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Case Series

Autosomal Recessive Pseudo Hypoaldosteronism- Type 1 in Four Patients from Mixteco-Speaking Families from Coastal California

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Abstract

Pseudo hypoaldosteronism type 1 (PHA1) is a rare condition characterized by hyponatremia, hyperkalemia, metabolic acidosis, and elevated serum aldosterone. Severe electrolyte derangements occur in the setting of aldosterone resistance. Autosomal recessive PHA1 confers aldosterone resistance through defective sodium epithelial channels present in the kidneys, sweat glands, salivary glands, and colon attributing to the systemic nature of the condition. Infants with this condition develop severe hyperkalemia, hyponatremia, and metabolic acidosis in the neonatal period. We present four infants of Mixteco dialect-speaking Hispanic parents, presenting in the neonatal period with severe hyperkalemia and hyponatremia due to PHA1b.

Keywords: Pseudohypoaldosteronism; Hyperkalemia; Autosomal Recessive; Metabolic Acidosis; Hyponatremia

Introduction

Pseudo hypoaldosteronism type 1 (PHA1) is a rare condition characterized by hyponatremia, hyperkalemia, metabolic acidosis, and elevated serum aldosterone. Severe electrolyte derangements occur in the setting of aldosterone resistance either isolated to the kidneys (PHA1a) or occurring in multiple organ systems (PHA1b). The subtypes of PHA1 differ by the mode of inheritance, genes involved and the severity of the disease. PHA1a, also known as renal PHA1, is due to an autosomal dominant mutation on the *NR3C2* gene, resulting in a nonfunctional or abnormally functioning mineralocorticoid receptor in the nephron of the kidney. The condition is relatively mild, requiring less aggressive therapy, and often improves with age. In contrast, PHA1b, which is an autosomal recessive mutation on the *SCNN1A, SCNN1B,* or *SCNN1G* genes confers aldosterone resistance through defective sodium epithelial channels. These channels are present in the kidneys, sweat glands, salivary glands and colon attributing to the systemic nature of the condition [1,2]. Infants with this condition may experience arrhythmia, shock, recurrent lung infections or skin lesions [3-5]. They require aggressive therapy and there is no improvement with age. The estimated incidence of PHA1 is around 1 in 80,000 individuals with the incidence of PHA1b calculated to be 1 in 166,000 newborns [6]. We report four infants of Mixteco dialect-speaking Hispanic parents, presenting in the neonatal period with severe hyperkalemia and hyponatremia due to PHA1b.

Case Presentation

Case One

A 6-day-old Mixteco-Spanish male from Santa Maria, California was admitted to the emergency department for vomiting and poor oral intake. He was lethargic and severely dehydrated. Otherwise, his history and exam were unremarkable. Laboratory studies demonstrated hyponatremia (116 mmol/L) and hyperkalemia (>9 mmol/L). A blood gas demonstrated metabolic acidosis; pH of 7.28, bicarbonate of 14 mmol/mL, and base deficit of 13 mmol/mL. The results of the endocrinological

evaluation were normal ACTH 5.6 pg/mL, Cortisol 17.3 mcg/dL, 17-Hydroxyprogesterone 69 ng/dL, and Aldosterone: Renin ratio 3.5 (ref 0-30). He had elevated levels of Renin at 518 ng/mL/hr and Aldosterone at 1001 ng/dL. Initial management included fluid resuscitation, dextrose-insulin infusion, albuterol, sodium bicarbonate, and calcium gluconate. He remained hyperkalemic which required the addition of Fludrocortisone, Kayexalate, and Lasix. He was started on low potassium formula feeds, sodium chloride, and sodium phosphate supplementation. Attempts to wean low potassium formula feeds resulted in the development of hyperkalemia. Additionally, he developed significant dry skin which required frequent emollient application. He was discharged on home nasogastric feeds decanted with Kayexalate and electrolyte supplementation. Since discharge, he has been admitted to the hospital twice for hyperkalemia. Currently, the results of his genetic studies are pending.

