Diagnosis and Management of Pseudohypoaldosteronism type 1 in Children

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Abstract

Pseudohypoaldosteronism type 1 (PHA1) is a rare autosomal recessive disease characterized by impaired transepithelial sodium transport. Affected children develop life-threatening salt loss of neonatal onset, hyperkalemia, acidosis, elevated sweat, salivary and urinary sodium concentrations with the absence of glucocorticoid deficiency. Typically, these children have highly elevated renin and aldosterone levels due to end organ resistance to aldosterone. Therefore, they are insensitive to mineralocorticoid treatment, but respond to high doses of sodium supplementation and potassium-lowering therapies. Two clinical forms of PHA1 can be distinguished. The renal form of PHA1 (PHA1A; OMIM # 177735) is characterized by salt loss exclusively through the kidneys which is caused by autosomal dominant inactivating mutations in the human mineralocorticoid receptor (MR, *NR3C2*) gene. The systemic form of PHA1 (PHA1B; OMIM # 264350), results from biallelic inactivating mutations in the genes encoding the α (SCNN1A), β (SCNN1B) or ɤ (SCNN1G) subunit of the epithelial NaC channel (ENaC). In most of the patients with the renal form of PHA1, sodium supplementation can be weaned in early ages of life, probably due to the maturation of the renal sodium handling. However, the salt loss in PHA1B results not only from the kidneys but also from the colon, salivary glands, and sweat ducts. Children with

PHA1B require life-long salt supplements and medical support. Some children with PHA1B develop a cystic fibrosis-like pulmonary phenotype with recurrent infections and cutaneous findings, which are not seen in PHA1A. Replacement of sodium and hydration fluids, treatment of hyperkalemia and acidosis, nutritional and pulmonary supportive therapies, close monitoring of growth and development by a multidisciplinary team are the mainstay of the treatment. Indomethacin, thiazide diuretics and carbenoxolone therapies may be tried with limited success. The TNF lectin like domain derived peptides that have been shown to activate the epithelial sodium channel (ENaC) in various cell- and animal-based studies are promising candidates for the treatment of PHA1B. This review summarizes clinical, biochemical and molecular features and current management of PHA1 in children.

Key words: Pseudohypoaldosteronism type 1, Children, ENaC, MR, *NR3C2*, *SCNN1A, SCNN1B, SCNN1G*

Introduction

Aldosterone is an adrenocortical steroid hormone whose main role is to regulate the body's fluid and sodium-potassium by acting on the distal renal tubules. It binds to the ***mineralocorticoid receptor*** (MR) in the renal tubules, and enables ion transport between the lumen and the cells via ***amiloride-sensitive epithelial Na^+ channels*** (ENaC) by inducing various pathways **(Figure 1)**. [1-3]

