



## Pseudohypoaldosteronism Type 1: a case report supported by a literature review

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### Abstract

In the neonatal period, hydro electrolytic disorders with dehydration and metabolic acidosis can cause admission to an intensive care unit and become a diagnostic challenge. Among such disorders, hyponatremia and hyperkalemia become diagnostic challenges with hormonal involvement, including aldosterone. Pseudohypoaldosteronism (PHA) resulting from the lack of response to aldosterone in target cells can be classified into three types and its suspected diagnosis in cases of hyponatremia, hyperkalemia with an elevation of serum aldosterone, can be confirmed by exome sequencing with identification of a potentially pathogenic. This study was based on the case report of a newborn of consanguineous parents who, after birth, evolved in the first week of life with shock, hyponatremia, hyperkalemia, and metabolic acidosis. An initial investigation ruled out congenital adrenal hyperplasia. The presence of hyperaldosteronism with increased plasma renin activity, associated with hyperkalemia and hyponatremia difficult to control with electrolyte replacement, led to a molecular investigation that confirmed PHA type 1 by a mutation in the *SCCN1A* gene. In neonates with severe hyponatremia that is difficult to resolve with conventional treatment and elevation of serum aldosterone, this pathology must be remembered and investigated, avoiding high morbidity and mortality.

**Keywords:** Pseudohypoaldosteronism type 1. Hyponatremia. Hyperkalemia.

### Introduction

Aldosterone is the main mineralocorticoid hormone produced in humans, having a steroidal origin and cholesterol is the basis of its biosynthesis. The production of aldosterone occurs in the zona glomerulosa of the cortex of the adrenal glands [1-3]. Positive regulators of aldosterone secretion are the renin-angiotensin-aldosterone system (RAAS) and serum potassium level. These factors are followed by several others with minimal influence, such as adrenocorticotrophic hormone (ACTH), proopiomelanocortins; sodium ion; dopamine,  $\beta$ -adrenergic agents, serotonin, and somatostatin. Classically, dopamine; atrial natriuretic peptide, and heparin are known to inhibit the secretion of this hormone [4-6].

The inadequate action of aldosterone or its final signaling pathways generates a very heterogeneous spectrum of manifestations [7-10]. Among them, we can mention Pseudohypoaldosteronism (PHA) resulting from the lack of response to aldosterone in target cells and, thus, characterized by resistance to mineralocorticoids [11,12]. This condition is commonly classified as PHA type 1 (PHA1) and PHA type 2 (PHA2), and some authors also refer to type 3 (PHA3) [13-15].

PHA1, initially described in 1958, is a rare disease

with an incidence of about 1:166,000 births that manifests itself with elevated levels of aldosterone and plasma renin activity, loss of sodium, hypotension, hyperkalemia, hyponatremia and metabolic acidosis, and with it, has high mortality and morbidity even in the neonatal period and was the main focus of this study [14-16].

This study carried out a literature review and a case report of a patient with PHA1 secondary to a mutation in the *SCCN1A* gene. In addition, scientific basis related to bio cellular, molecular, clinical aspects, and differential diagnosis approach. The recognition and early treatment of PHA are the main weapons to be used to reduce morbidity and mortality and improve the quality of life of its patients.

## Methods

### Study Design

The present study was elaborated according to the rules of the CARE case report (<https://www.care-statement.org/>). A descriptive literature review was also carried out to provide sufficient scientific data for the theoretical basis of this study. The study follows the retrospective, secondary and descriptive model. For the research, data from PubMed and Scielo in the last 20 years were used, using the descriptors: "Pseudohypoaldosteronism", "Aldosterone resistance", "pseudohypoaldosteronism type I", "Pseudohypoaldosteronism and Hyperkalemia".

### Ethical Approval

This study was analyzed and approved with the number 3.682.724 by the Research Ethics Committee from the University of Marilia, Faculty of Medicine, Marilia, Sao Paulo, Brazil, and obtaining the Informed Consent Form according to CNS/CONEP Resolution 466/12. Data from the child under study were obtained through the collection and analysis of information contained in the patient's medical record, duly authorized by those responsible using signing the Informed Consent Form.

