Transient pseudohypoaldosteronism type 1 in a preterm neonate: A case report and literature review

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ABSTRACT :

Pseudohypoaldosteronism type 1 (PHA1) is a rare pediatric disease characterized by a resistance to mineralocorticoid hormones. Renal PHA1, also called autosomal dominant PHA1, is the most frequent form of PHA1. Secondary PHA1 is typically a brief state of mineralocorticoid resistance in infants, associated with urinary tract malformations or infections. The clinical course is less severe in older infants than in neonates suggesting a pathophysiologic role for the tubular immaturity. Usually, patients present with severe salt wasting in the neonatal period, with hyponatremia, hyperkalemia and metabolic acidosis even though they have very high levels of plasma renin and aldosterone. Here, we report the case of a 4-day-old preterm male neonate with transient PHA1 in the course of urinary tract infection. Clinically, he presented a dehydration, a polyuria and a weight loss. Laboratory tests showed normal anion gap metabolic acidosis with large variations in blood sodium and potassium levels. Urinary sodium level was constantly increased in all samples while urinary potassium remained low. Elevated plasma renin activity and plasma aldosterone levels suggested pseudohypoaldosteronism. Renal ultrasonography and cystouretherography showed no anomaly. The patient was discharged from hospital at 2 months of age, while still receiving oral supplementation of sodium bicarbonate with hydrochlorothiazide-amiloride. These treatments were stopped after 4 weeks given biological normalization. After a 14-months follow up, he had proper growth and weight gain.

Key words : Pseudohypoaldosteronism type 1, neonate, salt wasting, urinary tract infection.

INTRODUCTION :

Pseudohypoaldosteronism type 1 (PHA1) is a rare pediatric disease characterized by a resistance to mineralocorticoid hormones, owing to anomalies of the mineralocorticoid receptor (MR) and the epithelial amiloride-sensitive sodium channel ENaC. Usually, patients present with severe salt wasting in the neonatal period, with hyponatremia, hyperkalemia and metabolic acidosis even though they have very high levels of plasma renin and aldosterone. Classically, two different forms of PHA1 have been reported, a renal mild form and a severe generalized form, caused by multiple genetic mutations. Furthermore, a secondary form of PHA1 associated with urinary tract infection or malformations was also described.

CASE REPORT :

A 4-day-old preterm male neonate, born at 36 weeks gestation because of acute foetal distress of unknown cause, was admitted due to biological inflammatory syndrome. He was born to non consanguinous parents of Mauritian origin via caesarean section with meconial amniotic fluid, after an uneventful gestation. A vaginal smear of the mother was positive for Candida Glabrata. The family history was unremarkable. His birth weight was 2,300g (10th percentile) and height was 48 cm (50th percentile). His C reactive protein which was initially normal at 12 hours after birth, increased gradually, reaching 105 mg/L after 3 days though he was asymptomatic. At the time of presentation in our paediatric unit, the baby was afebrile, his weight was 2,360g. No skin hyperpigmentation was observed, and genital and other system

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examinations were normal. Initial laboratory investigations showed a normonatremia (Na+= 140 mmol/l), hypokalemia (K+= 3 mmol/l), hyperchloremia (Cl-= 114 mmol/l) and metabolic acidosis (pH=7.23, HCO3-= 6.9 mmol/l). The blood count was normal, as well as the lumbar puncture. Urine culture was positive for Klebsiella pneumoniae resistant to C3G. Electrolyte resuscitation was performed and the patient was treated with Imipenem and gentamicin. He eventually developed apathy, abdominal distension and projectile vomiting associated with elevated C reactive protein. Acute bacterial enteritis was suspected and an X-ray was performed, showing intestinal distension. The patient received 7 days of antibiotics together with intravenous nutrition. Gradually, he started showing clinical signs of dehydration accompanied by weight loss. Laboratory tests showed normal anion gap metabolic acidosis along with large variations in blood sodium and potassium levels (natremia: 115-160 mmol/L and kaliemia: 3.0 – 6.5 mmol/L).

