# Pseudohypoaldosteronism Type 1 Newborn Patient with a Novel Mutation in *SCNN1B*

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**Abstract**

Pseudohypoaldosteronism is a rare disease characterized by resistance to aldosterone-targeted organs, hyponatremia, hyperkalemia, metabolic acidosis, and severe salt loss in hyperaldosteronism. Homozygous mutations in *SCNN1A*, *SCNN1B,* and *SCNN1G* genes were found to be responsible for the etiology. About 80 cases with molecular basis have been reported to date. In this case, a newborn patient admitted to our neonatal intensive care unit due to feeding problems was examined. The parents of the patient had a consanguineous marriage, and they had lost their three sons due to hyperkalemia. Since she had hyponatremia and hyperkalemia, congenital adrenal hyperplasia was primarily considered. Although the initial evaluation was made in this direction, the patient was diagnosed as pseudohypoaldosteronism type 1 with the findings obtained during the process such as dehydration, cortisol levels, adrenocorticotropic hormone levels, and negative *CYP21A2* analysis result. This clinical diagnosis was confirmed by the novel homozygous frame-shift variant c.1245_1246insC (p.N416Qfs*35) in *SCNN1B* shown by gene analysis. In this report, we seek to emphasize that aldosterone deficiency should be one of the first diagnoses to be considered in neonatal patients with hyponatremia, hyperkalemia, metabolic acidosis, and dehydration.

**Keywords**
- pseudohypoaldosteronism
- hyperkalemia
- SCNN1B

## Introduction

Pseudohypoaldosteronism (PHA) is a salt-wasting condition stemming from peripheral resistance to aldosterone. Peripheral resistance may primarily result from receptor defects due to mutations in the mineralocorticoid receptor or epithelial sodium channel. Second, it may also develop as a result of infection, uropathy, and drug-induced receptor resistance.[1] The disease is seen in less than 1/1,000,000 in the world. About 80 cases with a molecular basis have been reported to date.[2] In general, PHA is discovered through the symptoms of hyponatremia, hyperkalemia, and metabolic acidosis in the newborn period. It is also diagnosed by laboratory tests showing significant increases in plasma renin activity and aldosterone levels.[3]

In this case report, we present a 9-day-old baby girl who was admitted to our neonatal intensive care unit for severe dehydration resulting from salt wasting in the newborn period and was diagnosed with PHA. We aim to analyze the clinical characteristics and anticipated clinical progression of this very rare disease throughout this case report.

## Case Report

Following a healthy pregnancy the patient's mother, aged 34, gave birth to her sixth baby via cesarean section. This was

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also the sixth live birth for the mother. The birth weight of the baby girl was 3,450 g (50–75 p). On the ninth day of life, the baby presented to our emergency service with absence of suckling. She was hospitalized due to hyponatremic dehydration with hyperkalemia. The parents of the patient had a consanguineous marriage, and had lost three sons due to hyperkalemia. There was no other finding in the pedigree analysis. Heart rate was found to be 150/min, respiratory rate was 45/min, and blood pressure was 65/40 (48) mm/Hg. On the physical examination of the patient, skin rashes on her palpebrae and body were observed. Her muscle tone and skin turgor were decreased. Other systemic examinations were found to be normal. Ambiguous genitalia or hyperpigmentation was not observed. In laboratory blood analysis, severe hyponatremia (113 mEq/L), hyperkalemia (9.4 mEq/L), hyperbilirubinemia (total bilirubin was 15.5 mg/dL, direct bilirubin was 0.5 mg/dL), increased urea (85.6 mg/dL), normal levels of creatinine (0.6 mg/dL), and metabolic acidosis (pH:7.26, base excess: –9.7 mmol/L, lactate: 3 mmol/L, $HCO_3$:17.0 mmol/L) were determined.

