

Case report

Clinical Management in Systemic Type Pseudohypoaldosteronism Due to *SCNN1B* Variant and Literature Review

Running Head: Pseudohypoaldosteronism Due to *SCNN1B* Variant

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What is already known on this topic? Pseudohypoaldosteronism is a life threatening disease due to serious salt loss. Differential diagnosis from other adrenal insufficiencies is important because the treatments are different. Patient compliance is difficult due to the need for excessive amounts of oral treatments.

What this study adds? We presented a patient with difficult diagnostic process due to hypertension. A novel variant that is causing stop codon was detected in our patient. Also clinical and laboratory features of all cases with *SCNN1B* variant in the literature were reviewed.

Abstract

Systemic pseudohypoaldosteronism is a rare salt wasting syndrome that is caused by inactivating variants in genes encoding epithelial sodium channel subunits. Hyponatremia, hyperkalemia, metabolic acidosis, increased aldosterone and renin levels are expected findings of this disease. It is difficult to manage this disease due to high dose oral replacement therapy. Furthermore patients with systemic pseudohypoaldosteronism require life-long therapy. Here we report a patient with systemic PHA due to *SCNN1B* variant whose hyponatremia and hyperkalemia was detected at the 24th hour of life. Hyperkalemia did not improve with conventional treatments and dialysis was required. Also he developed myocarditis and hypertension in follow-up. Difficulties in diagnosis and treatment of this patient were discussed in this report. Also we review the literature on common features of patients with *SCNN1B* variant.

Keywords: systemic pseudohypoaldosteronism, hyponatremia, hyperkalemia, metabolic acidosis, epithelial sodium channel, *SCNN1B*

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Introduction

Aldosterone is a mineralocorticoid hormone that provides sodium absorption and potassium secretion. Sodium crosses the apical membrane in the principal cells in kidney and enters the epithelial cell through the ion selective epithelial sodium channel (ENaC). Potassium is also secreted into the tight epithelium in the kidney. The epithelial sodium channel is located in the apical membranes of the sensitive tissues such as distal nephron, distal colon, salivary and sweat glands and creates a rate-limiting step in sodium reabsorption (1, 2). Epithelial sodium channel is a heteromultimeric protein consisting of 3 subunits, α , β , γ (3).

ENaC subunits are encoded by *SCNN1A* genes in chromosome 12p13, *SCNN1B* and *SCNN1G* genes in chromosome 16p12.2 – p12.1.

Pseudohypoaldosteronism (PHA) is a salt wasting syndrome that develops due to variants in the mineralocorticoid receptor (MR) or ion channels in the kidney tubules. The estimated incidence of this rare disease is between 1/ 47.000 and 1/ 80.000, and its prevalence is <1/ 1.000.000 (4, 5, 6). PHA1 is divided into renal (PHA1A) and systemic (PHA1B) forms depending on mutation in the *NR3C2* gene that codes the MR or in the *SCNN1A*, *SCNN1B* and *SCNN1G* genes that code ENaC, respectively. In systemic form, there is serious salt loss from the lung, colon, sweat and salivary glands besides the kidney, and the symptoms begin in the neonatal period. Systemic PHA, which is inherited as autosomal recessively, develops life-threatening hyponatremia, hyperkalemia and metabolic acidosis. Plasma renin and aldosterone levels increase significantly, indicating end organ resistance. Treatment requires high doses of sodium replacement and potassium-lowering approaches. In this article, the clinical management of a patient with PHA due to *SCNN1B* variant and the common features of patients with *SCNN1B* variant were presented.