## Case report

### Patient Information and Clinical Findings, Timeline, Diagnostic Assessment, Therapeutic Intervention, and Follow-up

Newborn, male, white, son of consanguineous parents (first cousins), coming from the interior of São Paulo. Prenatal care performed without complications evolved into spontaneous vaginal delivery at 40 weeks and 4 days. The hospital discharged the mother at 4 days of life, due to neonatal physiological jaundice.

At eight days of age, he evolved with respiratory distress, prostration, hypoxia, sweating, cyanosis, moaning, fixed gaze, decreased responsiveness, and cold extremities. Admitted to the emergency department in a serious condition, where resuscitation measures were initiated for hypovolemic shock, requiring mechanical ventilation as respiratory support.

On admission, he had metabolic acidosis associated with severe hyperkalemia and severe hyponatremia, according to the tests: serum potassium of 9.6 (Reference value (RV): 3.5 to 5 mmol/L), serum sodium of 112 (RV: 135-145 mEq/L) and arterial blood gas analysis pH: 7.25; pCO<sub>2</sub>: 26.4mmHg; pO<sub>2</sub>: 69.3mmHg; bicarbonate: 11.4mEq/L; base excess: -11; lactate 7.1 mmol/L (on mechanical ventilation and after hydration); Electrocardiogram showed sinus tachycardia, right bundle-branch block, QRS widening and peaked T wave.

Transferred to the pediatric/neonatal intensive care unit being treated with fluid replacement, antibiotic therapy for sepsis of a pulmonary focus, management of metabolic acidosis requiring bicarbonate replacement, and correction of severe hyperkalemia associated with electrocardiographic alterations with calcium gluconate and potassium-depleting measures.

Due to the evidence associated with metabolic and electrolyte alterations, Congenital adrenal hyperplasia (CAH) was proposed as a differential diagnosis, the exams were collected and glucocorticoid replacement therapy with hydrocortisone and fludrocortisone was initiated. The patient had a good initial partial clinical response but soon returned to maintain the intensity of the hydro electrolytic disturbances with hyponatremia and hyperkalemia, requiring sodium and calcium replacement.

The results of the adrenal exams arrived and the hypothesis of congenital adrenal hyperplasia with precursor values within the expected was not confirmed. However, during this metabolic investigation, hyperreninemia (plasma renin activity: 8.8 ng/mL/h (RV: 0.32 to 1.84), hypercortisolism (Cortisol 51mcg/dL - RV 4.46 to 22 .7) and hyperaldosteronism (Aldosterone 1000ng/dL -RV: 1.8 to 23.2).

Because of the lack of hydro electrolytic response associated with the very high serum level of aldosterone, the diagnostic hypothesis of Pseudohypoaldosteronism was raised, and weaning off glucocorticoids was initiated. It is worth mentioning that in periods of metabolic stress related to infectious and inflammatory disorders, the patient presented a worsening of the hydro electrolytic pattern with a drop in sodium, an increase in potassium, and a resurgence of metabolic acidosis. After weaning from

corticosteroids, the patient maintained a condition of hyponatremia and hyperkalemia and required oral sodium replacement and exchange resin, maintaining good clinical evolution.

Given the strong clinical and laboratory suspicion of PHA, genomic analysis was performed by exome sequencing with the identification of a potentially pathogenic variant in homozygosity in the *SCCN1A* gene, confirming systemic type 1 pseudohypoaldosteronism. The patient was referred to nephrology with sodium supplementation and therapy for hyperkalemia. Directed family to a geneticist for genetic counseling and, if possible, family molecular assessment.

At 4 years of age, z score 0 and at the 50th percentile of weight and height, in follow-up with a nephrology team, using 10 grams of exchange resin every 8/8 hours, 2 grams of bicarbonate every 8/8 hours, and 4 grams of salt a day. Serum sodium levels were 148 mEq/L and potassium 4.8 mEq/L.

