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CASE REPORT

Pseudohypoaldosteronism: report of three cases

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Primary pseudohypoaldosteronism type 1 (PHA-1) is a heterogeneous syndrome characterised by salt-wasting due to unresponsiveness of target organ to mineralocorticoids. It is inherited in an autosomal recessive or autosomal dominant pattern, and often is a result of the mutation *de novo*. It can be sub-classified into two distinguishable clinical entities: renal PHA type 1 (renal PHA-1) and multiple PHA type 1 (multiple PHA-1). Secondary (transient) PHA type 1 is usually associated with urinary tract infections complicating structural urinary tract anomalies. PHA type 2 (PHA-2, Gordon syndrome) is an entity inherited in an autosomal dominant pattern.

Three cases of PHA, two with renal PHA-1 and one with secondary PHA type 1, are reported.

In all patients with salt-wasting and dehydration differentiation between congenital adrenal hyperplasia and PHA should be performed. Also, in the case with hyperkalaemia, hyponatremia and metabolic acidosis, urinary tract infection and obstructive uropathy should be excluded.

Keywords: child, pseudohypoaldosteronism, renal type, transient

Introduction

Primary pseudohypoaldosteronism type 1 (PHA-1), first described in 1958 by Cheek and Perry,[1] is a heterogeneous syndrome characterised by salt-wasting due to target organ unresponsiveness to mineralocorticoids. It is inherited in an autosomal recessive or autosomal dominant pattern, and rarely as a result of the mutation *de novo*.[2] The clinical expression of PHA-I varies widely, but usually occurs in the neonatal period with hyperkalaemia, hyponatremia, metabolic acidosis and elevated levels of renin and aldosterone in the blood. It can be sub-classified into two distinguishable clinical entities: renal PHA type 1 (renal PHA-1) and multiple PHA type 1 (multiple PHA-1) (Table 1).[3,4]

Renal PHA-1 is inherited in an autosomal dominant pattern. Due to mutation of the gene that encodes mineralocorticoid receptors, aldosterone cannot bind to its receptors. More than 50 genotypes with no significant correlation to clinical phenotypes have been described. Its clinical expression is highly variable. The mild form is the most frequent, with spontaneous remission within 1–3 years as a result of the maturation of renal salt conservation ability.[3,5]

Multiple PHA-1, caused by mutation of the epithelial sodium channel (ENaC) gene, is inherited in an autosomal recessive pattern. A defect in sodium transport in many organs, including lungs, kidneys, colon, salivary and sweat glands, is present. Clinical expression is usually severe, with salt-waste episodes starting soon after birth and lasting into adulthood. The incidence of lower respiratory tract infections in this population is usually higher.[6]

Secondary (transient) PHA type 1 is usually associated with urinary tract infections complicating structural urinary tract anomalies.[7–9]

PHA type 2 (PHA-2) (Gordon syndrome) is an entity inherited in an autosomal dominant pattern. Its main clinical features are short stature and arterial hypertension (Table 1).[10,11]

Three cases of PHA, two with renal PHA-1 and one with secondary type 1 PHA, have been reported.

Case reports

Case one

A 14-day-old newborn female presented with a history of poor feeding, coughing and dyspnoea without temperature instability commencing two days prior to hospital admission. She was born at term, birth weight 2740 g (25th percentile). Both prenatal and postnatal courses as well as family history were uneventful. On admission, the baby was pale, dyspnoeic, heart rate 110–145/min, oxygen saturation 91–95%, with reduced adipose tissue and body weight 2500 g (240 g below the birth weight). Chest examination revealed numerous early and late inspiratory crackles bilaterally, and neurological examination showed axial and segmental hypotonia. The main laboratory findings are given in Table 2. Fractional excretion of sodium in the urine was increased (19.2%) despite the concomitant presence of hyponatremia. Cortisol and 17-OH progesterone levels were normal. Chest X-ray revealed right-sided pneumonia. Head and abdominal ultrasound were normal.