Case Report

The male patient was born 3600 grams on term with NSVD and was followed up in the neonatal intensive care unit due to respiratory distress. It was learned that hyponatremia and hyperkalemia were detected (Na 118meq/ L, K 8meq/ L) at the 24th hour of hospitalization. He received 6x1 gr salt, 4x2 gr/kg calcium polystyrene sulfonate, 12x1ml/kg NaHCO₃ and 12x4 ml/kg 3% NaCl treatment during this period. Then he was consulted to our clinic because of lack of response to treatments at the age of 1 months 15 days. On physical examination, his weight was 4000 grams (-1,32 sds), his height was 55 cm (-0.34 sds), and he did not have hyperpigmentation and any abnormality in genital examination. His daily weight gain was insufficient. His blood pressure was high with 110/80 mmHg (95 p of systolic and diastolic blood pressure for this age group is 94/46 mmHg). There was a 3rd degree consanguinity between the parents. His brother had died at the age of seven days with hyponatremia and hyperkalemia. On admission, Na level was 123 meq/ L, K 7.1 meq/L, blood PH 7.12, and HCO₃ was 10.8 mmol/ L. Echocardiography was normal. He was diagnosed with congenital adrenal hyperplasia. Hydrocortisone and fludrocortisone treatments were started. Calcium gluconate, glucose-insulin infusion, NaHCO₃ infusion, salbutamol inhalation were administered for hyponatremia and hyperkalemia. Despite these interventions, hyponatremia continued. Anti hypertensive treatment was started for hypertension (0.1 mg / kg / day amlodipine). Oral 2x0.5 grams of salt was also added to the treatment and the dose was gradually increased. The laboratory findings were as followed: 17-OHprogesterone 1.22 ug / L, DHEASO₄ 241.8 µg / dL, total testosterone 215.6 ng / dl, ACTH 255 pg / ml, cortisol 43.8 µg / dL, renin 16.3 ng / ml / h (2.4-37), aldosterone 6.4 µg / L (0.065-0.86), urine Na 134 mmol / L, urine K 2 mmol / L (when blood Na 123 meq / L, K 7.1). The transtubular potassium gradient (TTKG) was 1.3, indicating very low renal potassium excretion. Based on the laboratory test results, hydrocortisone and fludrocortisone treatments were discontinued. Urinalysis, urine culture and renal ultrasonography were normal. In this process, hypertension continued. The diagnosis of systemic PHA was considered in the patient who was admitted with hyponatremia and hyperkalemia in the neonatal period, with high aldosterone level, increased urinary Na excretion, decreased K excretion. When hyperkalemia did not respond to conventional treatments (in addition to the above treatments, calcium polystyrene sulfonate was given as 1 gr/kg/dose in four doses) peritoneal dialysis was required. After three days of peritoneal dialysis, K decreased to 4.18 meq/ L. Electrolyte values of the patient were kept in the normal range with 6x1 g of oral salt and 4x3 g of antipotassium treatment. The patient had fever during the follow up. But although the body temperature was normal afterwards the tachycardia resisted. The patient was diagnosed with myocarditis due to an increase in the acute phase reactants, troponin I level and electrocardiographic findings. Myocarditis findings regressed on the 10th day. On the other hand, the cause of hypertension could not be explained and was thought to be related to the salt treatment. Then his blood pressure returned to normal ranges and amlodipine and propranolol treatments were discontinued on the 14th day. The Sanger sequencing analysis of the *SCNN1A* gene, which is the most common gene that is mutated in systemic PHA Type1B, was found to be normal. In subsequent Illumina MiSeq sequencing, a homozygous c. 978 C > A (p.Tyr326Ter) variant was detected in the 6th exon of the *SCNN1B* gene (NM_000336). After oral salt (6x1g) and antipotassium (4x3g) administration, the patient had normal electrolyte values and was discharged. One month after discharge, during an infection period the patient had to be hospitalized again due to the loss of oral intake and salt wasting crisis. At the last control, the patient was 7 months old, his weight was 7,3 kg (-1,3 sds), height was 68 cm (-0,83 sds) and blood pressure was 80/35 mmHg (50p). His growth and development was appropriate for the age with the current treatments (6x1 gr oral salt, 4x3 gr antipotassium (calcium polystyrene sulfonate), 4x2 ml NaHCO₃). It was planned to continue the clinical follow-up.