## Discussion

### Biocellular Basis

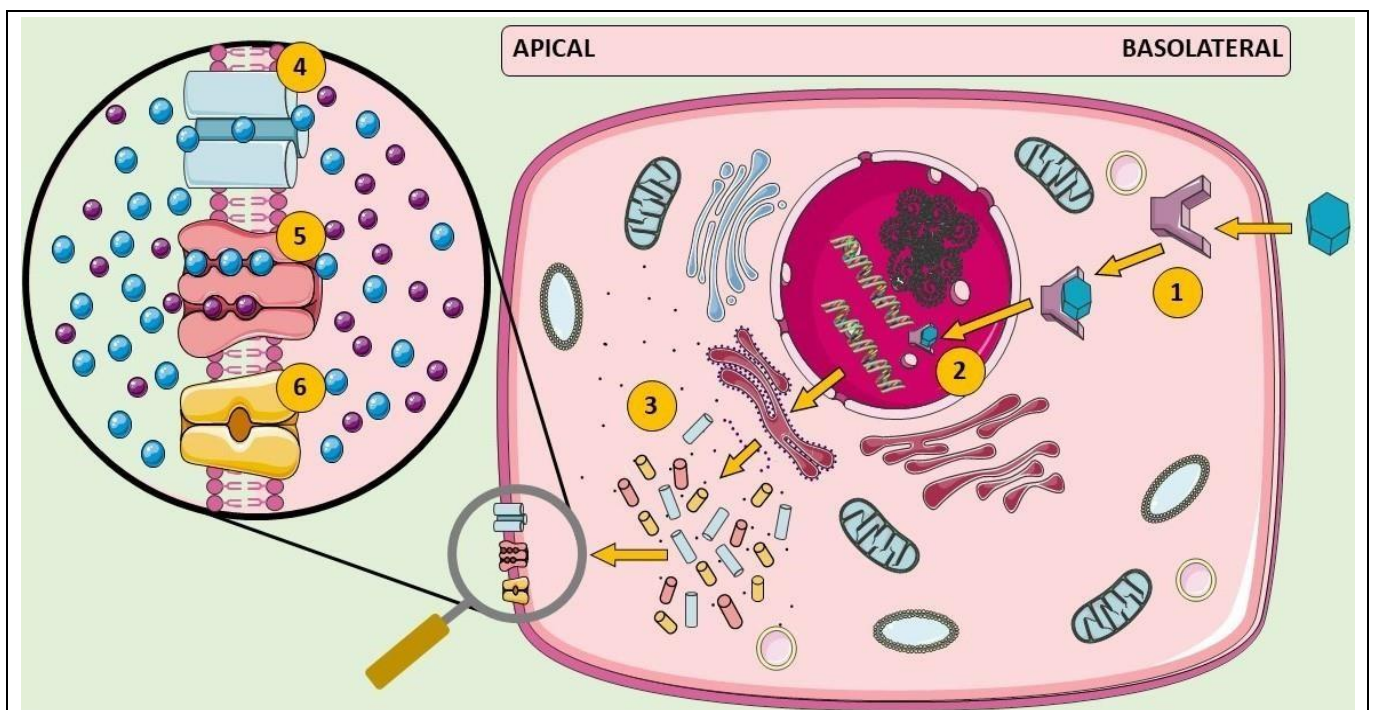
After synthesis and secretion stimuli, aldosterone is released into the bloodstream and binds to

mineralocorticoid receptors (MR), located in the cytosol of target tissue cells: distal nephron, colon, salivary, and sweat glands [5,7,10,11].

The aldosterone-MR complex migrates to the cell nucleus and induces the transcription of genes that lead to the synthesis of peptide subunits that will originate from cell membrane transporters. Among the carriers formed are epithelial sodium channels (ENaC); sodium-potassium ATPase (NakATPase) and serum/glucocorticoid-regulated protein kinase 1 (SGK1) channels. These molecules are responsible for the elimination of potassium and conservation of sodium by the epithelial cells of the target tissues and, thus, the maintenance of hydro electrolytic homeostasis [2,4,5,7].

Biological alterations in the function of aldosterone or one of the pathways of its action have varied manifestations with important clinical repercussions. In the case of the aforementioned patient with PHA1, he has aldosterone resistance secondary to inadequate ENaC formation, as we will see in more detail below. Loss of ENaC function decreases sodium reabsorption in multiple organs and secondarily decreases potassium and hydrogen excretion and water reabsorption in the distal nephron, justifying the changes presented in the clinical case (Figure 1).