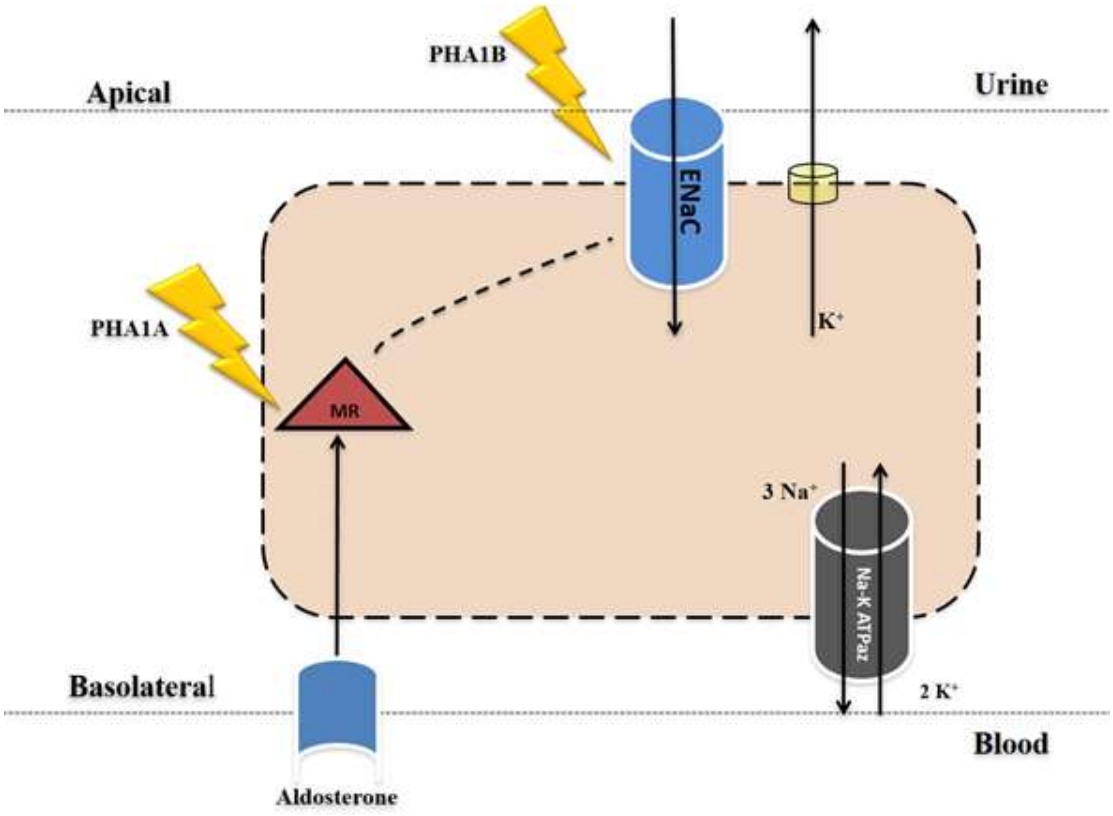

Figure 1. Development of PHA 1. Adolestrone binds mineralocorticoid receptor (MR). Activation of MR increases the expression of the epithelial sodium channel (ENaC) in distal renal tubules. ENaC reabsorbs Na^+, and excretes K^+ in the apical cell membrane. Na^+-K^+-ATPase provides intracellular Na^+ and K^+ balance by reabsorbing $2K^+$ and excreting $3Na^+$ in the basolateral cell membrane. While inactivating mutations encoding MR (*NR3C2* gene) cause pseudohypoldosteronism Type 1A (PHA1A), bialletic inactivating *ENaC* mutations result pseudohypoaldosteronism Type 1B (PHA1B).

The mineralocorticoid receptor is encoded by the *NR3C2* gene. This gene is located on Chr.4q31.1, consists of 10 exons and codes MR protein consisting of 984 amino acids. The *NR3C2* gene consists of an N-terminal domain, a DNA-binding domain and a C-terminal ligand-binding domain. The C-terminal ligand-binding domain region is conserved between species. This region is responsible for numerous functions, such as ligand binding, nuclear localization, dimerization, and interaction with heat shock proteins and transcriptional coactivators. [4-7]

ENaC is found in the apical parts of the epithelium in the distal nephron. ENaC plays an important role in Na^+ and K^+ homeostasis, and has a high affinity for the potassium-sparing diuretics amiloride and triamterene. It mediates the rate-limited step in aldosterone-related sodium reabsorption and plays a role in blood pressure regulation. ENaC is a heterotrimeric protein complex consisting of α, β and γ subunits, which are essential for a properly functioning channel. The α, β and γ subunits are coded by the *SCNN1A, SCNN1B* and *SCNN1G* genes, respectively. The α subunit is responsible for channel activity and plays a role in Na^+ flow. The β and γ subunits are necessary for cell surface activity, channel expression, and channel flow regulation. Each subunit possesses two transmembrane segments in the form of intracellular and extracellular loops arising from the N and C terminals. The C terminal, where interaction with other proteins occurs, is a proline-rich region, and mutations affecting this region give rise to pseudohypoaldosteronism type 1 (PHA1). The epithelial sodium channel is present throughout the body, in the kidney, and also in the airway, colon, and saliva and sweat glands. ENaC regulates sodium reabsorption and electrolyte balance in the kidneys and respiratory fluid distribution in the lungs. [1, 5, 8-11]

Death occurs early in the life of mice without ENaC, while gradual recovery has been reported in humans, probably due to involvement of other factors in airway development. The importance of aldosterone in embryological development and neonatal physiology is apparent considering that ENaC is found in several tissues, and the clinical outcomes resulting from developmental disorder. [10, 12, 13]

Inactivating mutations in the genes coding MR and ENaC in which aldosterone exhibits its effect result in the development of PHA1. [1,2] PHA1 is a rare, congenital, life-threatening disease with a resistance to mineralocorticoids. The estimated prevalence is <1/1,000,000. [8, 11, 14]

PHA1 was first described by Cheek and Perry in 1958, in a male baby with severe sodium loss with no renal or adrenal defect.[15] Since then, around 120 more paediatric cases have been described **(Table 1).** [2-4, 7-11, 13, 16-47]

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 **(Figure 2).** [8, 9]

The renal form (PHA1A) (OMIM177735) develops in association with inactivating mutations in the *NR3C2* gene that affect the MR only in the kidney. Although the majority of cases of renal PHA1 are associated with heterozygous mutations in *NR3C2*, no mutation in the *NR3C2* gene has been shown in 30% of cases. The pathogenesis of PHA1A has still not been fully explained. The focus in terms of pathogenesis has been on the possibility of disorder in another gene causing electrolyte imbalance, or on various environmental factors. The disease is autosomal dominant, and the pathology is limited to the kidney. The most common initial symptom is growth retardation. The renal form may be asymptomatic or take the form of salt

loss. Salt loss exhibits a milder clinical course compared to the systemic form and generally resolves spontaneously. [4-6, 8, 36, 42] There are also autosomal recessive (AR) cases reported with renal form. The phenotype may be relatively more severe in cases in with the AR inheritance. [48]