Discussion

Systemic PHA type 1 is a rare life-threatening disease. Clinical manifestations are similar to other adrenal gland insufficiencies, such as congenital adrenal hyperplasia, hypoaldosteronism, secondary pseudohypoaldosteronism. The clinical presentation is characterized with insufficient weight gain, vomiting, and dehydration (4, 6, 7). Our patient had normal genitalia with hyponatremia, hyperkalemia. Hydrocortisone and fludrocortisone treatments were started until adrenal androgen results were obtained. Since adrenal hormone levels were normal in the follow-up, the patient was diagnosed with PHA1B. In the differential diagnosis of our patient, transient aldosterone resistance secondary to urinary tract infection was also considered (4), and this diagnosis was ruled out when urinalysis, urine culture and renal ultrasonography were normal. Elevated aldosterone level accompanying hyponatremia and hyperkalemia supported resistance to aldosterone in the kidney and directed the treatment of our patient.

To date, more than 40 variants have been reported in the genes encoding ENaC subunits (7), and these variants have often been found in the gene encoding the alpha subunit. Less than 11 variants have been reported in the gene encoding the beta subunit (Table 1). In our patient, we first investigated the *SCNN1A* gene encoding alpha subunit, but when we did not detect a pathogenic variant, we sequenced the *SCNN1B* gene. In our patient, a novel c. 978C > A (p.Tyr326Ter) homozygous variant was detected presumably forming an early stop codon in the *SCNN1B* gene. This variant has not been previously reported in the literature or in the GnomAD database including genome data from healthy individuals, and is anticipated to be a pathogenic change by Variant Taster, one of the in silico assessment tools used to predict pathogenicity of a variant. In addition, this change has been considered pathogenic according to the criteria of ACMG 2015 (PVS1, PM2, PP3).

SCNN1B gene consisting of 13 exons encodes a transmembrane protein with 2 transmembrane segments with 640 amino acids (Figure 1) (7). The detected variant is located in the extracellular part of the protein, and, it is estimated cause loss of function by creating an early stop codon presumably resulting in nonsense mediated decay at the mRNA level.

Figure 1 is presented in a separate file.

To date, 11 variants with PHA due to *SCNN1B* variants have been reported (Table 1). These cases were diagnosed in infancy with classical findings. In follow-up, one case died due to salt wasting crisis (6, 8). In four cases, there were skin manifestations such as dry skin, severe eczema, bullous dermatitis and hidradenitis suppurativa (7, 10, 11). Recurrent lung infections developed in four cases (7, 11, 12, 13) and gastrostomy was required in four cases due to the salt wasting (8, 10, 11, 13). Pulmonary hypertension developed in 1 case during follow-up (11). No other cases except for ours developing viral myocarditis and hypertension were encountered during attacks.

Both urgent and long-term treatments of pseudohypoaldosteronism involve many difficulties. Hyperkalemia can be life threatening due to the risk of cardiac arrhythmia. In the literature, similar to our case, there were cases where peritoneal dialysis should be opened due to hyperkalemia (7, 14, 15, 16). Cases requiring gastrostomy due to difficulties in continuing oral treatment have been reported (4, 5, 8, 10, 11, 13, 17). Patients with pseudohypoaldosteronism are prone to pulmonary infections due to a decrease in sodium-dependent fluid absorption in the lungs. Rapid decompensation may occur in infections or in the clinical situation where oral intake is impaired. After the electrolyte balance was achieved in the follow-up of our patient, salt wasting occurred again due to intervening viral myocarditis, and during this period, the patient's treatments could be administered with a nasogastric tube.