Case Two

A 4-day-old female neonate of Mixteco-speaking parents from Santa Maria, California was admitted to the neonatal intensive care unit (NICU) for poor oral intake, decreased urine output, and increased work of breathing. Her birth history and family history were noncontributory. Laboratory studies at admission demonstrated hyponatremia (126 mmol/L), hyperkalemia (9.6 mmol/L), and severe metabolic acidosis (pH 7.21, bicarbonate of 7 mmol/L, base deficit of 19). Endocrine studies showed normal ACTH 11.5 pg/mL, Cortisol 16.2 mcg/dL, 17-Hydroxyprogesterone 17 ng/dL, and Aldosterone: Renin ratio 3.7 (ref 0-30). She had an elevated renin level of 270.3 ng/mL/hr and an Aldosterone level of 1003.4 ng/dL. Initial management included extensive fluid resuscitation, calcium gluconate, albuterol, Lasix, kayexalate, dextrose insulin infusion, and sodium supplementation. Within three days, potassium levels normalized, and she was started on low-potassium formula feeds. She was discharged on full low potassium formula feeds decanted with Kayexalate, fludrocortisone, and sodium chloride supplementation. Her genetic testing confirmed autosomal-recessive pseudo hypoaldosteronism type 1: homozygous SCNN1B c. 1542+1G>A. Three days after discharge, at 6 weeks of life, she presented again to the Emergency Department for lethargy, increased fussiness and decreased oral intake. Despite parent adherence to the discharge instructions, she was found to be hyponatremic (124 mmol/L) and hyperkalemic (>10 mmol/L). She was admitted to the Pediatric ICU and treated for severe hyperkalemia and hyponatremia.

Case Three

A 9-day-old female was brought by her Mixteco speaking mother to the Emergency Department for diarrhea, significant dehydration, and hyperkalemia. At 6 days of life, she started having poor intake and multiple yellow watery stools. Laboratory studies demonstrated a sodium of 127 mmol/L, potassium of 9.5 mmol/L, and bicarbonate of 10mmol/L. She was given a normal saline bolus and was admitted to the intensive care unit. She did not exhibit any systemic manifestation of hyperkalemia and her EKG was within normal limits. Hyperkalemia was treated with Insulin dextrose infusion and albuterol. Due to her diarrhea, sodium polystyrene was not administered. Additional laboratory studies revealed plasma renin activity at 8.8 ng/dl/h (range 2-37 ng/dl/h), renin at 68 ng/mL, and serum aldosterone >1168 ng/dL. A head ultrasound showed lenticulostriate mineralizing vasculopathy which improved in the follow-up studies. Genetic studies revealed a mutation in the SCNN1B gene. She was discharged home with a gastrostomy tube, low potassium formula with sodium polystyrene, sodium bicitra, and sodium chloride supplements. She was readmitted with dehydration, seborrheic infantile dermatitis, and acute bilateral bacterial conjunctivitis.

Case Four

Patient D Mixteco speaking Hispanic family from Santa Barbara, was to a tertiary NICU for management of hyperkalemia and respiratory difficulty at 7 days of life. He was diagnosed with the recessive form of pseudo hypoaldosteronism type 1 due to an inactivating mutation in the epithelial Na channel (ENaC) encoded by SCNN1A-B. After a cardiorespiratory arrest event, he developed seizures and his MRI showed supratentorial infarcts with cortical mineralization. He developed cortical blindness. His seizures were controlled with gabapentin and phenobarbital. Additionally, during his hospitalization, he developed a COVID and parainfluenza infection for which he received remdesivir and Decadron. The sleep study showed mixed central and obstructive apnea, and hence he was discharged home on oxygen supplementation. A gastrostomy tube was placed due to feeding and medication administration difficulty. He required multiple readmissions in our hospital for respiratory deterioration and hyperkalemia. Antihypertensives started as his blood pressure were consistently high and his renal ultrasound showed possible mild renal artery stenosis. He was started on antihypertensive medication.

Discussion

PHA1 was initially described by Cheek and Perry in 1958. Aldosterone has an important role in the regulation of sodium–potassium balance and blood pressure through its effects on the epithelial sodium channel (ENaC). ENaC is a hetero-multimeric protein consisting of α, β, and γ subunits and is present in multiple epithelial tissues, including the distal tubule of the kidney, the distal colon, and salivary and sweat glands [7,8]. In the state of hypovolemia or hyperkalemia, aldosterone helps with sodium retention, and increases intravascular volume and the excretion

of potassium [9]. Mineralocorticoid deficiency or receptor non-responsiveness to aldosterone leads to renal salt wasting with hyponatremic dehydration, hyperkalemia, and metabolic acidosis [9].

