Salt-Losing Syndrome in a Girl with Type I and II Pseudohypoaldosteronism

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Patient: Female, 2-month-old

Final Diagnosis: Hyperkalemia • hyponatremia • shock

Symptoms: Hyperkalemia • hyponatremia • hypovolemic shock • pseudohypoaldosteronism

Medication: —

Clinical Procedure: —

Specialty: Pediatrics and Neonatology

Objective: Rare disease

Background: Pseudohypoaldosteronism (PHA) is characterized by renal tubular resistance to aldosterone and leads to hyponatremia, hyperkalemia, and metabolic acidosis. PHA is divided into 2 types: PHAI and PHAII. PHAI can be dominant (systemic disease) or recessive (renal form). PHAI causes hypertension with hyperkalemia and is recognized mostly in adults. PHA can be a life-threatening disease due to salt-wasting syndrome and severe hypovolemia.

Case Report: We describe the case of a 2-month-old girl who was admitted to our hospital with hypovolemic shock due to salt-wasting syndrome. Laboratory tests revealed severe electrolyte abnormalities: hyponatremia (Na-116 mmol/L), hyperkalemia (K-10 mmol/L) and metabolic acidosis (pH-7.27; HCO3-12 mmol/L). Serum aldosterone was >100 ng/dL. Genetic analysis confirmed mutations in SCNN1A and CUL3 gene responsible for PHAI and PHAII. Supplementation with NaCl, pharmacological treatment of hyperkalemia, and restriction of potassium in the diet resulted in the normalization of serum electrolytes and proper future development.

Conclusions: Pseudohypoaldosteronism should always be considered in the differential diagnosis of hyponatremia and hyperkalemia in children. Salt loss syndrome can lead to hypovolemic shock and, when unrecognized and untreated, to death of a child due to arrhythmias and brain edema. The presence of 2 types of PHA in the same patient increases the risk of salt loss and at the same time significantly increases the risk of hypertension because of genetic predisposition and regular diet. Increased salt concentration in sweat and saliva may suggest pseudohypoaldosteronism.

Keywords: Aldosterone • Hyperkalemia • Hyponatremia • Pseudohypoaldosteronism • Shock

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Background

Aldosterone plays a crucial role in the maintenance of fluid and electrolytes (sodium and potassium). Pseudohypoaldosteronism (aldosterone resistance, PHA) is a rare genetic disorder causing hyponatremia, hyperkalemia, metabolic acidosis, and failure to thrive. PHAI (type I) is inherited either in a dominant or a recessive manner. Autosomal recessive PHAI (PHA1B, OMIM #264350, multi-system form) is characterized by mutations in the epithelial sodium channel (ENaC) encoded by SCNN1A, SCNN1B, SCNN1G, and SCNN1D.

Autosomal dominant PHAI (PHA1A, OMIM #177735, renal type) results from mutations in the mineralocorticoid receptor coding gene NR3C2. PHAII (type II, familial hyperkalemic hypertension disease, Gordon disease, autosomal dominant type of monogenic hypertension) is caused by mutations in 3 different genes encoding for Kelch-like protein 3 (KLHL3), Cullin-3, and with-no-lysine kinases (WNKs) [1-3].

Case Report

A 35-day-old girl was admitted to the emergency room with vomiting, lethargy, and decreased oral intake. She was born by cesarean section from the second twin, with birth weight 3.35 kg (46th percentile), Apgar score 10. She was the second child of her parents, and the older sister was healthy. However, the family history revealed an unexplained death of 2 cousins during infancy. On physical examination the child was severely dehydrated (weight 3.56 kg, 10th percentile), with blood pressure 71/41 mmHg, pulse rate 156/min, respiratory rate 48/min, capillary refill test >3 s, and temperature 36.7°C. She was pale and lethargic. Subtle seizures manifesting as upward eye movements were observed. Other physical examination results were normal. Laboratory tests showed severe electrolyte disturbances: hyponatremia (Na 116 mmol/L), hyperkalemia (K 10 mmol/L), hypochloremia (Cl 67 mmol/L), metabolic acidosis (pH 7.27, HCO3-12 mmol/l, and base excess (-10 mmol/L). Serum glucose was 81 mg/dL. Ultrasound of the abdomen was normal. The results of endocrinological evaluation were normal: ACTH 52 pg/ml and cortisol 54 μg/dl. The girl was homozygous for the SCNN1A mutation responsible for the multi-system form of PHAIB. A defect in epithelial sodium channel (ENaC) protein complex leads to high concentration of sodium in sweat, saliva, colonic epithelium, and the lungs. On admission, signs of dehydration were present. Serum laboratory tests again revealed: hyponatremia (Na 126 mmol/L), hyperkalemia (K 6.9 mmol/L), hypochloremia (Cl 87 mmol/L), metabolic acidosis (pH-7.31, and HCO3-17 mmol/l). Infusion with normal saline was administered. Further laboratory studies revealed serum aldosterone >100 ng/dL (normal range 2.52-39.2 ng/dL). PHA was suspected and genetic analysis was performed. We found mutations in genes responsible for type I and II PHA. The girl was homozygous for the SCNN1A gene (variant NM_001159576: c.1053-25A>G) and heterozygous for the CUL3 gene (variant NM_003590: c.265+59C>T). She received salty diet (10mEq of sodium/kg/day) and sodium kayexalate (1 g/kg/day) under electrolytes control. This treatment was continued for 1 year, then kayexalate was discontinued. She is still on a high-salt diet, and laboratory test results are normal.