Conclusion

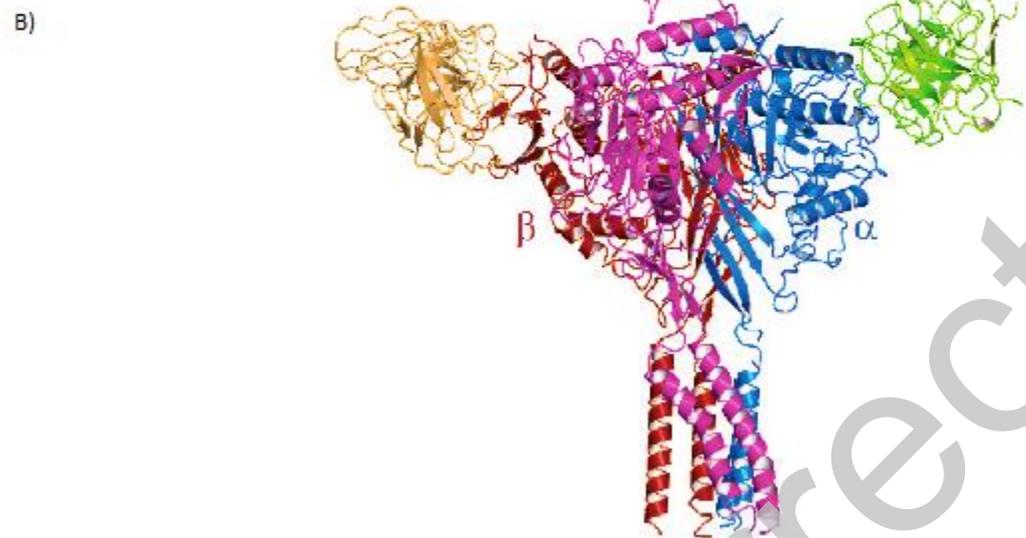
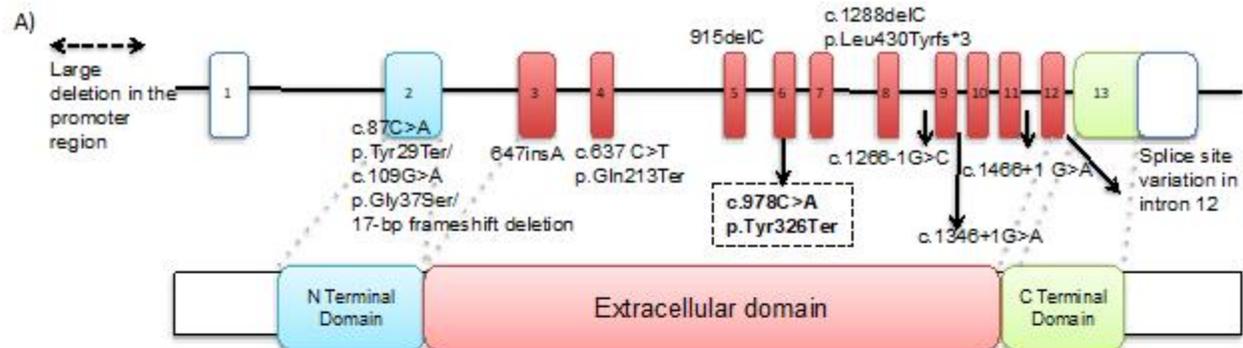
Systemic type PHA is a challenging disease to manage with severe salt wasting that starts in the neonatal period. In this disease, life-threatening arrhythmias can be seen due to recurrent salt wasting and severe hyperkalemia. PHA1B can be confused with congenital adrenal hyperplasia. If a patient with hyperkalemia has hyponatremia, elevated urinary sodium excretion and low TTKG, mineralocorticoid resistance/deficiency should be considered. Treatment compliance is difficult due to the need for high dose oral salt and antipotassium treatment. Long-term follow-up and treatment of these patients should be done carefully, as the patients are frequently incompatible with treatment and the frequency of rapid decompensation is high especially during periods of infection.

Table-1 is presented in a separate file.

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Figure 1.