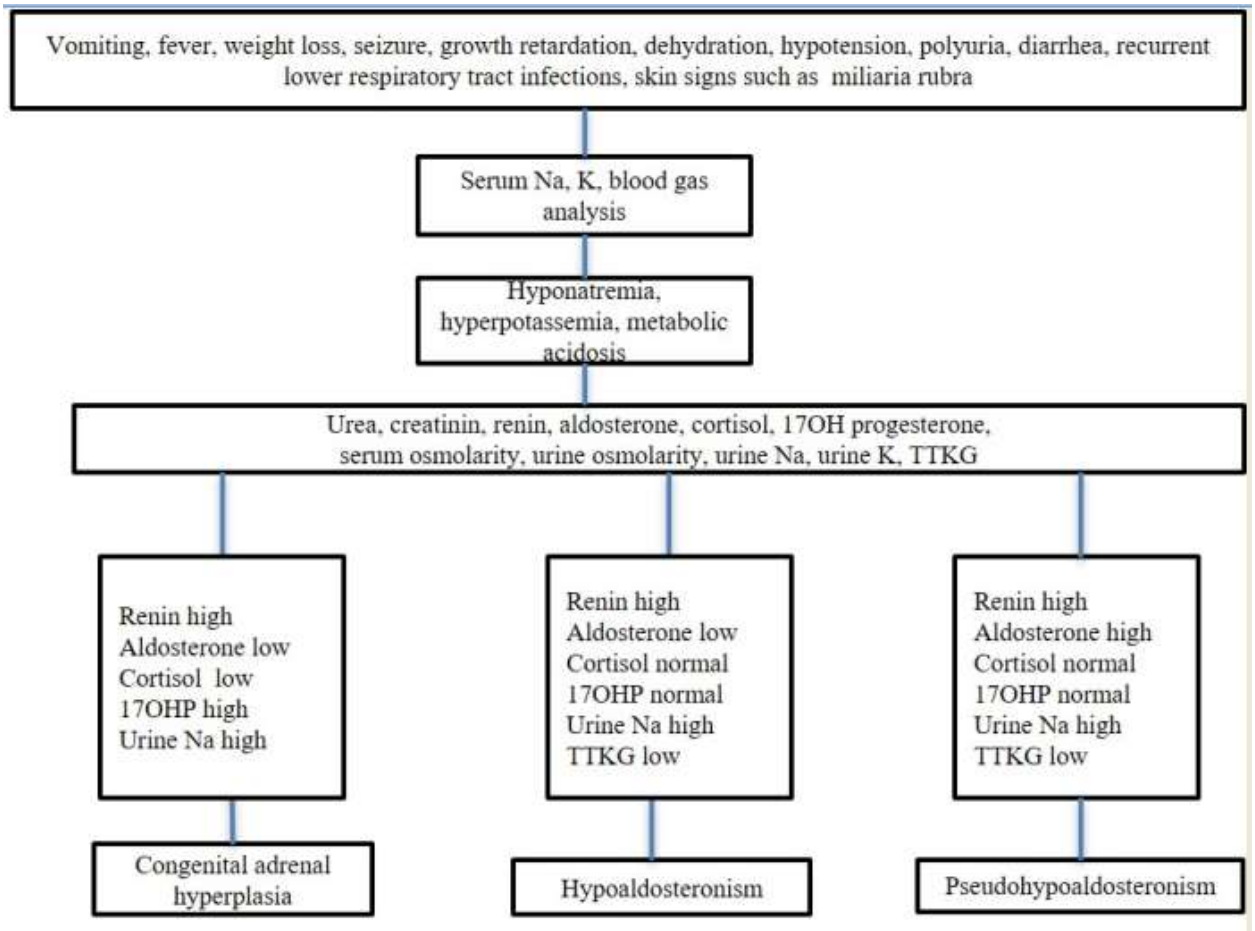

Figure 2. clinical evaluation in pseudohypoaldosteronism.

The systemic form (PHA1B) (OMIM264350) is the more severe form of the disease, and is inherited in an AR manner. It derives from homozygous or combined heterozygous mutations leading to function loss in the *SCNN1A* (Chr12p13.31), *SCNN1B* (Chr16p12.2-p12.1) or *SCNN1G* (Chr16p12.2) genes that code the epithelial sodium channel subunits α, β, and γ. Eighty percent of PHA1B mutations are seen in the *SCNN1A* gene exon 8, while 20% occur in the *SCNN1B* or *SCNN1G* genes. The great majority of mutations responsible for PHA1B are nonsense and result in the absence of a protein or in a short protein, and are clinically severe. In missense mutations, a normal length protein is synthesized, but the disease emerges as a result of a functional subunit being affected, and is associated with a milder phenotype. PHA1B causes salt loss from several organs, including the kidney, colon, saliva, Meibomian glands, and sweat glands. Systemic PHA1B has a more severe clinical phenotype than the renal form and is characterized by diffuse end-organ

resistance or multiple target organ failure require requiring lifelong sodium support.[5, 24, 35, 49-51]

Clinical presentation and diagnosis

Correlation is not always present between the genotype and the clinical phenotype in cases described in the literature, and the severity of the disease can vary even in patients with the same mutation. A clearer understanding of the mild and severe forms of the disease has begun being achieved as numbers of patients reports have increased in recent years. The clinical manifestation of PHA1 in the neonatal period may begin over a broad spectrum from mild to severe hyponatremia, generally in the first week of life. Sodium absorption and potassium release in the collecting ducts in the kidney is defective. The condition may manifest with clinical findings such as salt-losing crises, severe acid-base disorders, life-threatening hyperkalemia, and cardiac arrest.[2, 28, 40, 52, 53]

Salt-losing crises frequently recur, and patients require high-dose lifelong salt replacement. In addition to salt-losing crises, findings such as weight loss, growth-development delay, fever, vomiting, diarrhea, polyuria, dehydration attacks. Hypotension, seizure, dermatological findings such as miliara rubra, recurring lower respiratory tract infections, cystic fibrosis-like symptoms, abnormal salt and sebum accumulation in the Meibomian glands in the eye and secondary infection, an increased risk of cholecystitis, pneumothorax, sudden infant death, and thrombocytosis may also be seen. Polyhydramnios developing in association with fetal polyuria is one of the prenatal signs of pseudohypoaldosteronism. [8, 9, 27, 36, 46]

