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Case Report

Neonate with Respiratory Distress, Failure to Thrive, Pancreatic Insufficiency and Hyperkalemia: Pseudohypoaldosteronism; Not Cystic Fibrosis!

Kiran Kumar Lanka MD[1]*, Hanaa Nik Rushdi MD[1], Mia Sethna MD, Karen Schmidt MD[1], Leonard Hymes MD[1], David Collier MD[1], Guillermo Hidalgo MD[1].

[1]*East Carolina University/Vidant Medical Center, NC*

**Corresponding author:* *Dr. Kiran kumar Lanka, East Carolina University/Vidant Medical Center, 3719 Langston Blvd, Winterville, NC. 28590., Tel: 631-579-1535; Email: kiranlanka@rediffmail.com*

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Abstract

This is a case of a neonate who presented with respiratory distress and failure to thrive; and on further testing, was found to have hyperkalemia and pancreatic insufficiency. As he had respiratory distress and pancreatic insufficiency, he was evaluated for cystic fibrosis and found to have a positive sweat chloride test. However, the cystic fibrosis transmembrane conductance regulator (CFTR) sequencing was negative for mutation. The hyperkalemia and hyponatremia prompted the work up for aldosterone defect. The adrenocorticotropic hormone (ACTH) levels were normal with elevation of aldosterone levels and plasma renin activity (PRA) which was suggestive of Pseudohypoaldosteronism (PHA). This was confirmed by the genetic testing which was positive for a mutation in the sodium channel non voltage-gated 1 alpha gene (SCNN1A), a known cause of autosomal recessive PHA type 1B. There can be a significant overlap between PHA and cystic fibrosis features making a clinical diagnosis extremely challenging. Genetic testing is essential to avoid misdiagnosing PHA as cystic fibrosis (CF).

Keywords: Neonate; Hyperkalemia; Pancreatic Insufficiency; Pseudohypoaldosteronism; Cystic Fibrosis

Case report

A one week old male term infant was taken to the Emergency Department for decreased feeding, bilious, non-bloody emeses and decreased activity for one day. He was born to a 27 year-old gravida 3 para 3 mother with gestational diabetes by spontaneous vaginal delivery. The infant was being followed by his pediatrician for inadequate weight gain. He was being breast fed along with formula supplementation.

There was no history of fever, cough or shortness of breath, skin rash, sick contacts or dependent edema. He was noted to be pale and lethargic; the vital signs were: heart rate of 180/min, respiratory rate of 56/min, systolic blood pressure of 80 mmHg, and oxygen saturation of 85%; glucose was 50mg/dL. He was given a bolus of 20ml/kg of NS, started on IV Dextrose with ¼ NS; and was started on ampicillin and gentamicin after a full sepsis screen. Basic metabolic panel showedsodium of 131 mEq/L, potassium 9.1 mEq/L, bicarbonate of 14 mEq/L andlactic acid of 12 mmol/L. Electrocardiogram showed wide complex tachycardia. The patient was promptly given calcium gluconate, sodium bicarbonate and started on insulin drip with dextrose and Normal saline. Abdominal radiograph showed no signs of obstruction or perforation. The patient was transferred to Pediatric intensive care unit; continued on sodium bicarbonate, insulin and dextrose infusion; and was started on kayexalate for hyperkalemia; acidosis treated with correction of dehydration and bicarbonate. The family history was positive for a renal problem in the patient's older sibling, requiring hospitalization as a newborn for 3 months.

The urine electrolytes showed a low transtubular potassium gradient (1.5) and a high fractional excretion of sodium (4.24). As the hyponatremia, hyperkalemia and acidosis suggested an aldosterone defect, further tests were ordered. The cortisol (25.5 ug/dl) and

adrenocorticotropic hormone (ACTH) levels(16 pg/ml) were normal with elevation of aldosterone levels (684 ng/dl) and plasma renin activity (PRA-51.27 ng/ml/h). The 17-OH progesterone levels(87 ng/dL) were normal. The renal function tests and urinalysis were normal. The patient's genetic testing was positive for a mutation in the sodium channel non voltage-gated 1 alpha gene (SCNN1A), which is a cause of autosomal recessive Pseudohypoaldosteronism type 1B. The patient also had a very low fecal elastase of <50 mcg/g of stool, suggestive of severe pancreatic insufficiency. He was also evaluated for cystic fibrosis due to persistent oxygen requirements and had a positive sweat chloride test (139 mEq/L). The cystic fibrosis transmembrane conductance regulator (CFTR) gene sequencing was negative.

