

CASE REPORT

A Case Report of Pseudoaldosteronism Type I Complicated with Subependymal Hemorrhage

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ABSTRACT

Background: Systemic pseudohypoaldosteronism type I (sPHA I) is a rare genetic disorder characterized by impaired aldosterone responsiveness due to inactivating mutations in genes encoding epithelial sodium channel subunits.

Methods: This case report describes a 25-day-old female infant presenting with vomiting, metabolic acidosis, recurrent hyperkalemia, and hyponatremia. The cause of the disease was eventually confirmed through clinical evaluation and genetic sequencing.

Results: The patient's gene sequencing results showed a homozygous variation in exon 13 of the SCNN1B gene (NM_000333.3): c.1653_1655delCAT/p.Ile552del. This novel variant has not been reported. The final diagnosis confirmed sPHA I.

Conclusions: The clinical features of sPHA I mainly include neonatal vomiting, and the skin may have typical miliumary rash changes. The main laboratory features are hyperkalemia, hyponatremia and hyperaldosteronemia. Definitive diagnosis requires genetic verification.

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KEYWORDS

pseudohypoaldosteronism type I, hyperkalemia, hyponatremia, SCNN1B gene

INTRODUCTION

Pseudoaldosteronism (PHA) is a rare salt-loss syndrome caused by aldosterone resistance in renal tubules during the neonatal and infant periods [1]. PHA can be classified into PHA type I, PHA type II and PHA type III. Among them, PHA type I can be further classified into renal PHA type I and systemic PHA type I (sPHA I) based on the involved organs and genetic variations [2]. sPHA I results from inactivating mutations in genes encoding subunits of the epithelial sodium channel (ENaC), with an estimated incidence of 1:166,000 [3]. The clinical manifestations include electrolyte imbalances such as dehydration, hyponatremia, hyperkalemia and

metabolic acidosis and may also be accompanied by respiratory tract infections, cholestasis and rashes, etc. [4]. This case report describes a neonate with sPHA I caused by a SCNN1B gene variant, aiming to analyze its clinical characteristics and explore diagnostic and therapeutic strategies.

CASE PRESENTATION

First Admission

The patient is a 25-day-old female infant who was admitted to the hospital due to a 5-day history of coughing, lethargy, and metabolic acidosis. The patient was delivered by cesarean section at 37 + 6 weeks of gestational age, with a birth weight of 2,500 g and an apgar score of 10-10-10. Physical examination upon admission: temperature: 36.6°C, pulse: 137 bpm, respiratory rate: 49 breaths/minute, blood pressure: 65/44 mmHg, weight: 2,100g (16% decrease from birth weight), poor skin elasticity, depressed anterior fontanelle, coarse breathing sounds in both lungs.

Laboratory findings: severe metabolic acidosis (pH 7.1, HCO₃⁻ -6.5 mmol/L, BE -21.7 mmol/L), hyperkalemia (serum potassium 6.58 mmol/L), hyponatremia (serum sodium 98.7 mmol/L). There was no abnormal thyroid function, hepatic, renal, and cardiac enzyme profiles. The initial diagnosis is "neonatal pneumonia, congenital genetic metabolic disease? Electrolyte imbalance."

During hospitalization, it was difficult to correct the electrolyte imbalance and metabolic acidosis of this patient. Her weight did not increase but decreased instead. Serum potassium fluctuated between 5.4 - 7.9 mmol/L, and serum sodium remained at 120 - 135 mmol/L. The serum cortisol (8:00 AM) was 59.93 nmol/L. 17 α -hydroxyprogesterone was 4.42 nmol/L. Angiotensin II was 124.78 pg/mL. Angiotensin I (37°C) was 50 ng/mL. Angiotensin I (4°C) was 29.85 ng/mL. Plasma renin activity was 20.15 ng/mL. Adrenocorticotrophic hormone was 7.57 pmol/L, aldosterone was over 3,930.72 pg/mL. On the seventh day of admission, the patient presented with scattered rashes all over the body. On the eleventh day of admission, the serum potassium was 7.9 mmol/L, the sodium was 135.9 mmol/L, and the chlorine was 102.1 mmol/L. At the same time, subependymal hemorrhage and liver function impairment occurred (ALT: 136 U/L, AST: 131 U/L). As shown in Table 1 and Figure 1, genetic sequencing of the patient revealed a homozygous variant in exon 13 of the SCNN1B gene (NM_000333.3): c.1653_1655delCAT/-p.Ile552del. Both parents were confirmed to be carriers of this variant. Notably, this variant has not been reported in dbSNP and ClinVar database. According to the ACMG/AMP guidelines, this variant was classified as a variant of uncertain significance (VUS) with the following evidence codes: PM4, PM2_Supporting, and PP4.

Therefore, the patient's treatment regimen was adjusted to include Nuintec formula milk, a low-potassium diet, insulin plus glucose to lower potassium levels, hydro-

chlorothiazide for diuresis, oral concentrated sodium chloride supplementation, and anti-infective therapy. The patient was discharged after temporary stabilization of electrolyte levels and was maintained on hydrochlorothiazide and concentrated sodium chloride upon discharge.