Uncorrected proof

Table 1: Clinical and laboratory features of our case and other cases with SCNN1B mutation in the literature

thoma

	Gender	Age of diagnosis	Na meq/L	K meq/L	Aldosterone ng/dl	Renin ng/ml/h	Genetic	Treatment	Current age	Additional Findings	Clinical follow-up
Our case	M	1 month 25 days	123	7.1	640	16.3	c.978C>A (p.Tyr326Ter) (E6) Homozygous	NaCl, NaHCO ₃ , sodium polystyrene sulphate	7 months old	Myocarditis and hypertension	Once experienced salt wasting crisis during infection, now his development is appropriate for age
Chang et al. ¹⁸	-	19 days	133	8.2	*	-	c.109G>A (p.Gly37Ser) (E2) Homozygous	-	-	-	-
Kerem et al. ²¹	F	-	-	-	-	-	Two frame shift variations 647insA (E3) / 915delC (E5) Compound heterozygous	-	18 years	High serum IgE concentration, normal spirometry and chest radiography	
Thomas et al. ¹²	-	4 days	127	10.2	1.281	235.5	Large homozygous deletion in the promoter region of of β ENaC	NaCl, NaHCO ₃ , sodium polystyrene sulphate	7 years old	Recurrent lung infection	There is a decrease in the frequency of lung infections
Saxena et al. ⁸	M	7-8 days	< 120	8.5- 10.5	>1440	-	1669+1G>A splice site mutation in intron 12, Homozygous	NaCl, kayexalate	-	-	Recurrent salt-wasting crisis in newborn and infancy, gastrostomy was required, his growth and development was normal but he died at

											the age of 6.5 yr after cardiac arrest
Edelheit et al. ¹³ and Hanukoglu et al. ²⁰	M	6 days	135	5.9	39.6-248.7	>50	1669+1G>A splice site mutation in intron 12, Homozygous	NaCl, kayexalate	7 years old	Persistent clear nasal discharge, frequent lower respiratory infections and failure to thrive	Recurrent salt-wasting crisis, gastrostomy was performed at 14 months of age
Belot et al. ¹⁰	F	6 days	126	6.8	1.627	1335	c.637 C>T (p.Gln213Ter) (E4), Homozygous	-	3 years old	Bullous dermatitis	During follow-up, gastrostomy was opened, normal development at the age of 3 but still experiencing diarrhea and respiratory distress attacks
Dogan et al. ¹⁹	M	3 days	125	9	946	140	c.1266-1G>C splice site mutation in intron 8, Homozygous	NaCl, NaHCO ₃ , sodium polystyrene sulphate	3,5 years old	Vomiting, poor feeding	Short stature, decrease in dehydration attacks and in hospitalization with age
Nobel et al. ¹¹	F	2-3 weeks	135	5,1	2.800	190	c.1288delC (p.Leu430Tyrfs*3) (E9) / c.1466+1 G>A splice site mutation in intron 11 Compound heterozygous		32 years	Myalgia, hidradenitis suppurativa, pulmoner hypertension	Continuous hospitalization from 2 weeks to 2 years and NaCl, NaHCO ₃ and potassium chelation support with gastrostomy tube up to 3.5 years old, recurrent episodes of chronic bronchitis during childhood
Cayir et al. ⁶	M	9 days	106	11,8	317.5	98.2	c.87C>A (p.Tyr29Ter) (E2) /	NaCl, sodium	-	-	During the follow up had seven salt wasting crisis

							c.1346+1G>A splice site mutation in intron 9 Compound heterozygous	polystyrene sulphate			and died in the last crisis at 6 months of age
Gopal-Kothandapani et al. ⁷	F	1 day	128	7.8	64.7	-	c.1542+1G>A splice site mutation in intron 12	NaCl, NaHCO ₃ , sodium resonium	8 years old	Severe eczema	Recurrent electrolyte imbalances
Gopal-Kothandapani et al. ⁷	M	8 days	113	11	600	-	17-bp frameshift deletion in exon 2	NaCl, NaHCO ₃ , sodium resonium	14 years old	Dry skin	Peritoneal dialysis need at the first application, frequent lung infection

* Plasma aldosteron concentration stated as 1 g/L (1-95) in the article.

* Nomenclature of the variations are written as in the original publications.