Discussion

Pseudohypoaldosteronism (PHA) is associated with congenital renal tubular unresponsiveness to aldosterone. PHA is classified into 2 types: PHAI (IB, IA) and PHAII. It is unusual that this patient with severe hyponatremia and hyperkalemia had not 1, but 2 forms of PHAI and II. In our search of the medical literature, we did not find another description of such a coincidence of mutations. For the first form of PHA mutations, the girl was homozygous for the SCNN1A mutation responsible for the multi-system form of PHAIB. A defect in epithelial sodium channel (ENaC) protein complex leads to high concentration of sodium in sweat, saliva, colonic epithelium, and the lungs. Figure 1 shows salt crystals on the child’s head, which were observed by her mother. The condition of a child with PHAI is usually severe, and changes in physical examination results are most often associated with dehydration. Severe electrolyte disturbances and metabolic acidosis, when untreated,
can lead to arrhythmias, convulsions, hypovolemic shock, and death [4]. Normal glucose and cortisol levels should exclude the most common cause of hyponatraemia and hyperkalaemia in neonates, which is congenital adrenal hyperplasia [5,6]. The treatment of PHA in our case included aggressive fluid therapy with NaCl (initially i.v., then oral) to correct hyponatraemia and treatment of hyperkalaemia and acidosis with sodium bicarbonate, kayexalate, furosemide, calcium gluconate, and potassium restriction diet [7]. PHAI requires an increased amount of salt in the diet, but the severity of hyponatraemia manifestation improves with age. Our patient received a high-salt diet (10-8-6 mmol/kg/day of Na) for 2 years and kayexalate (Resonium Na 1 g/kg/day) for 1 year. After 2 years of follow-up, blood pressure and electrolyte levels were normal (Na 136 mmol/l, K 4.6 mmol/l). In addition to routine laboratory tests, it is important to remember that, due to salt crystallization in tissues (especially the lungs), the parameters of lung function should be monitored periodically [9].

For the second form of PHA mutations, the girl was heterozygous for the CUL3 gene responsible for Gordon disease. Mutations in genes KLHL3 and CUL3 account for 80% of families with PHAII. The patients with CUL3 mutations have the most severe phenotype and present at a younger age. Severe hyperkalaemia, hypertension, and metabolic acidosis lead to failure to thrive and to growth impairment. In Gordon syndrome, hyperkalaemia may be present from birth, but hypertension may not be manifested until later in life. The clinical symptoms are chloride-dependent and can be corrected with thiazide diuretics, which inhibit salt reabsorption in the distal nephrons. In our patient, blood pressure was normal during follow-up, but should be monitored for her whole life [3].

The family history of our patient was especially significant. Two cousins of the girl died in infancy with the diagnosis of sudden infant death syndrome. The cause of death was unknown. If they had PHA, hyponatremia could cause cerebral edema and apnea. Hyperkalemia can cause cardiac arrest and death [10]. This fate could have occurred in our patient if no further diagnosis and treatment had been implemented.

Conclusions

Pseudohypoaldosteronism, which is renal tubular resistance to aldosterone, is a rare condition and should be kept in mind in the differential diagnosis of a patient with hyponatraemia, hyperkalaemia, and metabolic acidosis. In our patient, we observed 2 severe salt-wasting episodes with hypovolemic shock. If not diagnosed early, it can lead to death. Genetic tests were very helpful in establishing management and explaining the severity of electrolyte abnormalities. The presence of 2 types of PHA (IB and II) in the same patient increases the risk of severe electrolytes disturbances and hypertension. Increased salt concentration in sweat and saliva may suggest pseudohypoaldosteronism.

Declaration of Figures’ Authenticity

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