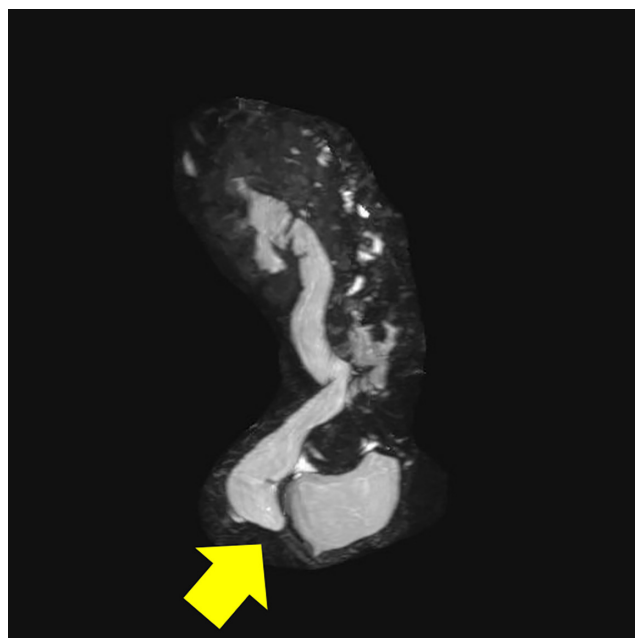


FIGURE 2 Magnetic resonance urography (MRU). MRU showed a duplicated right collecting system with an upper pole ectopic ureter that extended to the bladder neck. Arrow: Right vesicoureteral junction stenosis was observed.

Escherichia coli were isolated from the urine culture. Abdominal ultrasound revealed Grade 1 hydronephrosis and ureteral dilatation on the right. (Figure 1) The blood tests ruled out renal failure (i.e., no increase in the urea nitrogen or creatinine level) and hypertrophic pyloric stenosis (i.e., no evidence of hypokalemia or hypochloremic metabolic alkalosis). Abdominal ultrasound showed UTM and UTI; therefore, secondary pseudoaldosteronism was suspected. The levels of 21-hydroxylase and cortisol were normal. Aldosterone was elevated at 20,000 pg/mL (normal 4–80 pg/dL). Plasma renin activity (PRA) was elevated at >20 ng/mL/h (normal 0.2–4.1 ng/mL/h), implying tubular unresponsiveness. Adrenal insufficiency

was ruled out by 17-OHP, adrenocorticotrophic hormone (ACTH), and cortisol levels.

On the seventh day of illness, there were improvements in the serum levels of sodium to 140 mEq/L and potassium to 3.9 mEq/L, but he was transferred to our hospital, because of marked edema and difficult placement of intravenous access. Despite the absence of fever at the time of admission, intravenous infusion of meropenem (200 mg every 12 h) was started for the recent urine isolate of ESBL *E. coli* and because of the increased leukocyte count and C-reactive protein. On the fourteenth day, aldosterone level decreased to 207 pg/mL, PRA decreased to 5.6 ng/mL/h, and the edema improved.

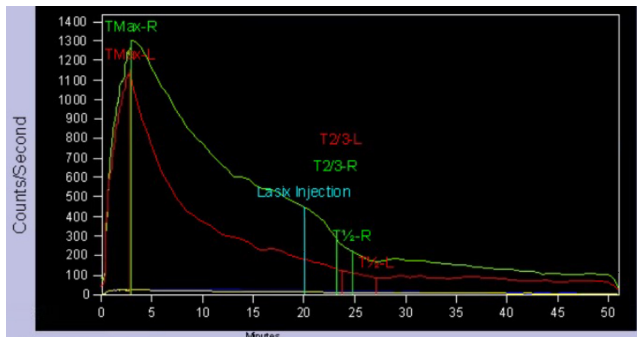


FIGURE 3 Diuretic renogram (99mTc DTPA MAG 3). No deterioration of both renal function, pattern of right renal ureter dilatation, and mildly decreased excretion.

Magnetic resonance urography (MRU), diuretic renogram, and voiding cystography (VCG) were performed to evaluate for UTMs. MRU showed a duplicated right collecting system with an upper pole ectopic ureter that extended to the bladder neck (Figure 2). VCG did not show regurgitation in the ureter or any abnormality in the lower urethra. On diuretic renogram (99mTc DTPA MAG 3), the left kidney had a normal renogram pattern but showed mild functional impairment, compared with the right kidney, while the right kidney had ureteral dilatation and mild hypoexcretion pattern (Figure 3). We diagnosed secondary PHA based on the findings of hyponatremia, hyperkalemia, and renal UTM, accompanied by high PRA and high blood aldosterone levels.