Second admission

The patient, aged 2 months and 14 days, was readmitted due to severe pneumonia and respiratory failure caused by influenza virus infection (pH 7.27, PO₂ 52 mmHg), accompanied by severe acidosis (pH 7.27), hyperkalemia (7.7 mmol/L), and hyponatremia (120 mmol/L). Physical examination upon admission: temperature: 37.8°C, pulse: 150 bpm, respiratory rate: 38 breaths/minute, weight: 3.7kg (< 3rd percentile). Signs: global developmental delay, protein-energy malnutrition, pharyngeal erythema, bilateral coarse breath sounds with scattered moist rales. During this period, complications such as Enterococcus faecium urinary tract infection (positive urine culture), myocardial damage (troponin T 0.095 ng/mL), and generalized pustular miliaria occurred. In clinical treatment, a multidisciplinary collaboration model is adopted: 1) Respiratory support: Transition to CPAP after 7 days of mechanical ventilation; 2) Anti-infection: Meropenem combined with linezolid; 3) Electrolyte management: Continuous sodium supplementation (5.5 mL concentrated sodium chloride/70 mL milk) and hydrochlorothiazide diuresis (increased to 4 mg bid); 4) Symptomatic support: Nourishing the heart muscle, skin care, etc. After 28 days of treatment, the child's condition was stable, and she was discharged from the hospital. After discharge, concentrated sodium chloride (5.5 mL/70 mL milk) and hydrochlorothiazide (4 mg bid) were orally administered for a long time, and electrolytes and neurodevelopment were monitored regularly.

Follow up

Three months after discharge, the patient's weight increased to 5.2 kg, serum potassium remained at 5.0 - 5.8 mmol/L, and serum sodium was 135 - 140 mmol/L. With a height of 63 cm, a weight of 5.5 kg, and a head circumference between the 10th and 25th percentiles, the patient lags behind children of the same age in terms of development. Clinically, hydrochlorothiazide (3 mg bid) and sodium supplementation treatment were continued, and electrolytes and renal function were monitored regularly. Eight months after discharge, the levels of serum potassium and sodium were 5.5 mmol/L and 138 mmol/L, respectively. Length: 72 cm, weight: 8.3 kg. Eighteen months after discharge, serum potassium: 4.5 mmol/L, serum sodium: 139 mmol/L, length: 82 cm, weight: 10.6 kg. The growth and development are basically on par with those of children of the same age. Our research was obtained with the informed consent of the patients' guardians.

Table 1. Classification and evidence of the novel variant.

			PS4	PM1	PM2	PP3
Variant	Gene	Classification	Frequency in 600 normal control	Located in functional domain	Frequency in east Asian population (and world-wide)	In-silico prediction
c.1653_1655delCAT/p.Ile552del	SCNN1B	VUS	0	NA	NA	NA

Classification and evidence system according to ACMG/AMP variants interpretation guidelines.

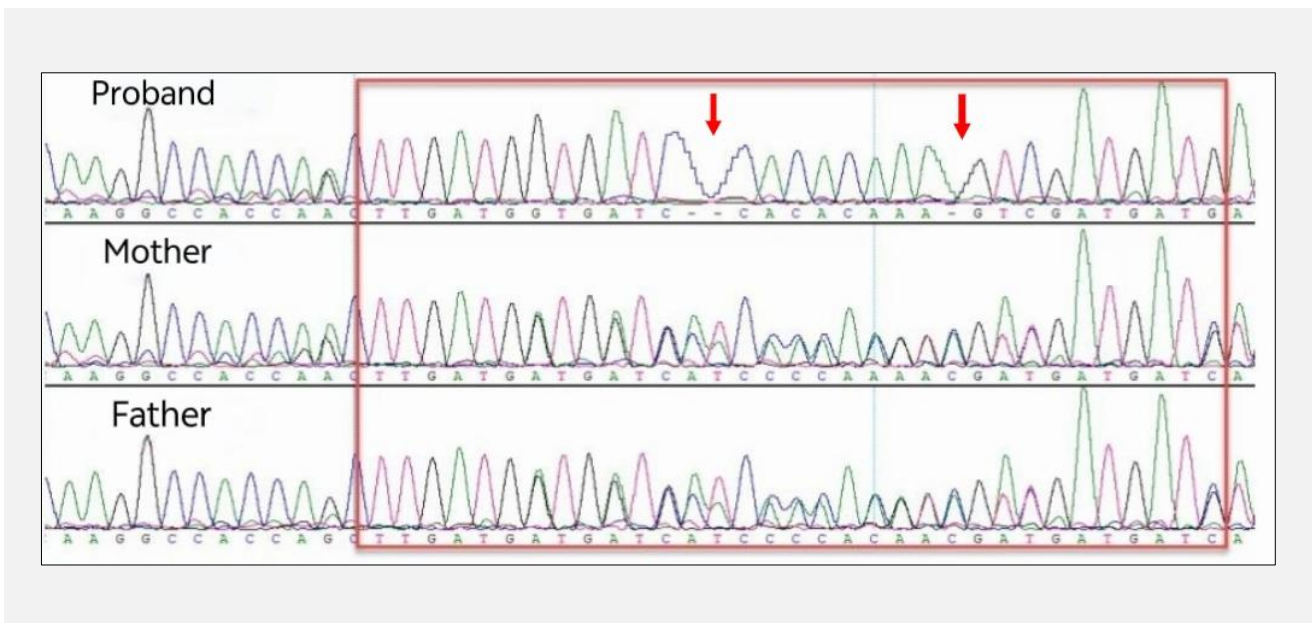
PS4: The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls.

