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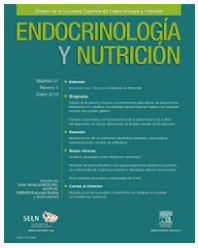

SPECIAL ARTICLE

A case of systemic pseudohypoaldosteronism with a novel mutation in the SCNN1A gene

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Abstract We report a neonatal case of systemic pseudohypoaldosteronism type 1 caused by a novel mutation in the SCNN1A gene (homozygous c.1052 + 2dupT in intron 3) in which the patient presented with life-threatening hyperkalemia, hyponatremia and metabolic acidosis. It remains uncertain if there is genotype–phenotype correlation, due to the rarity of the disease. This mutation, which to our best knowledge has not been described before, was associated with a very severe phenotype requiring aggressive therapy.

PALABRAS CLAVE
Pseudohipoaldosteronismo sistémico tipo 1;
Hiperpotasemia;
Hiponatremia;
Acidosis metabólica;
Gen SCNN1A

Un caso de pseudohipoaldosteronismo sistémico con una mutación nueva en el gen SCNN1A

Resumen Se presenta un caso neonatal de pseudohipoaldosteronismo sistémico tipo 1 causado por una nueva mutación en el gen SCNN1A (homocigotos C.1052 2 dupT en el intrón 3) en el que el se evidenció hiperpotasemia potencialmente mortal, hiponatremia y acidosis metabólica. Continúa sin saberse con certeza si hay correlación genotipo-fenotipo, debido a la rareza de la enfermedad. Esta mutación, que no ha sido previamente descrita, se asoció con un fenotipo muy grave por lo que requirió un abordaje terapéutico agresivo.

Introduction

Hyponatremia and hyperkalemia can represent a variety of renal and genetic disorders with significant long-term health implications.[2]

Pseudohypoaldosteronism type 1 (PHA 1) is a rare genetic aldosterone unresponsiveness syndrome.[5] The diagnosis is

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established by the presence of high levels of serum aldosterone and plasma renin activity associated with clinical and laboratory findings of hypoaldosteronism.[9] There are two forms that are clinically and genetically distinct. Systemic PHA 1 has an autosomal recessive transmission and result from mutations in the genes encoding the epithelial sodium channel (ENaC) that exists in multiple organs. Affected patients typically have a severe phenotype and require extremely high doses of sodium, indefinitely, to compensate their severe multiorgan salt wasting.[2] Renal PHA 1 has an autosomal dominant transmission and results from mutations in the gene that encodes the mineralocorticoid receptor (MR) that exists predominantly on the kidney. Generally, as the mineralocorticoid resistance is isolated to this organ, patients have a mild phenotype which often improves spontaneously after a variable period of time.[2]

Herein we report a 10-day-old male newborn, who developed severe hyperkalemia, hyponatremia and metabolic acidosis, initially diagnosed as congenital adrenal hyperplasia (CAH) based on an initial high level of 17-hydroxyprogesterone. Endocrinological study subsequently revealed high levels of renin and aldosterone, which led to the diagnosis of PHA 1. It was the severity of his clinical course and his systemic manifestations that made the clinical diagnosis of systemic PHA 1, leading to screening of ENaC mutations which found a homozygous mutation in intron 3 of the SCNN1A gene (c.1052 + 2dupT), which to our best knowledge has never been described before.

Case report

A 10-day-old male newborn was admitted to our hospital due to two episodes of vomiting and dehydration. He was born at full term with a birth weight of 3010 g (10–25th percentile) and there were no perinatal problems. There was no history of parental consanguinity. His older sibling, a 6-year-old female, had been diagnosed with Chediak–Higashi syndrome. Upon admission he looked sick, ''septic'' and dehydrated with a capillary refill time of 3 s. Heart auscultation revealed arrhythmic heart sounds, sometimes associated with bradycardia. He had no evidence of hyperpigmentation and other physical examination findings were unremarkable. Blood pressure was 89/59 mmHg, median arterial pressure (MAP) 76 mmHg (50–90th centile), heart rate varied between 60 and 120/min, respiratory rate was 40/min, oxygen saturation was 80% in room air and body temperature was 36.5 °C. Blood glucose was normal. Additionally, his weight was 2715 g (weight loss of 9.8%).