Complete blood count, C-reactive protein, and urinalysis were normal. Infectious workup with urinary culture was negative. As an initial diagnosis, congenital adrenal hyperplasia (CAH) was considered given the patient's hyponatremia and hyperkalemia. Blood samples were analyzed for hormone levels, and treatment with hydrocortisone (10–20 mg/$m^2$/day) and fludrocortisone (150 µg/$m^2$/day) was initiated. Calcium gluconate, sodium bicarbonate, insulin-glucose infusion, and nebulized salbutamol therapies were given for hyperkalemia during the acute period. Following potassium levels reduction, oral antipotassium therapy was started and subsequent serum potassium levels gradually decreased to 3.6 mEq/dL. Intravenous sodium repletion was given for hyponatremia followed by oral sodium supplementation (150 mEq/kg/day). A normal serum sodium level (134 mEq/L) was achieved by the second day of hospitalization.

On the third day of hospitalization, blood analysis revealed 17-hydroxyprogesterone: 2.01 ng/mL (0–3 ng/mL), cortisol: 13.1 µg/dL (4.6–22.8 µg/dL), adrenocorticotropic hormone: 13.3 pg/mL (5–48 pg/mL), aldosterone: 6392 pg/mL (50–1746) pg/mL, plasma renin activity >38 ng/mL/hour (2.4–37 ng/mL/hour). Arterial blood pressure values were found as normal. Therefore, the previously suspected diagnosis of CAH was excluded and confirmed by negative CYP21A2 gene analysis. Since aldosterone levels were high, but blood pressure levels were normal, the case was thought to be a primary PHA. In the urinary system ultrasonography, which was performed to eliminate secondary PHA, no abnormality was observed. Cranial ultrasonography obtained due to the patient's somnolence, indicated no abnormalities as well. In her metabolic analysis, blood-ammonia level, urine-blood amino acid levels, urine organic acid levels, and tandem mass were found to be normal. Based on the provided clinical information, first we planned the panel test including three genes (SCNN1B, SCNN1G, SCNN1A) that are frequently mutated in PHA patients. The blood sample was taken from the antecubital vein via vacutainer tubes containing ethylenediaminetetraacetic acid (BD, Franklin Lakes, New Jersey, United States). DNA was isolated from white blood cells using Magpurix Blood DNA Extraction Kit 200 (Zinexts LSC, New Taipei City, Taiwan [R.O.C.]). Quantitative-purity determinations and fluorometric analyses were performed. Next-generation sequencing was performed using Agilent HaloPlex (Agilent, California, United States) with a custom-designed multigene panel. The sequencing was performed on an Illumina MiSeq sequencer (Illumina, California, United States) using MiSeq Reagent Kit v3 ($2 \times 300$ bp). The fraction of target bases with at least 20 reads was approximate 98.7%. The analysis showed homozygous variant c.1245_1246insC (p.N416Qfs*35) in SCNN1B. To date this variant is not described in the Exome Aggregation Consortium, Genome Aggregation Database, 1000 genomes, or the NHLBI GO Exome Sequencing Project. In silico prediction tool (MutationTaster) defined this variant as a disease-causing variant. PhyloP and PhastCons scores were 3.66 and 1, respectively, and GERP (genomic evolutionary rate profiling) score was 4.65. This frame-shift variant was well-considered to be pathogenic according to American College of Medical Genetics classification with respect to PVS1, PM2, and PP3 criteria, and was confirmed by conventional Sanger sequencing method. The patient's parents were found to be heterozygous for this change (data not shown).

The electrolyte imbalance stemming from salt wasting was compensated for by adding salt supplementation into feeds, and was thereafter stabilized. Following intensive care treatments, hydrocortisone and fludrocortisone therapies were discontinued. The additional salt amount was increased to 3 g/day. Since her overall state of health was stable, serum potassium and sodium levels were between normal range, and dehydration problem was eliminated; the patient was discharged from the hospital with a 2 g/day sodium intake. Our patient is now 6 months old. Although she received antipotassium and salt support, she has been hospitalized due to hyponatremia and hyperkalemia a few times. In our recent interviews with the parents, we have learned that the patient's overall state of health is bad, and she is currently admitted in the intensive care unit.

This research was managed in accordance with the Declaration of Helsinki 2013. The patient's parents gave his informed consent for the molecular genetic analysis of the patient, the publication of patient data.