PHA is a rare heterogeneous syndrome of mineralocorticoid resistance leading to insufficient potassium and hydrogen secretion. The common clinical features are hyperkalemia, metabolic acidosis, and elevated plasma aldosterone levels. PHA has been classified into three distinct clinical forms. This includes primarily salt-losing syndromes, such as PHA type 1 (PHA1) and PHA type 3 (PHA3) and the potassium-retaining PHA type 2 (PHA2). Mineralocorticoid resistance may be isolated to the kidney (PHA1a or adPHA1), presents as mild disease, and often improves with time. In contrast, autosomal recessive PHA1 (PHA1b or arPHA1) is a more severe condition with mineralocorticoid resistance occurring in multiple organs and can result in fatal hyperkalemia. Mutations in the SCNN1A, SCNN1B, or SCNN1G genes cause arPHA1 (Table 1). Each of these genes provides instructions for making one of the pieces (subunits) of a protein complex called the epithelial sodium channel (ENaC) [8,10,11].

Pseudo hypoaldosteronism 1		
Type	Renal Type (PHA1a)	Systemic Type (PHA1b)
Inheritance	AD or sporadic	AR
Gene(s) Affected (Location)	NR3C2 gene (4q31.23)	SCNN1A (12p13.31)
		SCNN1B (16p12.2)
		SCNN1G (16p12.2)
Gene Function	Ability of aldosterone receptor to bind to aldosterone	Encodes for the alpha, beta, and gamma subunits of ENaC
*ENaC = epithelial sodium channel		

Table 1: Inheritance and affected genes in both forms of pseudo hypoaldosteronism 1.

Affected children present very early in life and typically require extremely high doses of sodium to compensate for their severe multiorgan salt wasting. Spontaneous remission has not been described [10]. Due to the epithelial sodium channel mutations, some patients are also prone to develop atopic dermatitis rash and respiratory infections. This type of dermatitis is thought to be secondary to inflammation in the eccrine structures from increased salt loss through the skin. Pulmonary epithelial sodium channel dysfunction and excess airway liquid lead to respiratory symptoms that can mimic cystic fibrosis [12-14]. Many patients have feeding difficulties and growth failure and need gastrostomy tube placement for adequate nutrition and medication administration. [10,11,15].

All four patients were admitted to a hospital in the neonatal period with dehydration, hyperkalemia, and hyponatremia. They all required aggressive therapy for hyperkalemia and had repeat admissions for hyperkalemia and dehydration. All four patients were born in 2022-2023. It is likely that these parents even though there was no reported consanguinity, originally came from the Baja Mexico region in Mexico, and married within the same community per history obtained during admission. The parents of all four patients are Mixteco speaking and currently live in Santa Maria, California. This could suggest the reason for the increased incidence of this very rare autosomal recessive condition in this population.

Even though the genetic testing for patient 1 is pending, the clinical presentation and ethnicity is like the other patients and hence likely have a similar gene mutation for PHA1b. The diagnosis of PHA1b should be considered in a newborn showing hyponatremia, hyperkalemia, and metabolic acidosis, after the exclusion of a salting-loss form of adrenogenital syndrome. Even though the corticosteroid level is not affected, severe hyperkalemia associated with dehydration can be life-threatening in this condition as well. The increased plasma levels of aldosterone and aldosterone/renin ratio, associated with a poor response to fludrocortisone/ corticosteroid administration can confirm the diagnosis.

The pattern of serum electrolytes for all four neonates raised the possibility of salt-losing forms of congenital adrenal hyperplasia, which was excluded by normal external genitalia,

hormonal evaluation, and non-responsiveness to steroid therapy [4]. The exceedingly early presentation (range for above patients 4-9 days after birth), suggests sodium loss through various routes like saliva, sweat, and stool [5,6].

Clusters of ethnic prevalence have been reported in the literature [16,17]. However, this is the first case report to present four neonates whose parents are of the same ethnicity, speaking a rarely known dialect called Mixteco, and now residing in the same geographic area in California.

We encountered significant communication issues with all the parents, as most of them were able to speak little or no Spanish. A three-way communication through both Mixteco and Spanish interpreters was needed. These infants have a life-threatening condition with multiple admissions due to noncompliance or difficulty following the treatment regimen at home. Parental education was crucial but challenging. This condition, being a lifelong condition, needs treatment and multispecialty follow-up for appropriate management.