**Figure 1.** Representation of the mineralocorticoid action of aldosterone on a target cell. 1- Aldosterone influx into the cytosol and binding to the mineralocorticoid receptor (MR); 2 – migration of the aldosterone-MR complex to the cell nucleus and stimulation of transcription of genes related to cell channels; 3 – translation and formation of cell carrier subunits; 4 – ENaC representation; 5 - NakATPase and 6 - SGK1.



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## Molecular Basis

The autosomal recessive variant, called systemic PHA 1, is caused by inactivating mutations in the SCNN1A (chromosome 12p13.31), SCNN1B (chromosome 16p12.1), and SCNN1G (chromosome 16p12.1) genes. These genes, responsible for encoding the  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits of ENaC, when inactivated promote anomalous and dysfunctional coding of these channels [17,18]. Thus, severe hydro electrolytic disorders occur, as it promotes salt loss in various organs and tissues such as the salivary, sweat glands, colon, kidneys, and lungs [14,16,19,20].

The autosomal dominant variant, renal PHA 1, is characterized by heterozygous inactivating mutations in the mineralocorticoid receptor gene. Fernandes-Rosa & Antonine (2017) [16] report that about 22 mutations in the gene encoding the MR have already been described in patients with PHA1, such as NR3C2, which is located on chromosome 4q31.1, both in sporadic and familial cases.

## Clinical Aspects

Clinical manifestations of systemic PHA1 occur more frequently in neonates and include severe dehydration and hyponatremia, as reported, due to salt loss and hyperkalemia. Changes in sodium and potassium are further combined with elevated plasma aldosterone and renin concentrations, reflecting target organ resistance [15]. Pulmonary changes also occur due to association with recurrent respiratory tract infections, as well as cholelithiasis, skin rashes, and polyhydramnios [20].

Laboratory tests include hyponatremia, hyperkalemia, metabolic acidosis, and decreased urinary potassium excretion, while adrenal function and glomerular filtration rate are normal [20]. Clinical aspects of renal PHA1 involve hyponatremia, hyperkalemia, metabolic acidosis, failure to thrive, and elevated plasma Renin and Aldosterone concentrations, these signs appear mainly in early childhood.

In renal PHA1, metabolic acidosis is not always present and hyperkalemia is milder than the systemic form. The main clinical sign of renal PHA1 is insufficient weight gain due to chronic dehydration. The spectrum of the renal form ranges from healthy, unaffected patients without electrolyte disturbances but with elevated plasma renin and aldosterone levels and patients with clinically manifest renal salt loss. Elevated aldosterone levels are the only biochemical marker in adulthood [15,16,20].

A fact that calls attention in the case presented is the evolution of severe hyperkalemia, including

electrocardiographic alterations, accompanied by hypovolemic shock associated with dehydration and sepsis of pulmonary focus – factors that corroborate the diagnosis of pseudohypoaldosteronism in the systemic form, allowing an initial detailed empirical approach [21-24], in due course, below. In cases of hyponatremia associated with hyperkalemia in neonates, the diagnosis of congenital adrenal hyperplasia is the main diagnostic hypothesis and in these cases, there is a good response to corticosteroid therapy. When there is no improvement in electrolytes and aldosterone is high, PHA should be considered [25].

## Treatment

The treatment of PHA consists of sodium supplementation, hydration, and correction of hyperkalemia and acidosis in the acute phase of the disease [26]. The use of exogenous corticosteroids is not indicated, as patients with PHA are unresponsive. However, fludrocortisone and hydrocortisone are the treatment of choice during the differential diagnosis with congenital adrenal hyperplasia [18].

Patients with the renal form of PHA1 show significant clinical improvement with the replacement of low doses of sodium chloride (1 to 2 g/day) during the first year of life, which often becomes unnecessary between one and three years of age. After this period, supplementation can be discontinued and the patient remains clinically asymptomatic [26,27].

In systemic PHA1, symptoms persist for life and there is a need to replace a large amount of sodium for the survival of affected individuals. Medical management consists of salt supplementation and potassium control, including the use of potassium-reducing agents such as ion exchangers [15,20]. Such treatment may have difficulty in therapeutic adjustment at the beginning, requiring high doses of sodium.