Figure 4 shows the clinical course. Oral administration of sulfamethoxazole/ trimethoprim (ST) was started on the sixteenth day to prevent UTI; however ST caused drug-induced eczema, and thus, had to use cefaclor for half a year. The patient's subsequent course was uneventful. He was able to crawl at 11 months, sit up at 1 year and 1 month, and walk at 1 year and 4 months of age. At the age of 2 years, the renin level was 4.4 ng/mL/h, and the aldosterone level was 171 pg/mL, which confirmed normalization. At the age of 4 years, he was growing well, with height of 101 cm (−0.1 SD), weight of 16.2 kg (+0.2 SD), and normal neurodevelopment (Figure 5).

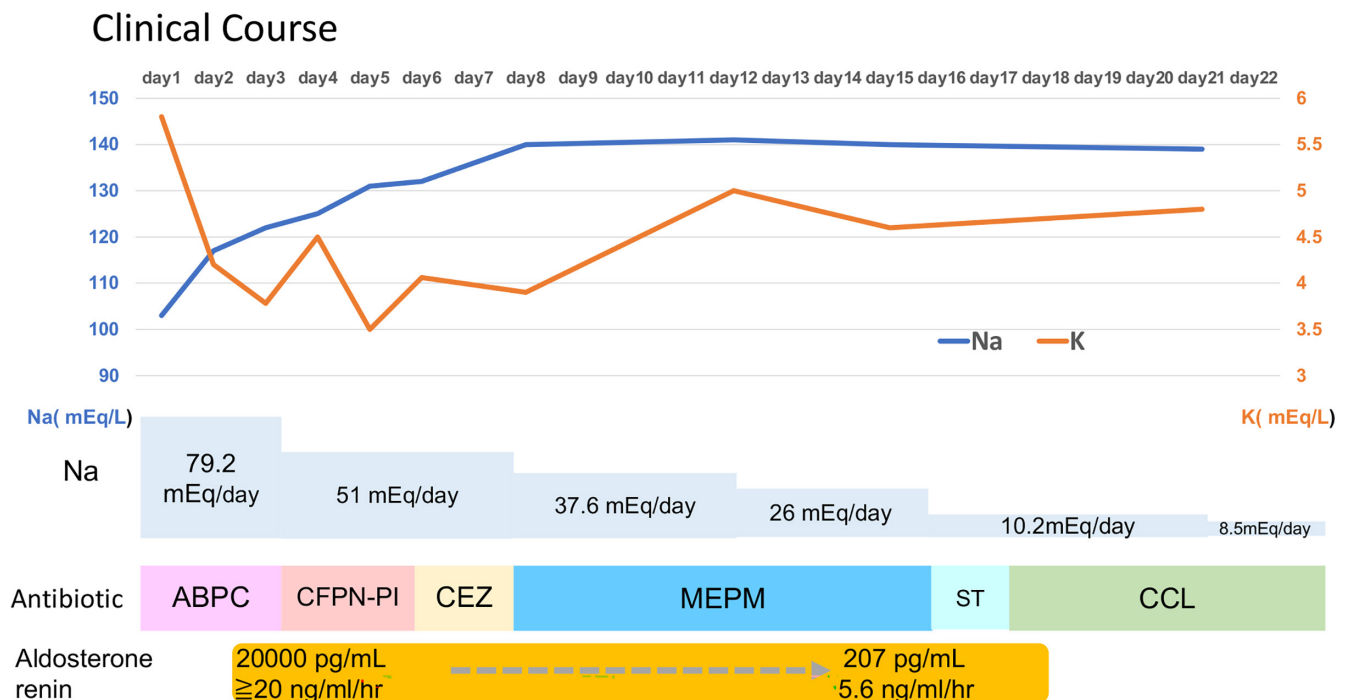


FIGURE 4 Clinical course. ABPC, ampicillin sodium; CCL, cefaclor; CEZ, cefazolin; CFPN-PI, cefcapene pivoxil; MEPM, meropenem; ST, sulfamethoxazole-trimethoprim.