Excessive sodium secretion during hyponatremic crises resulting from aldosterone resistance lead to sweat gland obstruction and infection. Hyperkalemia reduces vascular tone, and this leads to norepinephrine discharge-related vasoconstriction and stimulation of sympathetic postganglionic muscarinic receptors. This in turn results in excessive sweating. The high sodium chloride (NaCI) concentration in the sweat glands has a direct effect on the eccrine ducts. Excessive sodium loss through sweating causes the cutaneous lesions known as miliaria rubra. [27, 37, 54]

These cutaneous findings can also be seen in other diseases that cause an increase in NaCl concentrations in sweat, such as cystic fibrosis, pancreatic failure, hypoaldosteronism, Addison's disease, panhypopituitarism, and secondary PHA1.[27, 55]

Respiratory function disorder develops in association with mucociliary function disorder and an increase in airway fluid volume since the alveolar fluid hypersecreted in the airway cannot be absorbed in a regular manner. This results in recurring lower respiratory tract problems, such as cough, cyanosis, dyspnea, wheezing and cystic fibrosis attacks such as fever. All patients are generally born with normal APGAR scores. [6, 16, 25, 56]

Pseudohypoaldosteronism-specific laboratory findings; the condition is characterized by hyponatremia that fails to improve despite high-dose mineralocorticoid therapy in the early period of life, hyperkalemia, metabolic acidosis, and high urinary sodium levels

and low potassium expulsion despite high plasma aldosterone and renin levels. [1, 6]

Transtubular potassium gradient index (TTKG) is used to determine mineralocorticoid deficiency or resistance in cases with hyperkalemia. It is calculated as (Serum Osmolarity x Urine Potassium) / (Serum Potassium x Urine Osmolarity). This has been proposed as useful for determining whether or not mineralocorticoid deficiency or resistance in the early period has led to hyperkalemia. TTKG values in a healthy individual receiving a normal diet are 8-9. In conditions where more potassium is expelled in urine during hyperkalemia or high potassium intake, and TTKG should be greater than 10. If TTKG decreases during hyperkalemia in a baby with normal adrenal functions and glomerular filtration rates, and if this is also accompanied by hyponatremia and increased urinary sodium expulsion, then mineralocorticoid deficiency or resistance should be suspected (Figure 3). [11, 57, 58]

Kurtoglu et al. also suggested that thrombocytosis can be used as a marker of salt-losing crisis. [59]

Differential diagnosis

Symptoms, clinical and laboratory findings seen in patients with PHA1 may be confused with salt-wasting congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase or 3-beta-hydroxysteroid dehydrogenase deficiency, non-CAH primary adrenal failure, and hypoaldosteronism due to aldosterone deficiency. In addition, in contrast to CAH, serum cortisol and aldosterone levels rise in PHA, and resistance to aldosterone activity is present. Even if CAH is suspected, samples should be taken to test 17-hydroxyprogesterone, aldosterone, renin, cortisol, ACTH concentrations before hydrocortisone is started. If the patient's clinical manifestation is CAH, then the response to treatment is complete. When the patient is a girl with normal genitalia, or if the response to corticosteroids is weak, then aldosterone resistance must always be considered. Pseudohypoaldosteronism can be diagnosed based on clinical and laboratory data without waiting for genetic testing results.[52, 60, 61]

Treatment

Hyperkalemia is a life-threatening condition requiring early diagnosis and aggressive treatment. Intravenous (iv) fluid replacement, iv hydrocortisone and oral mineralocorticoid therapy should be considered on suspicion of adrenal failure in all patients with a previous history or with no index case. Mineralocorticoid and hydrocortisone therapy should be stopped once PHA has been diagnosed. The management of PHA1 patients is difficult. Improvement of general condition, salt replacement and potassium exchange resins represent the basis of treatment. [8, 9, 62]

In terms of treatment stages;

I. ***Stabilization of the initial condition and rectification of dehydration****;* The fluid deficit is calculated based on the degree of dehydration. i.v. 0.45% saline with 5% dextrose, and 0.9% sodium chloride may be used initially.[8]

II. ***Sodium supplementation to rectify the sodium deficit****;* High-dose sodium replacement (up to 110 mEq/kg/day) must be

administered. Sodium replacement may be given in the form of NaHCO3, NaCl (1 g contains approximately 17 mEq Na) or Na-citrate. Intake can be facilitated by dividing the calculated Na into doses and mixing it with mother's milk, baby food, or the child's meals. Na reaching the renal collecting ducts is increased, and increased sodium assists with potassium secretion. The high-dose salt needing to be administered orally to patients with severe hyponatremia and hyperkalemia is generally difficult for patients to tolerate. Sodium may need to be administered by nasogastric tube/jejunostomy without loss of time in patients developing poor tolerance in the early period. [8-10, 38]

III. Improvement of hyperkalemia and acidosis

i. Potassium exchange resins: High doses are difficult to tolerate orally, and it should not be forgotten that when administered in enema form they can result in rectal bleeding or prolapse. Gastrostomy is a good option for babies with PHA1 due to poor oral tolerance for large amount of fluid, sodium supplementation and potassium binders. Gastrostomy must be performed without delay in patients developing poor tolerance in the early period.[10]