## Differential Diagnosis

Cases that evolve with severe hyponatremia and hyperkalemia are rarely medical emergencies in childhood and the most common cause is congenital adrenal insufficiency, typically congenital adrenal hyperplasia with 21-hydroxylase deficiency or 3 $\beta$ hydroxysteroid dehydrogenase deficiency [21], an investigation should be considered for Primary Congenital Adrenal Hypoplasia and other causes of Adrenal Insufficiency, isolated deficiency of aldosterone synthesis and PHA.

The differential diagnosis of PHA is also based on laboratory findings: elevated serum levels of

aldosterone and plasma renin and normal levels of serum cortisol and 17OH pregnenolone, contrary to what is normally observed in adrenal hyperplasia (**Table 1**). In addition, a test of stimulation of cortisol release through ACTH can be performed, failure to increase serum cortisol levels suggests adrenal insufficiency [17].

PHA should always be considered in a child who has neuropsychomotor developmental delay, metabolic acidosis, dehydration, hyponatremia with hyperkalemia, lower respiratory tract involvement, urinary tract malformations associated with infections, and exocrine pancreatic insufficiency [22-24,27].

**Table 1.** Demonstrates the peculiarities of the systemic and renal forms of PHA1 for purposes of differential diagnosis between conditions.

VARIABLES / PHA TYPE	RENAL PHA	SYSTEMIC PHA
<b>GRAVITY</b>	Mild to moderate	Severe, high morbidity and mortality
<b>EVOLUTION</b>	Improves with age	No remission with age
<b>SALT LOSS</b>	Renal	Multiple organs
<b>SODIUM SUPPLEMENTATION</b>	3 to 20 mmol/kg/day – can be stopped around 18 to 24 months of age.	Up to 50 mmol/kg/day
<b>GENETIC MUTATION</b>	Related to the mineralocorticoid receptor	Related to ENac

## Conclusion

Hydroelectrolytic disorders in neonates with difficulty in hydroelectrolyte correction should arouse motivation in search of differential diagnoses of diseases related to aldosterone metabolism. Among the differences pointed out in cases where aldosterone is extremely high, PHA should be included since this disease has high morbidity and mortality and its early recognition is the main tool to reduce the drastic evolution of these conditions.

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## Funding

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## Ethics approval

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## Informed consent

Data from the child under study were obtained through

the collection and analysis of information contained in the patient's medical record, duly authorized by those responsible using signing the Informed Consent Form.

## Data sharing statement

No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

## Similarity check

It was applied by Ithenticate@.

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## References

1. Gromotowicz-Poplawska A, Szoka P, Kolodziejczyk P, Kramkowski K, Wojewodzka-Zelezniakowicz M, Chabielska, E. New agents modulating the renin-angiotensin-aldosterone system—Will there be a new therapeutic option?. *Experimental Biology and Medicine*, 2016, 241(17), 1888-1899.