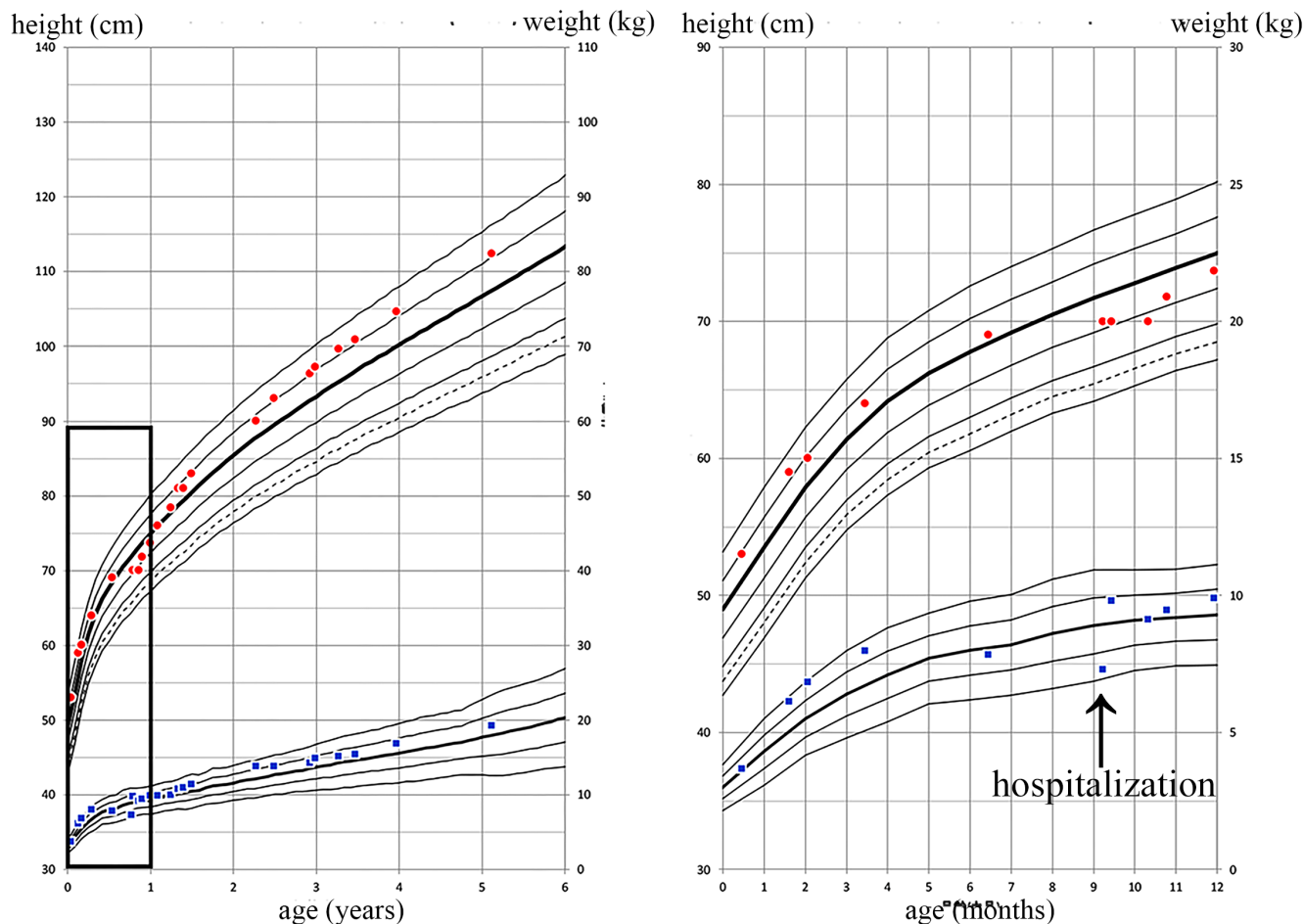


FIGURE 5 Growth curves. In this case, growth and development improved with treatment. The figure on the right shows details of the box in the figure on the left.

CONCLUSION AND RESULTS

Secondary PHA should be kept in mind as one of the differential diagnoses of hyponatremia and hyperkalemia in infancy and can be diagnosed by imaging. Secondary PHA had been thought to be caused by immaturity of the renal tubules, UTM, and UTI, but its pathophysiology remains unclear. In the future, further progress in elucidating the pathology, including basic research, is required.

DISCUSSION

Secondary PHA associated with UTI and UTM is most common in infants under 7 months of age⁵ and is characterized by diminished action of aldosterone receptors secondary to inflammation and pressure damages that are associated with the immaturity of the renal tubules. Urinary toxins and hyperaldosteronism had been thought to cause downregulation of aldosterone receptors,⁶ but the details of the pathogenic mechanism remain unknown.