The patient's acidosis and hyperkalemia resolved over the next 24 hours. He was continued on antibiotics for 48 hours until sepsis was ruled out. After the initial IV fluids with dextrose and normal saline, he was gradually transitioned over the next 3 days to oral feeds with Similac 60/40 formula with kayexalate to sequester the potassium and supplemental sodium in the formula. In spite of the chest physiotherapy and albuterol nebulization treatments for several days, the patient continued to require ½ liter/min supplemental oxygen. The patient was discharged home in stable condition on oxygen.

Discussion

Our patient presented early in the neonatal period with vomiting, failure to thrive, respiratory distress, acidosis and electrolyte abnormalities. Based on these symptoms, a broad differential was considered; sepsis, cardiac, metabolic and surgical abdominal causes ruled out by relevant labs. As he had respiratory distress and a very low fecal elastase suggestive of pancreatic insufficiency, he was evaluated for cystic fibrosis and found to have a positive sweat chloride test. However, the cystic fibrosis transmembrane conductance regulator (CFTR) sequencing was negative for mutation.

The hyperkalemia and hyponatremia on labs and the family history of possible renal disease prompted the work up for aldosterone defect. The adrenocorticotropic hormone (ACTH) levels were normal with elevation of aldosterone levels and plasma renin activity (PRA) which was suggestive of Pseudohypoaldosteronism. This was confirmed by the genetic testing which showed a mutation in the sodium channel non voltage-gated 1 alpha gene (SCNN1A), a known cause of autosomal recessive Pseudohypoaldosteronism type 1B. Thus the genetic testing confirmed that the patient's persistent oxygen requirement and pancreatic insufficiency cannot be attributed to CF but rather, are systemic manifestations of PHA type 1b.

Pseudohypoaldosteronism (PHA) is a rare heterogeneous syndrome of mineralocorticoid resistance causing insufficient potassium and hydrogen secretion. The common clinical features are hyperkalemia, metabolic acidosis and elevated plasma aldosterone levels. PHA is classified into three distinct clinical forms. This classification includes primarily salt-losing syndromes, such as PHA type 1 (PHA1) and PHA type 3 (PHA3) and the potassium- retaining PHA type 2 (PHA2). Two different forms of PHA1 can be distinguished on the clinical and genetic level, showing either a systemic or a renal form of mineralocorticoid resistance [1].

Fluid balance, sodium and potassium homeostasis and blood pressure are regulated through the effect of aldosterone on polarized epithelial cells. The aldosterone signal is transduced by the mineralocorticoid receptor (MR) inducing the amiloride-sensitive epithelial sodium channel (ENaC) as the leading intracellular factor necessary for sodium conservation and potassium secretion. Disruption of the intracellular MR signaling pathways leads to the clinical entity of pseudohypoaldosteronism (PHA). This could be secondary to a defect of the MR or ENaC [2]. ENaC is a heteromultimeric protein consisting of three subunits, termed alpha, beta and gamma which are coded by the SCNN1A gene on chromosome 12p13.31, and the SCNN1B and the SCNN1G genes on chromosome 16p12.1. The systemic form of PHA1 is caused by inactivating mutations of these ENaC subunit genes. Various SCNN1A, SCNN1B and SCNN1G mutations are reported to date [2]. The majority of mutations are frame shift or nonsense mutations leading to truncated or completely abnormal proteins, which are non-functional.

The first form of PHA 1 is caused by a defect of the mineralocorticoid receptor and has an autosomal dominant pattern of inheritance. Due to the limited distribution of the MR, this form of PHA1 affects only the kidneys and is the milder form of PHA1[1,2]. The patients usually present in infancy with insufficient weight gain due to chronic dehydration.The second, more severe form of PHA1 is due to a defect of the ENaC and displays autosomal recessive inheritance. These epithelial sodium channels are located in the kidneys, lungs, colon, sweat and salivary glands resulting in systemic involvement. The patients usually present in the neonatal period with severe dehydration, hyperkalemia, metabolic acidosis and hyponatremia. Children with this condition can have pulmonary symptoms including cough, wheezing, and tachypnea and due to poor sodium-dependent water reabsorption resulting in thickened secretions [3].Systemic PHA1 does appear to improve with age, but patients often have recurrent episodes of severe hyperkalemia and dehydration[4].