## Discussion

Aldosterone is a primary mineralocorticoid hormone that regulates blood electrolytes by absorbing sodium from distal tubule and secreting potassium. Lack of aldosterone results in hyponatremia, hyperkalemia, dehydration, and metabolic acidosis since the body loses particularly renal sodium and cannot secrete potassium. Lack of isolated aldosterone is a rarely seen situation. However, in salt wasting-initiative forms of CAH, we frequently see these clinical symptoms. In these cases, we can also observe sexual differentiation disorders.

In the newborn period, cases that reveal salt-wasting symptoms make us first consider CAH. In such cases, patients

often demonstrate sexual differentiation disorders and salt-wasting symptoms. The most common type of CAH form that results in salt wasting is the deficiency of 21-hydroxylase (90–95%). It is clinically classified as "classical" and "non-classical." Depending on the level of aldosterone deficiency, classical CAH has subgroups as "salt wasting" and "non-salt wasting" types. While 75% of cases are salt wasting, the rest is simple virilizing type. In CAH cases, salt-wasting symptoms might develop in the first week of life at the earliest. In infants, vomiting, hypotension, hypoglycemia, and unrecoverable dehydration are observed. In physical examination, macro genitalia is detected in boys, whereas ambiguous genitalia is seen in girls. In both sexes, in the genital zone and mammary areola, hyperpigmentation stands out.[4] In our case study, the genital examination of the patient revealed no sexual differentiation disorders. Moreover, aldosterone levels were found to be high. Therefore, any suspected CAH case was not considered.

In the newborn period, for patients diagnosed with salt-wasting syndromes, CAH should be the first disorder to consider. In such cases, treatment should be oriented for regulating liquid-electrolyte balance—hyperkalemia in particular. Patients' clinical and laboratory analyses should be carefully followed, and other rare underlying causes should also be taken into consideration. For patients with hyponatremia, hyperkalemia, and metabolic acidosis, if no clinical and laboratory response is observed despite appropriate liquid-electrolyte balance and steroid replacement, aldosterone resistance should be considered. In such cases, plasma renin and aldosterone levels should be evaluated. High levels of plasma aldosterone and renin are indicators of PHA. In cases of high renin levels accompanied by low aldosterone levels, hypoaldosteronism should be taken into consideration. Lastly, with the low levels of aldosterone and renin, hyporeninemic hypoaldosteronism should be considered.[5–7] In our case, since renin and aldosterone levels were high, the patient was diagnosed with PHA.

In PHA, despite high aldosterone levels, aldosterone deficiency is observed in target organs—for the renal system in particular, there is no response to aldosterone at the receptor level or the signaling system.[8] There are three types of PHA. Salt wasting is observed in types 1 and 3, but type 2 is a salt keeping form.[4] Type 1 PHA, first characterized by Cheek and Perry in 1958, begins in the newborn period with a wide spectrum of presentations. In all cases, sodium absorption in the collecting drain cells and potassium secretion are defective. Characteristic symptoms of the patients are hyponatremia, hyperkalemia, metabolic acidosis, and high aldosterone and renin levels.[8] In our case, all of these symptoms were observed. Systemic PHA type 1 is an autosomal recessively transmitted disease, and it is the most severe form. Its effect is seen mainly in epithelial sodium channel, renal collecting drain, respiratory pathway, and colon, salivary, and sweat glands.[3,5] Recently, for epithelial sodium channel activity, intracytoplasmic proteins such as neural precursor cell expressed developmentally down-regulated 4 (Nedd4), small-G protein K, cyclase associated actin cytoskeleton regulatory protein 1 (*CAP1*), cystic fibrosis transmembrane conductance regulator (*CFTR*) genes have been identified.[9] PHA type 2 is known as Gordon syndrome or familial hyperkalemic hypertension. Genetic transition is known to be through an autosomal dominant inheritance pattern. It is characterized by hypertension, hyperkalemia, and metabolic acidosis, accompanied by normal renal function, low-normal plasma renin activity, and aldosterone concentration.[4] Since blood pressure was normal and renin activity was high in our case, the possibility of PHA type 2 was excluded. On the other hand, transient and type 3 PHA is an acquired form of the disease, and often develops with intestine and urinary tract infections during infancy. Patients might have nutrition defects, failure to thrive, vomiting, diarrhea, and polyurea. Their general state of health might gradually deteriorate. Weight loss, high urea creatinine levels, and life-threatening hyperkalemia might also develop.[10] In laboratory analysis, hyponatremia, hyperkalemia, metabolic acidosis, increased sodium excretion in urine are detected. Two days after underlying causes are eliminated, patient show clinical improvement and do not need external support. Since no pathology was observed in urine culture analysis, and all ultrasonographic examinations of the patient were clear, the diagnosis of type 3 PHA was not taken into consideration.