Unlike primary PHA, secondary PHA does not demonstrate genetic mutations in the mineralocorticoid receptor (MR) or epithelial sodium channel (ENaC).⁷ Symptoms are nonspecific and include poor oral intake, poor weight gain, vomiting, diarrhea, and dehydration. Secondary PHA causes hyponatremia in infancy and is particularly important to differentiate from congenital adrenal hyperplasia (CAH),⁶ which has the same pattern of electrolyte abnormalities and may have similar time of onset and clinical symptoms. Urinalysis and imaging of the urinary system are useful in differentiating secondary PHA from CAH, but the diagnosis of secondary PHA requires confirmation of elevated renin and aldosterone levels and normal ACTH and cortisol levels.

In our case, there were no physical findings that strongly suggested CAH, an increase in vitality was observed after the start of fluid replacement, and UTM was confirmed by ultrasound; therefore, glucocorticoids were not administered. Some reports mentioned that patients should be treated with glucocorticoids until endocrine test results are available.^{8,9} Since the first report on secondary

PHA by G.W. Moll et al in 1982, over 100 cases have been reported worldwide.¹⁰ Approximately 90% of secondary PHA develops before 3 months of age. After 3 months of age, secondary PHA develops less frequently and rarely leads to electrolyte abnormalities.¹¹ Judging from the growth curve in our case, the onset was presumed to have occurred around 4–5 months after birth; notably, the serum sodium level was 103 mEq/L and led to marked hyponatremia. Although the neurological course in this patient was not poor, it should be noted that secondary PHA may develop severe hyponatremia even at 9 months after birth, as in our case. PHA has a wide range of clinical manifestations, the most prominent of which are gastrointestinal, including eating disorders, vomiting, bloating, and diarrhea.

Although secondary PHA is generally considered to have a favorable prognosis, there had been reported cases that developed serious conditions, such as convulsion and disturbance in consciousness secondary to hyponatremia, fatal arrhythmia secondary to hyperkalemia, and circulatory failure and shock.⁸ Therefore, early detection is important. Secondary PHA should be considered as one of the differential diagnoses not only in early infancy, as in our case, but also in cases with hyponatremia and hyperkalemia, for which urinalysis and urinary system evaluation should be performed.

Although the etiology of secondary PHA remains unclear, three factors, including age, urinary tract obstruction, and UTI, may be the key in developing secondary PHA. Secondary PHA is more common in infants under 6 months of age, and studies have validated that this may be associated with immature renal tubules.^{2,12,13} For children with UTM, urinary tract obstruction, or vesico-ureteral reflux, increased intrarenal pressure causes down-regulation of aldosterone receptors. In addition, immature renal tubules and UTM with children lead to a surge in the intrarenal synthesis of various cytokines, such as tumor necrosis factor- β 1 and tumor necrosis factor- α ; the former may block the action of aldosterone.^{14,15} In children with UTI, internal and external toxins not only directly damage the aldosterone receptors, but they also stimulate the immune system to produce inflammatory factors, such as interleukin-1, thromboxane, and natriuretic peptides.^{16,17} Although basic studies on secondary PHA are few, a transient decrease in lymphocyte MR expression is one of the mechanisms of aldosterone resistance in patients with secondary PHA. Examining the genetic polymorphisms in MRs and ENaCs is needed in order to understand the pathogenesis of secondary PHA, but there had been no reports on comprehensive genetic analyses.⁵ The pathophysiology of secondary PHA remains largely unknown, and advances in pathophysiological analysis, including basic research, are required.

AUTHOR CONTRIBUTIONS

Keisuke Goshima: Data curation; writing – original draft. **Hiroshi Tamura:** Conceptualization; data curation; formal analysis; writing – review and editing. **Yuko Hidaka:** Data curation. **Keishiro Furuie:** Data curation. **Shohei Kuraoka:** Data curation; formal analysis.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

ETHICS STATEMENT

All the procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards (64th WMA General Assembly, Fortaleza, Brazil, October 2013). Informed consent for examinations and to publish their cases, including images was obtained from patients parents and/or their family members.

CONSENT

Written informed consent was obtained from his parents for the publication of this case report.

ORCID

Hiroshi Tamura  <https://orcid.org/0000-0001-8786-217X>

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