PM1: Located in a mutational hot spot and/or critical and well - established functional domain.

PM2: Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes or ExAC.

PP3: Multiple lines of computational evidence support a deleterious effect on the gene or gene product.

VUS: Variants of Uncertain Significance, NA: Data not available.

**Figure 1. The gene sequencing results of the patient's family.**

DISCUSSION

As an autosomal recessive genetic disorder, sPHA I is caused by mutations in genes SCNN1A, SCNN1B and SCNN1G, resulting in abnormalities of the ENaC α , β and γ subunits encoded. Its main features are hyponatremia, hyperkalemia and metabolic acidosis, accompanied by elevated renin activity and aldosterone. The clinical manifestations include repeated vomiting and diarrhea, dehydration, and weight loss. In this case, the patient presented with hyponatremia, hyperkalemia combined with metabolic acidosis during the neonatal period. The concentrations of aldosterone and renin were elevated, while the serum 17-hydroxyprogesterone level was normal. These changes are consistent with the above altera-

tions and have significant diagnostic value for clinical indications. Whole exome sequencing of the patient revealed a homozygous SCNN1B (NM_000333.3) variant: c.1653_1655delCAT (p.Ile552del) in exon 13. This mutation is located in a highly conserved transmembrane domain (TM2) and disrupts the spatial conformation of ion channels through in-frame deletion, resulting in complete loss of ENaC function, which is consistent with the pathogenic mechanism of previously reported SCNN1B mutations (accounting for 30 - 40% of sPHAI cases) [5].

Interestingly, all 21 pathogenic variants of SCNN1B-TM2 included in the ClinVar and HGMD databases (as of July 2024) were missense or nonsense mutations, while p.Ile552del was the first in-box deletion mutation.

The weight loss rate of the patient reached 16% (higher than the 10 - 12% reported in the literature [3,4]) and was combined with subependymal hemorrhage, suggesting that this mutation may lead to more severe channel structure collapse.

In terms of differential diagnosis, acquired hyperkalemic renal tubular acidosis (RTA) caused by chronic kidney disease has similar manifestations to PHA. However, RTA patients have low levels of plasma renin and aldosterone, accompanied by hyperchlorinated acidosis and urine pH > 5.5, and are ineffective for hydrochlorothiazide hydrochloride, which is inconsistent with this case [6,7]. Congenital adrenal hyperplasia (CAH) is characterized by insufficient cortisol synthesis, electrolyte imbalance, abnormal sexual characteristics, etc. [8]. The 17-hydroxyprogesterone level in children is often above 300 nmol/L and the external genitalia are abnormal [9]. However, in this case, the 17-hydroxyprogesterone level is only 4.42 nmol/L, and the female external genitalia are normal. Therefore, CAH is excluded.

sPHAI can cause various complications and requires individualized treatment. The patient requires intravenous fluid replacement to correct dehydration and acidosis, as well as intravenous sodium chloride injection to treat hyponatremia. In this case, the patient ultimately needed 5.5 mL of concentrated sodium chloride (10%)/70 mL of milk to maintain serum sodium > 135 mmol/L, which is much higher than the initial dose. Hyperkalemia can be treated by lowering serum potassium levels through insulin, calcium supplements, and supplementation with potassium-lowering resins. In addition, infants can be fed high-sodium and low-potassium formula milk to maintain electrolyte balance. The indicators of effective treatment are the correction of the patient's salt-loss state, the recovery of thirst sensation, the return to normal growth and development, and the decrease or return to normal of plasma renin activity and blood aldosterone concentration.

CONCLUSION

In summary, the clinical features of sPHA I mainly include neonatal vomiting, and the skin may have typical milia rash changes. The main laboratory features are hyperkalemia, hyponatremia, metabolic acidosis and hyperaldosteronemia. Definitive diagnosis relies on genetic confirmation. The treatment of sPHA I requires comprehensive intervention and the establishment of a long-term follow-up mechanism, which is conducive to optimizing the treatment plan. This study, through a comprehensive analysis and summary of the currently confirmed cases, aims to enhance pediatricians' understanding of this disease and the ability to identify them early, thereby reducing misdiagnosis and missed diagnosis and improving the survival rate of children as much as possible.

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Declaration of Generative AI in Scientific Writing:

During the preparation of this work, the authors did not use any generative AI or AI-assisted technologies in the writing process. The content of this manuscript is solely the intellectual product of the human authors.

Declaration of Interest:

The authors declare that they have no conflict of interest.

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