Sodium polystyrene sulfonate (sodium resonium); Sodium ions are released from resin in the intestinal system and exchange with potassium, leading to potassium loss via stool. It may thus be possible to correct both hyponatremia and hyperkalemia at the same time. One gram of sodium polystyrene sulfonate has the capacity to exchange approximately 1 mEq potassium *in vivo*. It is not absorbed or metabolized in the gastrointestinal system, and 100% is expelled from the intestines via stool. Sodium polystyrene sulfonate can be administered by the oral or rectal routes. The dosage in infants and children is approximately 1-2 g/kg/dose every 6 h. Although it is only used rectally in newborns, if the total daily dose is very high, it can also be administered rectally and by nasogastric tube in split doses. Its effect begins in 1-2 h and lasts for approximately 4 h. Sodium polystyrene sulfonate has been reported to be more effective in chronic hyperpotassemia than in acute hyperpotassemia. Clinical studies have also reported a direct correlation between sodium polystyrene sulfonate dosage and decrease in serum potassium. [43, 63-65] Calcium polystyrene sulfonate (calcium resonium, anti-potassium granules, kayexalate) binds potassium in the gastrointestinal system, thus restricting absorption. It is used orally or rectally at a dosage of 2-3 g/kg. Hypercalcemia is a significant side-effect. [28, 40, 43, 66]

i. Peritoneal dialysis: Emergency procedures including peritoneal dialysis may sometimes be required to bring severe hyperkalemia under control. It is even recommended that the peritoneal dialysis catheter not be removed immediately in systemic cases with a severe course. [8, 10, 36]

ii. Nutrition: Low-potassium, sodium-containing foods must be advised. It should not be forgotten that the most

suitable food for this is mother's milk. It is not possible to eliminate potassium entirely in mother's milk or formula foods. Since these children exhibit weak growth, a high-calorie diet preferably via G tube is recommended. An erect position and feeding when the baby is very hungry can be used to increase adherence to treatment during oral salt therapy. [36, 43, 63, 66]

iii. Other treatments for hyperpotassemia; Calcium gluconate, sodium bicarbonate, iv or nebulized salbutamol, or insulin infusion can be administered. Bicarbonate is also needed to regulate acidosis. [2, 11, 35, 58]

Ca-Gluconate 10%: 0.5-1 ml/kg via iv infusion over at least 5-10 min Sodium bicarbonate 8.4%: Calculated at 1-2 mmol/kg or the base deficit, and administered 30-60 min infusion Salbutamol: iv. at 4-5 μg/kg in 15 ml 5% dextrose via infusion for less than 15 min

Nebulized: 2.5 mg <25 kg, or 5 mg >25kg

Dextrose/insulin: 2.5-5 ml/kg/h 20% dextrose (0.5-1 g/kg/h) with insulin 0.2 units for every gram of glucose administered.

i. Other treatments

Indomethacin, thiazide diuretics and carbenoxolone therapies may be tried. Their effects are limited, and success rates vary. [28, 33,63]

i. Indomethacin: A potent prostaglandin inhibitor, whose effect mechanism is still unclear. Indomethacin reduces sodium requirements in PHA1 patients. Used at a dosage of 1 mg/kg/day. [67]

ii. Thiazide group diuretics (hydrochlorothiazide): These accelerate distal nephron flow by increasing intraluminal chloride, and assist with the expulsion of potassium in urine. They may be added to treatment since they protect against nephrocalcinosis and can reduce kayexalate requirements. Used in a maximum dose of 2 mg/kg/day. [28, 68]

iii. Carbenoxolone: The focus is on the potential benefit of carbenoxolone in the treatment of the renal form. It has been suggested that mineralocorticoid resistance can be partially rectified through the glucocorticoid receptor or by inhibiting the enzyme 11-β-hydroxysteroid dehydrogenase type II that converts cortisol into cortisone enzyme. It can be used at 10-12 mg/kg/day. [6, 62]

iv. Experimental treatment (Soltanite A); The synthetically produced cyclic peptides solnatide (a.k.a. TIP or AP301) and its congener AP318, whose molecular structures mimic the lectin-like domain of human tumor necrosis factor, have been shown to activate the epithelial sodium channel (ENaC) in various cell- and animal-based studies. The treatment of PHA1B is only symptomatic. The TIP peptides solnatide and AP318 that directly target ENaC are promising candidates for the treatment of channelopathies that cause PHA1B. [69, 70]

Prognosis

In the renal form, salt requirements may decrease and cease after 18-24 months. This can be explained in terms of the maturation of the salt resorption properties of the proximal tubules. Treatment of systemic PHA1 must be life-long. Acute diseases can accelerate salt-losing crises in patients with PHA1. This may lead to severe dehydration and severe hyperkalemia. It is important to monitor serum electrolytes and fluid status during crises.

The long-term treatment of pseudohypoaldosteronism requires a multidisciplinary approach. The team should include endocrinology, neonatology, neurological, and genetic specialists, a dietician, and a social services specialist in order to assess patients' growth and neurological development.