The more immediate and life-threatening complication is that of cardiovascular collapse from severe hyperkalemia.

In addition, challenging situations such as gastrointestinal illnesses common to children can lead to severe dehydration and profound electrolyte disturbances despite ongoing salt supplementation.PHA can be associated with pubertal delay, weight and linear growth failure [4].

Pulmonary complications in PHA 1 arise from failure to reabsorb lung fluid resulting in increased liquid in the lungs and narrow airway lumens [5]. The majority of airway findings include chronic rhinorrhea and recurrent lower respiratory tract infections. The mutation of the epithelial sodium channel (ENaC) alpha-subunit results in increase in sodium concentration in the airway surface liquid which can promote Pseudomonas aeruginosa growth. As ENaC is expressed in the ducts of sweat glands, persistently elevated sweat electrolyte values are detected in patients with PHA1. Hence these patients may have a positive sweat chloride test with negative CFTR gene test as was the case with our patient. While similar in some regards to cystic fibrosis (CF), lung disease in PHA 1 is generally milder than in CF without bronchiectasis, microbial colonization or lung destruction [6].

The mainstay of therapy consists of aggressive salt supplementation and control of hyperkalemia [7]. Initial measures for stabilization at presentation as well as during salt-wasting crises include IV fluid administration, correction of acidosis with bicarbonate and correction of serum potassium. Once stable, maintenance sodium chloride should be initiated and the dose is guided by individual patient's needs. Sodium containing ion-exchange resins such as Kayexelate are preferred both to improve sodium deficit and to decrease the potassium overload. While Kayexelate is available as a rectal enema, there is a risk of impaction, hemorrhage and colonic necrosis. Therefore, administration with oral or gastrostomy feeds is the preferred route. The sodium supplementation becomes generally unnecessary by 1 to 3 years of age in autosomal dominant form with the maturation of the renal salt conservation abilities through the proximal tubules, whereas the patients with autosomal recessive form may need lifelong sodium supplementation [4,8].

Our patient presented early in the neonatal period with vomiting, electrolyte abnormalities and acidosis; and required initial stabilization. We sequestered the formula with Kayexelate (sodium polystyrene) to lower the potassium content of our infant's diet to less than 1-2 mEq/kg/day. In the case of multi-system PHA-1 patients, life-long supplementation is recommended to prevent serious morbidity and even death [7]. As he ages, challenges with solid foods and weaning off formula will need to be addressed.

To our knowledge, this is only the second case of PHA with both pulmonary manifestations and pancreatic insufficiency with a negative CFTR mutation[9]. The genetic testing revealed a frame shift mutation in SCNN1A gene at position c.505_506 consisting of a deletion of adenine and cytosine, resulting in a premature stop codon in exon 3 of SCNN1A. Our patient is either homozygous for this mutation or has one deleted SCNN1A allele, as only the abnormal sequence was identified. Parental testing would help to determine whether this reflects homozygous or hemizygous mutation.

This case highlights the importance of both family history and genetic testing in the accurate diagnosis of patients. There is significant overlap between the presentations of PHA and cystic fibrosis, making a clinical diagnosis extremely challenging. As patients with PHA may have positive sweat tests, genetic testing is needed to avoid misdiagnosing pseudohypoaldosteronism as cystic fibrosis. In this case, the history of the patient's sibling with renal problems and hyperkalemia increased the index of suspicion for PHA and helped direct the patient's work up. Functional interactions between CFTR and ENaC have been demonstrated[10], and it is suggested that ENaC may affect CFTR activity. It has been hypothesized that a combination of variants in CFTR and ENaC genes may predispose to atypical CF by a polygenetic mechanism [11]. Further research is required to determine the exact relationship between the CFTR and ENaC genes and how specific mutations cause the pulmonary, pancreatic, and renal manifestations of cystic fibrosis and pseudohypoaldosteronism.

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