2. Shibata S. Context-dependent mechanisms modulating aldosterone signaling in the kidney. *Clinical and experimental nephrology*, 2016, 20(5), 663-670.
3. Zavatta G, Casadio E, Rinaldi E, Pagotto U, Pasquali R, Vicennati V. Aldosterone and type 2 diabetes mellitus. *Hormone molecular biology and clinical investigation*, 2016, 26(1), 53-59.
4. Arai K, Chrousos GP. Aldosterone deficiency and resistance. 2016.
5. Stowasser M, Gordon RD. Primary aldosteronism: changing definitions and new concepts of physiology and pathophysiology both inside and outside the kidney. *Physiological reviews*, 2016, 96(4), 1327-1384.
6. El Ghorayeb N, Bourdeau I, Lacroix A. Role of ACTH and other hormones in the regulation of aldosterone production in primary aldosteronism. *Frontiers in endocrinology*, 2016, 7, 72.
7. Vecchiola A, Lagos CF, Carvajal CA, Baudrand R, Fardella CE. Aldosterone production and signaling dysregulation in obesity. *Current hypertension reports*, 2016, 18(3), 20.
8. Borghi F, Sevá-Pessôa B, Grassi-Kassisse DM. The adipose tissue and the involvement of the renin-angiotensin-aldosterone system in cardiometabolic syndrome. *Cell and tissue research*, 2016, 366(3), 543-548.
9. Rahimi Z. The role of renin angiotensin aldosterone system genes in diabetic nephropathy. *Canadian journal of diabetes*, 2016, 40(2), 178-183.
10. Valinsky WC, Touyz RM, Shrier, A. Aldosterone, SGK1, and ion channels in the kidney. *Clinical Science*, 2018, 132(2), 173-183.
11. Cat AND, Friederich-Persson M, White A, Touyz RM. Adipocytes, aldosterone and obesity-related hypertension. *Journal of molecular endocrinology*, 2016, 57(1), F7-F21.
12. Sabbadin C, Armanini, D. Syndromes that mimic an excess of mineralocorticoids. *High Blood Pressure & Cardiovascular Prevention*, 2016, 23(3), 231-235.
13. Perez Maraver M, Estepa Marin A. Hipoaldosteronismo. *Medicine - Programa de Formacion Medica Continuada Acreditado*. 2004;9(15):923-9.
14. Manipriya R, Umamaheswari B, Prakash A, Binu N. Rare Cause of Hyperkalemia in the Newborn Period: Report of Two Cases of Pseudohypoaldosteronism Type 1. *Indian J Nephrol*. 2018;28(1):69-72.
15. Riepe FG. Clinical and molecular features of type 1 pseudohypoaldosteronism. *Horm Res*. 2009;72(1):1-9.
16. Fernandes-Rosa FL, Antonini SR. [Mineralocorticoid resistance: pseudohypoaldosteronism type 1]. *Arq Bras Endocrinol Metabol*. 2007;51(3):373-81.
17. Sethi SK, Wazir S, Bansal S, Khokhar S, Wadhvani N, Raina R. Secondary Pseudohypoaldosteronism Masquerading Congenital Adrenal Hyperplasia in a Neonate. *Kidney Int Rep*. 2018;3(3):752-4.
18. Choudhry S, Najam Y. Life threatening hyperkalemia in a neonate with pseudohypoaldosteronism. *J Pak Med Assoc*. 2012;62(3):287-8.
19. *Nephrol*. 2018;28(1):69-72.
20. Casas-Alba D, Vila Cots J, Monfort Carretero L, Martorell Sampol L, Zennaro MC, Jeunemaitre X, et al. Pseudohypoaldosteronism types I and II: little more than a name in common. *J Pediatr Endocrinol Metab*. 2017; 30(5):597-601.
21. Miranda Margarida, Fontoura Manuel. Pseudohipoaldosteronismo tipo I na criança. *Arq Med [Internet]*. 2013 Dez [citado 2018 Set 19]; 27(6): 265-271.
22. Manikam L, Cornes MP, Kalra D, Ford C, Gama R. Transient pseudohypoaldosteronism masquerading as congenital adrenal hyperplasia. *Ann Clin Biochem*. 2011; 48(Pt 4):380-2.
23. Sartorato P, Khaldi Y, Lapeyraque AL, Armanini D, Kuhnle U, Salomon R, et al. Inactivating mutations of the mineralocorticoid receptor in Type I pseudohypoaldosteronism. *Mol Cell Endocrinol*. 2004; 217(1-2):119-25.
24. Metz J, Kesper MS, Uetz B, Burdach S, Warncke K. [Transient Pseudohypoaldosteronism - an Important Differential Diagnosis to Congenital Adrenal Hyperplasia]. *Klin Padiatr*. 2018; 230(4):229-30.
25. Turan I, Kotan LD, Tastan M, Gurbuz F, Topaloglu AK, Yuksel B. Molecular genetic studies in a case series of isolated hypoaldosteronism due to biosynthesis defects or aldosterone resistance. *Clin Endocrinol (Oxf)*. 2018; 88(6):799-805
26. Hanukoglu A, Hanukoglu I. Clinical improvement in patients with autosomal recessive pseudohypoaldosteronism and the necessity for salt supplementation. *Clin Exp Nephrol*. 2010;

14(5):518-9.

- 27.** Bandhakavi M, Wanaguru A, Ayuk L, Kirk JM, Barrett TG, Kershaw M, Höglér W, Shaw NJ. Clinical characteristics and treatment requirements of children with autosomal recessive pseudohypoaldosteronism. *Eur J Endocrinol.* 2021 May;184(5):K15-K20. doi: 10.1530/EJE-20-0152.