Patients must be properly informed in order to avoid life-threatening complications, including mortality, and families must be warned to take their children to a physician in the event of vomiting and diarrhea. Cases must be protected as much as possible from dehydration and systemic and urinary system infections. [9, 36, 62]

Summary

When hyponatremia, hyperpotassemia and metabolic acidosis are determined in children presenting with findings of vomiting, diarrhea, dehydration, and growth delay, a diagnosis of pseudohypoaldosteronism should be considered in addition to CAD progressing with salt loss. There is still uncertainly concerning the course of the disease, due to its rarity and the absence of genotype-phenotype correlation. Different mutations may equate to different clinical phenotypes. We think that cases and disease courses in which the clinical phenotype and genotype are correctly identified are needed to better illuminate the pathogenesis of PAH1.

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Table 1. Clinical, laboratory and genetic findings of children with PHA1.

	Age of presentation	Sex	Symptoms	Serum Na (mEq/L)	Serum K (mEq/L)	Serum HCO3 (mEq/L)	Urine Na (mmol/L)	Aldosterone (pmol/L)	PRA*/Renin** (ng/ml/h)/ (pg/ml)	Sweat Test (mEq/mL)	Site of mutation	Live/Dead
Schaedel, et al. (16) 1999	9d	F	Fever with coughing, wheezing	116	10.4	-	-	33000	4125*	131	*SCNN1A* c.1449delC S483Tfs*14 Homozygous	L
	5d	M	Severe dehydration	124	10.4	-	-	30900	60*	-	*SCNN1A* c.729delA/ c.1449delC S243*/ S483Tfs*14 Compound Heterozygous	L
	4d	M	Severe hyponatremia and hyperkalemia	129	8.4	-	-	13300	27.4*	110	*SCNN1A* c.729delA/ c.1449delC S243*/S483Tfs*14 Compound Heterozygous	L
	11d	M	Disturbance of salt and water balance	106	11.4	-	-	6000	60.3*	155	*SCNN1A* c.1685C>T/ c.1449delC S562L/S483Tfs*14 Compound Heterozygous	L
Saxena, et al. (17) 2002	-	M	-	116	10	-	-	>3900	-	129	*SCNN1A* c.1621C>T R508* Homozygous	L
	6w	M	Severe dehydration	118	10.2	-	-	>40000	-	136	*SCNN1B* c.1669 +1G>A Abnormal Splicing Homozygous	L

	-	M	-	122	>12	-	-	>8300	-	170	*SCNN1A* c.1439insT Y447Lfs*12 Homozygous	L
Thomas, et al. (18) 2002	1m	M	Severe dehydration	127	10.2	-	-	35534	235.5*	-	*SCNN1B* Homozygous deletion in promoter region	L
Edelheit, et al. (19) 2005	3d	M	Poor feeding, vomiting and weight loss	127	7.6	13.7	93	16491	45*	91	*SCNN1A* c.1078G>T / c.1404delC G327C/F435fs Compound Heterozygous	L
	3d	M	Severe dehydration	135	5.9	-	107	1110	> 180*	-	*SCNN1B* c.1669 +1G>A Abnormal Splicing Homozygous	L
	8d	F	Vomiting	128	6.8	-	101	12259	> 1800*	140	*SCNN1A* 1455delC S452fs Homozygous	L
Belot, et al. (9) 2008	6d	F	Bullous dermatitis	126	6.8	15	82	45070	1335**	Positive	*SCNN1B* c.637C>T Q213* Homozygous	L
	6d	F	Weight loss	130	9.8	16	-	>15000	>1400**	Positive	*SCNN1A* c.1621C>T R508* Homozygous	L
	7d	F	Weight loss	129	8.5	15	-	20136	960**	Positive	*SCNN1G* c.1318C>T R440* Homozygous	L

	19d	F	Failure to thrive	125	8.0	12	27	26768	-	-	*NR3C2* c.2310C>A N770K Heterozygous	L
	22d	M	Failure to thrive	127	7.2	-	75	>4460	>340**	-	*NR3C2* c.1757+1G > A Abnormal Splicing Heterozygous	L
	30d	M	Routine investigation	133	6.4	-	18	18374	350**	-	*NR3C2* c.1029C>A Y343* Heterozygous	L
	15d	M	Failure to thrive	132	6.3	18	-	43048	>340**	-	*NR3C2* c.1954C>T R652* Heterozygous	L
Hanukoglu, et al. (20) 2008	First 10 days of life	Patient A	Dehydration	Hyper natremia	Hyper kalemia	-	-	-	-	-	*SCNN1A* c.1078G>T/ H450fs G327C/H450fs Compound Heterozygous	L
	First 10 days of life	Patient B	Dehydration	Hyper natremia	Hyper kalemia	-	-	-	-	-	*SCNN1A* c.1621C>T R508* Homozygous	L
	First 10 days of life	Patient D	Dehydration	Hyper natremia	Hyper kalemia	-	-	-	-	-	*SCNN1B* c.1669 +1G>A Abnormal Splicing Homozygous	L
Schweiger, et al. (2) 2009	17d	F	Failure to thrive hyperkalemia	128	9	-	178	20361	10.5*	-	*SCNN1A* c.505_506delAC T169Sfs*36 Homozygous	L