As discussed above, PHA type 1 is identified by certain clinical symptoms such as life-threatening weight loss, early phase dermatitis, isolated growth retardation, repetitive lower respiratory tract infection, dehydration, life-threatening hyperkalemia, and cardiac arrest. Early-onset symptoms, high aldosterone levels, and daily salt intake greater than 30 mmol/kg make us consider systemic PHA type 1.[1] No spontaneous remission is seen in this disease, and no curative treatment has been identified yet. Salt supplementation might sometimes remain insufficient as well.[4] In our case, physical examination revealed dermatitis and dehydration consistent with PHA type 1 clinical symptoms. Laboratory analyses were also consistent with type 1 PHA.

In cases of PHA, it is difficult to make a differential diagnosis via monitored mutations because of genetic heterogeneity. In addition to the multigenic notion of the disease, the presence of allelic heterogeneity in PHA cases leads to a lack of certain clinical association with a specific mutation. However, in our case, having the frame-shift mutation that leads to the generation of a stop codon is clear evidence of pathogenicity for the monitored insertion. Therefore, when these data are evaluated with the clinical and laboratory findings, the diagnosis of type 1 PHA becomes definite.

## Conclusion

In conclusion, for patients presenting with hyponatremia, hyperkalemia, metabolic acidosis, and dehydration during the newborn period, aldosterone deficiency should be the first condition to consider. In these cases, CAH and PHA must be included in the differential diagnosis and consideration of maternal drug use history may be helpful. Moreover, evaluation for, and elimination of, urinary tract infections and congenital urinary tract abnormalities help make the correct diagnosis.

Conflict of Interest
None declared.

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## References

1 Belot A, Ranchin B, Fichtner C, et al. Pseudohypoaldosteronisms, report on a 10-patient series. Nephrol Dial Transplant 2008;23 (05):1636–1641
2 Tetti M, Monticone S, Burrello J, et al. Liddle syndrome: review of the literature and description of a new case. Int J Mol Sci 2018;19 (03):812
3 Amin N, Alvi NS, Barth JH, et al. Pseudohypoaldosteronism type 1: clinical features and management in infancy. Endocrinol Diabetes Metab Case Rep 2013;2013:130010
4 Kurtoğlu S, Hatipoğlu N, Büyükayhan D. Neonatal tuz kaybı tablosu. Türkiye Klinikleri Journal of Pediatric Sci. 2008;4:90–105
5 Arai K, Chrousos GP. Syndromes of glucocorticoid and mineralocorticoid resistance. Steroids 1995;60(01):173–179
6 Zennaro MC, Lombès M. Mineralocorticoid resistance. Trends Endocrinol Metab 2004;15(06):264–270
7 Mendes C, Vaz Matos I, Ribeiro L, Oliveira MJ, Cardoso H, Borges T. [Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: genotype-phenotype correlation]. Acta Med Port 2015;28 (01):56–62
8 Ağladıoğlu SY, Aycan Z, Kendirci HN, Erkek N, Baş VN. Does pseudohypoaldosteronism mask the diagnosis of congenital adrenal hyperplasia? J Clin Res Pediatr Endocrinol 2011;3(04):219–221
9 Gormley K, Dong Y, Sagnella GA. Regulation of the epithelial sodium channel by accessory proteins. Biochem J 2003;371(Pt 1): 1–14
10 Arai K, Chrousos GP. Aldosterone deficiency and resistance. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. South Dartmouth, MA: MDText.com, Inc.; 2016