He also had polyuria up to 7.8 ml/kg/hour, requiring intravenous fluid intake reaching 250 ml/kg/day. Urinary sodium was 81 mmol/L and urinary potassium was 3 mmol/L. The urine pH fluctuated between 5 and 6. Hypercalciuria reaching 17 mg/kg/day was also noted. Distal renal tubular acidosis was initially suspected. The patient was treated with sodium bicarbonate and indometacin later replaced by hydrochlorothiazide-amiloride. On the 13th day of hospitalization, the patient had 1 episode of prolonged focal seizure treated with phenobarbital. He had hyponatremia and hyperkaliemia. A cerebral CT scan showed superior sagittal sinus thrombosis and left basal ganglia infarction. He had no recurrence of seizure and received phenobarbital for 3 months. Platelet count, haemoglobin electrophoresis, and anticoagulant protein levels (protein S, C, antithrombin III) were normal. His hydration status improved steadily with a decrease in polyuria. His intravenous fluid intake was reduced progressively and replaced with ingestion of diluted milk protein hydrolysates. Laboratory investigations showed normal sodium level (while receiving sodium bicarbonate treatment) and hyperkaliemia, together with metabolic acidosis. Urinary sodium level was constantly increased in all samples while urinary potassium remained low. The initially elevated calciuria turned to normal values. Congenital adrenal hyperplasia was considered but blood cortisol and 17-hydroxyprogesterone levels were normal. Elevated plasma renin activity (122 ng/L) and plasma aldosterone (316 ng/L) levels suggested pseudohypoaldosteronism. Meanwhile, the patient had a second episode of urinary tract infection treated with Imipenem. Renal ultrasonography showed no anomaly.

The patient was discharged from hospital at 2 months of age, while still receiving oral supplementation of sodium bicarbonate, together with hydrochlorothiazide-amiloride, phenobarbital and cotrimoxasol. Voiding cystourethrography showed no vesicoureteral reflux. These treatments were eventually stopped after 4 weeks. He had proper growth and weight gain. An MRI scan performed at the age of 8 months showed a cystic lesion in the left basal ganglia together with mild loss of volume of bilateral fronto temporal lobes. His neurologic examination then showed normal psychomotor development apart from impaired movement of the right arm.

DISCUSSION :

Renal PHA1, also called autosomal dominant PHA1, is the most frequent form of PHA1, with an incidence estimated at 1 per 66,000 newborns (1). It is caused by inactivating mutations in the NR3C2 gene encoding the aldosterone receptor, which prevents the binding of aldosterone to the receptor. To date, more than 100 mutations in this gene have been reported (2). Generalized PHA1 is a severe, autosomal recessive, form of PHA1. It is characterized by salt wasting from multiple organs, including kidney, distal colon, and the salivary and sweat glands. Patients can present with severe dehydration, vomiting, fever, diarrhea, polyuria, recurrent pulmonary infections, dermatitis-like skin lesions and failure to thrive in the neonatal period which may lead to complications like cardiac dysrhythmias, collapse, shock or cardiac arrest (3). Systemic PHA1 is caused by mutations in SCNN1A, SCNN1B, and SCNN1G genes coding for the ENaC subunits α, β and ϖ, respectively. Secondary PHA1 is typically a brief state of mineralocorticoid resistance in infants, associated with urinary tract malformations or infections. More than 130 cases have been reported since the 1980s (4). Many kinds of congenital obstructive uropathies such as ureteropelvic junction obstruction, ureterovesical junction obstruction, posterior urethral valves or ureterocele may cause PHA (5). Some rare cases of PHA as a result of systemic lupus erythematosus and sickle cell nephropathy have been reported, as well as certain drugs like angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, heparin, ketoconazole, cyclosporin, tacrolimus, nonsteroidal anti-inflammatory drugs, beta blockers, spironolactone and potassium-sparing diuretics (6).