Adachi, et al. (21) 2010	7d	M	Marked hyponatremia	116	8.6	-	-	41614	-	-	*SCNN1G* 1570-1G>A Abnormal Splicing Compound heterozygous	L
O'Connell, et al. (22) 2011	6w	F	Failure to thrive	130	5.4	-	<10	8760	2676**	-	*NR3C2* gene disrupted between exons 7 and 8	L
Hubert, et al. (23) 2011	2mo and 3 mo	M	Failure to thrive	130	5.6	-	26	44000	885**	-	*NR3C2* c.497_498delCT S166* Heterozygous	L
	8d	F	Vomiting and severe dehydration with weakness and hypotonia	117	10.5	-	112	79000	101.2**	-	*NR3C2* gene, c.497_498delCT/ c.2418G>A S166*/W806* Compound heterozygous	L
Dirlewanger, et al. (24) 2011	16d	-	Hypotonia and feeding problems	106	7.9	-	-	57921	>500*	-	*SCNN1A* c.727T>C S243P Homozygous	L
Nasir A and Najab IA. (25) 2012	6d	F	Lethargy and poor feeding	129	10.2	21	-	78350	>116.73*	-	-	L
Dogan, et al. (26) 2012	3d	M	Vomiting and poor feeding	125	9	-	51	26242	140*	-	*SCNN1B* c.1266-1G>C Abnormal Splicing Homozygous	L
Onal, et al. (27) 2012	6m	F	Poor nutrition, cutaneous eruptions, vomiting, dehydration	123	10	-	124	51873	900**	40	-	L

Saravanapandian, et al. (28) 2012	7d	M	Poor feeding progressive lethargy	122	8.9	13	140	3861	24.4*	-	-	L
Mostofizadeh, et al. (29) 2012	3m	F	Poor weight gain	117	7.4	14.5	-	1298	369**	-	-	L
Mora-Lopez, et al. (30) 2012	6m	F	Severe hyponatremic dehydration	114	5.4	-	20	2774	6410000*	106	*SCNN1A* c.301C>A Q101K Homozygous	L
Ekinci, et al. (31) 2013	9d	F	Failure to thrive, dehydration hypothermia	123	8.4	-	-	12848	43*	133	*SCNN1A* c.684+2 T > A Abnormal Splicing Homozygous	L
Welzel et al. (10) 2013	10d	M	Failure to thrive,dehydration	118	10.3	-	-	10319	427*	124	*SCNN1A* c.587_588insC P197Afs*9 Homozygous	L
	8d	F	Vomiting, dehydration, somnolence	116	12.1	-	287	943	492**	-	*SCNN1A* c.1342_1343insTACA R448Ifs*13 Homozygous	L
	11d	M	Dehydration	121	9.5	-	167	>3606	>13*	119	*SCNN1A* c.742delG V248* Homozygous	L
	9d	F	Apathy, dehydration	119	8.4		167.7	>3328	1224**	128	*SCNN1A* c.587_588insC P197Afs*9 Homozygous	L

	9d	M	Hyperbilirubinemia	127	9.7	-	260	12205	41*	-	*SCNN1A* c.1474C>T R492* Homozygous	L
	2d	M	Hyperbilirubinemia	109	11	-	228	>13870	>300*	142	*SCNN1A* c.189C>A C63* Homozygous	D
	10d	M	Failure to thrive, dehydration	118	10.3	-	-	10319	427*	124	*SCNN1A* c.587_588insC P197Afs*9 Homozygous	L
Amin et al. (8) 2013	25d	M	Vomiting and weight loss	119	NA	19.4	50	35700	13.5*	-	-	L
	28d	M	Weight loss and poor feeding	126	6.8	17.9	16	39900	78.6*	-	-	L
	8d	F	Weight loss	118	8.2	19.6	15	83390	>78.6*	-	-	L
	23d	M	Vomiting and weight loss	118	7.3	NA	20	48000	5*	-	-	L
	10d	F	Inpatient	109	6.8	18.6	35	49500	>78.6*	-	-	L
	5d	F	Jaundice and weight loss	112	11.3	19.3	111	57000	>78.6*	-	-	L
	10d	M	Weight loss and drowsiness	126	10	10.4	142	16580	41.3*	-	-	L

Hatta et al. (32) 2013	30d	M	Failure to thrive	121	6.1	-	-	38836	>50*	-	*NR3C2* c.1951C>T R651* Heterozygous	L
	30d	M	Failure to thrive	129	5.6	-	-	84884	>50*	-	*NR3C2* c.1951C>T R651* Heterozygous	L
	29d	F	Failure to thrive	120	6.5	-	-	55757	>25*	-	*NR3C2* c.1951C>T R651* Heterozygous	L
	4m	M	Failure to thrive	131	5.1	-	-	>11096	>50*	-	*NR3C2* c.2839A>G R947* Heterozygous	Not available
	29d	M	Failure to thrive	121	7.1	-	10	81943	>20*	-	*NR3C2* c.603delA T201fs*34 Heterozygous	L
	14d	F	No symptoms	121	7.2	-	-	25909	25.5*	-	*NR3C2* c.304_305delGC A102fs*103 Heterozygous	L
Javed et al. (13) 2013	5w	M	Vomiting, dehydration, and failure to thrive	135	6.2	-	-	18863	330*	-	*NR3C2* c.2919_2920insG E975fs*1004 Heterozygous	L
Sharma et al. (33) 2013	10d	F	Lethargy and refusal to feed for one day	124	10.3	12.7	97	6518	300**	-	*SCNN1A* c.1339dupT Y447Lfs*13 Homozygous	L
Bhullar et al. (34) 2013	5w	M	Dehydration vomiting,	122	8.1	-	-	60306	103.9*	-	-	L