Conclusion

This report suggests that the incidence of autosomal recessive PHA1 in neonates of the Mixteco dialect-speaking parents who came from the Baja Mexico region is higher than the reported incidence in the literature. It is important to identify this potentially life-threatening condition in this population and manage it appropriately. Adequate interpretation services should be available for this rare language to communicate and educate the families about this complex condition.

Ethical Board: Consent obtain from Valley Childrens healthcare review Board for this case study.

Conflict of Interest: No conflict of interest to disclose.

References

1. Kuhnle U, Nielsen MD, Tietze HU, Schroeter CH, Schlamp D, et al. (1990) Pseudohypoaldosteronism in eight families: Different Forms of Inheritance Are Evidence for Various Genetic Defects, The Journal of Clinical Endocrinology & Metabolism, Volume 70: 638–641.
2. Geller DS, Rodriguez-Soriano J, Vallo Boado A, Schifter S, Bayer M, et al. (1998) Mutations in the mineralocorticoid receptor gene cause autosomal dominant pseudohypoaldosteronism type I. Nat Genet 19(3):279-81.2.
3. Attia NA, Marzouk YI (2016) Pseudohypoaldosteronism in a neonate presenting as life-threatening hyperkalemia. Case Rep Endocrinol 2016:1-3.
4. Cheek DB, Perry JW (1958) A salt wasting syndrome in infancy. Arch Dis Child 33:252–256.
5. Giapros VI, Tsatsoulis AA, Drougia EA, Kollios KD, Siomou EC, et al. (2004) Rare causes of acute hyperkalemia in the 1st week of life. Three case reports. Pediatr Nephrol 19(9):1046-9.
6. Amin N, Alvi NS, Barth JH, Field HP, Finlay E, et al. (2013) Pseudohypoaldosteronism type 1: clinical features and management in in infancy. Endocrinol Diabetes Metab Case Rep 2013:130010.
7. Garty H, Palmer LG (1997) Epithelial sodium channels: function, structure, and regulation. Physiol Rev 77: 359-396.
8. Anantharam A, Palmer LG (2007) Determination of epithelial Na + channel subunit stoichiometry from single-channel conductances. J Gen Physiol 130: 55-70.
9. Zennaro MC, Lombes M (2004) Mineralocorticoid resistance. Trends Endocrinol Metab 15: 264-270.
10. Bandhakavi M, Wanaguru A, Ayuk L, Kirk JM, Barrett TG, et al. (2021) Clinical characteristics and treatment requirements of children with autosomal recessive pseudohypoaldosteronism. Eur J Endocrinol 184(5): K15-K20.
11. Belot A, Ranchin B, Fichtner C, Pujo L, Rossier BC, et al. (2008) Pseudohypoaldosteronisms, report on a 10-patient series. Nephrol Dial Transplant 23:1636-1641.
12. Martín JM, Calduch L, Monteagudo C, Alonso V, García L, et al. (2005) Clinico-pathological analysis of the cutaneous lesions of a patient with type I pseudohypoaldosteronism. J Eur Acad Dermatol Venereol 19:377-9.
13. Kerem E, Bistritzer T, Hanukoglu A, Hofmann T, Zhou Z, et al. (1999) Pulmonary epithelial sodiumchannel dysfunction and excess airway liquid in pseudohypoaldosteronism. N Engl J Med 341:156–162.
14. Schaedel C, Marthinsen L, Kristoffersson AC, Kornfalt R, Nilsson KO, et al. (1999) Lung symptoms in pseudohypoaldosteronism type 1 are associated with deficiency of the -subunit of the epithelial sodium channel. J Pediatr 135: 739-745.
15. Önder A, Çetinkaya S, Kara C, Zenciroğlu A, Aycan Z (2016) Multisystemic severe form pseudohypoaldosteronism: can gastrostomy be useful in management? Turkish J Pediatr Dis 2: 134-136.
16. Serra G, Antona V, D'Alessandro MM, Maggio MC, Verde V, et al. (2021) Novel SCNN1A gene splicing-site mutation causing autosomal recessive pseudohypoaldosteronism type 1 (PHA1) in two Italian patients belonging to the same small town. Ital J Pediatr 47(1):138.
17. Pugh CP (2022) Pseudohypoaldosteronism Type 1: The Presentation and Management of a Neonate with a Novel Mutation of the SCNN1B Gene Found in Two Hispanic Siblings. Cureus 14(4): e23918.