The clinical course is less severe in older infants than in neonates suggesting a pathophysiologic role for the tubular immaturity. In fact, cases of secondary PHA have been reported in the literature in infants aged younger than 7 months age. There is a significant decrease in incidence after postnatal third month. A review of 93 children with secondary PHA1 showed that 90% of patients were younger than 3 months, and all were younger than 7 months of age (7). Because obstructive uropathies are mostly seen in boys, 88% of patients with secondary PHA1 were male (8). Breast feeding has low sodium content which makes newborns more sensitive to sodium deficiency (5). In our case, the patient was 4-day-old at the time of admission and approximately 3 months old when treatment was stopped, which reflects those findings.

The pathogenesis of transient PHA has not been fully elucidated.The pathogenesis of this condition involves tubular dysfunction as a result of excess intrarenal pressure and intrarenal cytokines, leading to interstitial renal damage which causes tubular resistance to

aldosterone by directly affecting cellular responses or indirectly through modification in renal autacoids, such as prostaglandins (6). The renin angiotensin-aldosterone system is highly activated in PHA, indicating renal tubular insensitivity to aldosterone. The diagnosis of PHA is thus confirmed by elevated aldosterone and renin levels (4). In our study, the diagnosis was delayed because of large variations in blood sodium and potassium levels. The severe polyuria and dehydration in our patient required massive fluid intake which in turn needed large quantities of electrolytes. This might explain those variations, considering the renal immaturity, which might be more severe in our case owing to prematurity. This immaturity might also be responsible for the transient elevated calciuria. The superior sagittal sinus thrombosis was attributed to the intense dehydration of the neonate, after common causes such as anticoagulant protein (S,C and antithrombin III) deficiency or hyperhomocysteinemia were excluded.

The patient later started showing a more constant trend towards hyperkalemia and normonatremia, together with elevated urinary sodium and reduced urinary potassium. It is important to point out that he had normonatremia while already receiving sodium bicarbonate treatment, which was initiated when distal renal tubular acidosis was suspected. The initially elevated calciuria returned to normal values. Facing a, then more obvious, salt-wasting crisis, the foremost diagnosis considered was congenital adrenal hyperplasia. Blood cortisol and 17-hydroxyprogesterone levels were normal.

Even though the clinical and laboratory features of primary type 1 PHA and secondary PHA are alike, their treatment and prognosis are very different. Thus, in patients diagnosed with PHA, the differentiation between primary and secondary PHA should be made initially. Assessment with urine culture and urinary ultrasonography are hence recommended (5).The main treatment in secondary PHA is medical and/or surgical treatment of the underlying cause. Moreover, correcting hyperkalemia and acidosis, together with replacement of salt wasting and rehydration are also necessary. Salt loss is supplemented by giving 3-20 mEq/kg/day sodium through NaCl or NaHCO3 in secondary PHA. NaHCO3 is preferred for sodium supplementation in patients with metabolic acidosis (5). Most authorities currently recommend a ≤ 6 mmol/L daily increase in sodium (8). In PHA, isotonic solutions correct not only volume depletion and hyponatremia but also hyperkalemia. Hence, treatment of hyperkalemia with ß-agonists, insulin, or cation exchangers may not be necessary (8). Our patient received 5 mEq/kg/day of sodium.

In secondary PHA, there are no clear data on the duration of salt supplementation requirement. After medical or surgical treatment of underlying disease in these patients, the aldosterone response becomes normal and laboratory findings recover in a few days. However in a few cases, partial tubular resistance to aldosterone may persist for three years after early correction of congenital urinary tract obstruction (5). In our study, the infant received sodium bicarbonate until the age of 3 months. Subsequently, all laboratory investigations were normal.

CONCLUSION :

PHA should be considered when dealing with salt wasting crisis in the newborn. Causes of secondary PHA should be looked for as their treatment and prognosis are different. Neonates with urinary tract infection or malformations should be examined for salt wasting crisis. Prevention of urinary tract infection is compulsory, thus showing the importance of antibiotic prophylaxis and circumcision. We also emphasize on the importance of repeating laboratory investigations because of variations in the early neonatal period due to renal immaturity.

Conflict of Interest :

the authors have no conflict of interest to declare.

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