Electrocardiogram at admission in Intensive Care Unit was compatible with ventricular tachycardia and initial laboratory evaluation revealed the following: sodium 125 mEq/L; potassium >10 mEq/L; chloride 104 mEq/L; urea 62 mg/dL; creatinine 0.2 mg/dL; C-reactive protein <2.9 g/dL; hemoglobin 21.5 g/dL and hematocrit 58%. The venous blood gas analysis showed a mild metabolic acidosis (pH 7.28, PCO_2 48.9 mmHg, HCO_3 22.6 mmol/L, BE −4 mEq/L). Initial 17-hydroxyprogesterone level was slightly raised (10.76 ng/mL) and the rest of the endocrinologic study was in progress. He received normal saline to correct dehydration and calcium gluconate, sodium bicarbonate, nebulized salbutamol, glucose insulin infusion and ion exchange resin to control hyperkalemia. Intravenous hydrocortisone (30 mg/kg/day) was started as CAH was initially suspected. Despite these measures, he did not improve clinically and hyponatremia did not correct with large amounts of fluid and sodium intake. Attempts at tapering treatment of hyperkalemia resulted in recurrence of severe hyperkalemia. Thus, higher doses of intravenous hydrocortisone (maximum: 200 mg/kg/day) and oral fludrocortisone (1.5 mg/day) were administered. Determination of 17-hydroxyprogesterone on Guthrie card and molecular study of CYP 21A2 were performed and were normal.

The endocrinological study obtained at the time of presentation subsequently revealed normal levels of serum cortisol, ACTH, 17-hydroxyprogesterone and DHEA sulfate but markedly elevated levels of serum aldosterone (1750 ng/dL: range 7–184 ng/dL) and plasma renin activity (70 ng/ml/h; range 0.4–1.9 ng/ml/h), hence a diagnosis of pseudohypoaldosteronism was made and steroids were tapered. Hyponatremia and dehydration continued severely in spite of large fluid and sodium intake and sodium balance was only achieved with 35 mEq/kg/day of sodium chloride. Glucose and insulin infusion, calcium gluconate, sodium bicarbonate and nebulized salbutamol were tapered and stopped and potassium controlled with high dose of ion exchange resin. During hospitalization, he was noted to have episodes of sweating and also recurrent episodes of tachypnea and fever mimicking respiratory infections.

He was discharged home with 5.5 months on oral 20% saline (30 mEq/kg/day) and ion exchange resin (6 times a day). Since then he has had recurrences of fluid and electrolyte imbalances necessitating repeated short-term hospitalizations.

The study of the SCNN1B, SCNN1G and SCNN1A was carried out subsequently and a homozygous mutation in intron 3 of the SCNN1A gene was detected (c.1052 + 2dupT) (Fig. 1).

The patient is currently 8.5 months old and his growth, in weight and length, is below the third percentile. He also has a mild development delay and is under a stimulation program achieving some improvements.

Discussion

Our patient presented with hyponatremic dehydration, metabolic acidosis and severe hyperkalemia. CAH is the most frequent cause of severe dehydration, hyponatremia and hyperkalemia in the newborn period, and therefore this was our first diagnosis, supported by a initial high level of 17-hydroxyprogesterone. However, such severe hyperkalemia, that almost leads to cardiac arrest, is unusual in hyponatremic dehydration without hemolysis, renal failure or significant intake of potassium.[2] Also, the disappointing response to increasing doses of steroids made CAH a less likely diagnosis. 17-hydroxyprogesterone may be falsely high in sick newborns; therefore a repeated assessment may be required for the diagnosis. This could explain our initial high level of 17-hydroxyprogesterone. PHA 1 can be differentiated clinically from CAH by an earlier onset and by no response to steroid therapy, given the delay in obtaining results for many hormonal assays.[10]

PHA 1 was first described in 1958 by Cheek and Perry[4]. Since then, various case reports have been published and