Wang et al. (4) 2013	5d	F	Refusal to be breastfeed, poor response, weak cries	105	10.1	-	-	1080	14.0*	-	*SCNN1A* c.1311delG / c.1439+1G>C R438Gfs*44/ Abnormal Splicing Compound Heterozygous	L
	2m	F	Electrolyte imbalance	125	6.1	-	-	580	10.1*	-	*SCNN1A* c.814_815insG E272Gfs*39 Homozygous	L
Silva et al. (35) 2013	10d	M	Vomiting dehydration	125	10	22.6	-	48545	70*	-	*SCNN1A* c.1052+2dupT Abnormal Splicing Homozygous	L
Kala Ahluwalia G, et al. (11) 2014	7 d	M	Hyperkalemia, hyponatremia, dehydration	123	9	17	69	587.6	93.96	104	*SCNN1A* c.416G>A / c.1360 + 1G>T R139K/ Abnormal Splicing Compound Heterozygous	L
Rajpoot et al. (36) 2014	10d	F	Difficulty in breathing and lethargy	117	>9	-	140	18308	58*	<25	-	L
Korkut et al. (37) 2015	7d	F	A skin rash and lacrimation	129	8.1	-	31	>16644	100000**	-	-	L
Khalil ST, Cabacungan E. (38) 2015	7d	M	Poor feeding, reduced urine output and lethargy	127	9.3	17.7	439	8960	56.32*	-	*SCNN1A* Abnormal Splicing Homozygous	L
Morikawa et al. (39) 2015	1m	F	Weight gain was insufficient	124	5.8	-	28	5318	> 20*	-	*NR3C2* c.492_493insTT M166Lfs*8 Heterozygous	L

	1m	F	Poor weight gain was noticed	125	5.1	-	-	30999	> 20*	-	*NR3C2* c.2683A>G / c.2581C>T M895V/ R861X Compound Heterozygous	L
Attia , et al. (40) 2016	14d	F	Hypovolemic shock	122	8.6	4.7		4022	28.6*	-	-	L
Nishizaki et al. (41) 2016	1m	M	Poor weight gain	130	5.4	-	-	64745	162.5*	-	*NR3C2* c1894G>T E632* Heterozygous	L
Tsunogai et al. (42) 2016	3m	F	Failure to thrive, dehydration, vomiting	125	5.6	21.6	-	93473	20*	-	*NR3C2* c.2724insT K909fs*1 Heterozygous	L
Tunc et al. (43) 2016	7d	M	Vomiting, dehydration	114	>10	18.5	-	>8322	>200000**	-	*SCNN1A* c.1052+1G>A Abnormal Splicing Homozygous	L
	38d	F	Cardiopulmonary arrest	123	8.4	19	-	7767	225000**	-	-	D
Nur et al. (44) 2017	6d	F	Vomiting, lethargy,severe dehydration	124	10	10	150	8970	13.39*	34	*SCNN1A* c.1685C>T S562L Homozygous	L
Kawashima Sonoyama Y, et al. (7) 2017	10d	M	Hyperkalemia vomiting	136	7.2	18.6	-	81455	560*	-	*NR3C2* c.3252delC I963fs*31 Prolonged protein Heterozygous	L

Casas-Alba et al. (45) 2017	12d	M	Poor weight gain	115	6	18.3	-	11400	90.3*	-	*NR3C2* c.403C>T Q135* Heterozygous	L
	28d	F	Poor weight gain	121	6	16.2	-	3200	18.5*	-	*NR3C2* c.403C>T Q135* Heterozygous	L
Turan et al. (3) 2018	18d	-	Failure to thrive	130	6.1	-	-	>4715	8.3*	-	*NR3C2* c.2657T>G, L886R Heterozygous	L
	28d	-	Vomiting	109	11	-	-	>23579	>170*	-	*SCNN1G* c.187G>C A63P Homozygous	L
	4d	-	Vomiting, failure to thrive, dehydration, diarrhea	120	11	-	-	>4161	-	-	*SCNN1A* c.1678G>A G560S Homozygous	L
	10d	-	Jaundice, dehydration	107	11	-	-	>4161	>500*	-	*SCNN1A* c.1582_1584delTTC F527del Homozygous	L

	9d	-	Jaundice, inability to breastfeeding	120	10.3	-	-	>5548	-	-	*SCNN1A* c.1582_1584delTTC F527del Homozygous	L
Manipriya et al. (46) 2018	11d	F		118	11.6	11.5	79	>41600	23.03*	-	-	D
	8d	M		123	8.9	14.5	136	>41600	42.36*	-	*SCNN1A* c.1360+1G>C Abnormal Splicing Homozygous	D

***In addition to these patients, Zennaro et al, have reported more than 30 patients with PHA1A who are not mentioned in this review due to unavailability of individual clinical information (Reference number 47; Zennaro MC, Fernandes-Rosa F. 30 YEARS OF THE MINERALOCORTICOID RECEPTOR: Mineralocorticoid receptor mutations. J Endocrinol. 2017;234(1):T93-T106.).This elegant paper summarizes many patients with inactivating *NR3C2* gene mutations reported so far.