On admission, parenteral antibiotics and parenteral salt supplementation were introduced. Within 24 h electrolyte imbalance was corrected and no sodium supplementation was required thereafter. Clinical and laboratory signs of lower respiratory tract infection gradually improved. After hospitalisation, the child was fed with infant formula, gain in bodyweight was satisfactory, and psychomotor development was normal. The serum sodium values were in the normal reference range (135 mmol/l), with no additional sodium

Table 1: Characteristics of different types of PHA

Characteristics	Renal PHA-1	Multiple PHA-1	PHA-2
Affected organs	Kidney	Kidney, sweat and salivary glands, colon	Kidney
Clinic manifestations	From asymptomatic to failure to thrive due to chronic dehydration	Severe dehydration, failure to thrive, pulmonary infections	Hypertension, short stature
Inheritance (genes)	Autosomal dominant (NR3C2)	Autosomal recessive (SCNN1A, SCNN1B, SCNN1G)	Autosomal dominant (WNK1, WNK4)
Salt-wasting	Variable	Severe	No
PRA and aldosterone concentration	Very high, PRA decreases with age	Very high (lifelong)	Decreased renin, normal aldosterone
Treatment	Salt supplementation, 1–3 years (or less)	Lifelong salt supplementation, potassium-binding resins	Low-dose thiazide diuretics
Prognosis	Improvement with age	Absent improvement with age	?

Table 2: Summary of cases with initial and control biochemistry and therapy

Factor	Case 1	Case 2	Case 3
Age at presentation (days)	14	42	22
Symptoms	Poor feeding, weight loss, cough	Weight loss, oliguria	Weight loss, poor feeding, seizures
Plasma sodium (mmol/l) (RR 135–145)	115	128	108
Plasma potassium (mmol/l) (RR3.5–5)	7.9	7.11	9.9
Plasma HCO3 (mmol/l) (RR 17–25)	24.2	13.7	10.9
pH	7.17	7.31	7.13
Creatinine (µmol/l)	56.2 (normal)	78.8 (mild elevation)	440 (severe elevation)
Serum aldosterone (ng/dl) (RR neonate 17–154; infant 6.5–86)	–290—at admission; 200—5 months	–171—at admission; 128—7 months; 46—1 year; 7.1—1.5 year	–198.2—at admission; 100—3 months
PRA (µIU/ml) (2.8–39.9)	–72—at admission; 52—5 months	–330.1—at admission; 112.8—7 months; 57.9—1 year; 37.3—1.5 year	–89.8—at admission; 11.2—3 months
Sodium supplementation	1 day	1.5 year	1 day (peritoneal dialysis afterwards)

Notes: RR = reference range; mmol/l-millimoles per litre; µmol/l = micromoles per litre; ng/dl = nanogram per decilitre; µIU/ml = microInternational Units per millilitre.

supplementation. At the age of five months aldosterone and plasma renin activity (PRA) values were still above standard reference values, but lower than those on admission (Table 2).

Case two

A six-week-old previously healthy male infant was admitted with a three day history of loose stools, low-grade fever and decreased urine output. He was born at term, birth weight 4000 g (50th percentile). Both prenatal and postnatal courses as well as family history were uneventful. On admission, the infant was alert with a high-pitched cry, pale, heart rate 136/min, respiratory rate 46/min, oxygen saturation 98%. His bodyweight was 4300 g (< 3 percentile), skin turgor was decreased and subcutaneous adipose tissue was reduced. On physical examination, only axial hypotonia with segmental hypertonia was noticed. The initial laboratory findings are shown in Table 1. Urine analysis was normal. Blood, stool and urine cultures were negative. Cortisol and 17-OH progesterone levels were normal, as well as a sweat-chloride test. Chest X-ray, and head and abdominal ultrasound were normal.

On admission, parenteral antibiotics, rehydration and salt supplementation were introduced. After two saline boluses, the infant started to void urine. Within 48 h renal function and serum electrolyte values were normal. After discontinuation of parenteral salt supplementation, mild hyponatremia and potassium levels in the upper range of reference levels with polyuria were noticed, and oral sodium supplements were introduced (+1 g NaCl/day). Serum electrolyte values remained in the reference ranges thereafter. The aldosterone value was normalised by the age of one year, but the PRA level remained slightly higher until the age of 18 months (Table 2), when salt supplementation was discontinued. The child has normal bodyweight and normal psychomotor development.

Case three

A male, previously healthy 22-day-old newborn presented with a history of poor feeding and hypotonia. He was born at term, his amniotic fluid was meconium-stained, the Apgar score was seven in the first minute and nine in the fifth minute and birthweight 3720 g (50th percentile). On admission the newborn was pale, alert, hypothermic (rectal temperature 35.1°C), heart rate 136/min, respiratory rate 30/min, oxygen saturation 98–100%, bodyweight 3300 g (420 g less than the birthweight). Skin turgor was decreased and subcutaneous adipose tissue reduced. On physical examination only axial and segmental hypotonia were noticed.

The initial laboratory findings are given in Table 1. Urine analysis revealed proteinuria (5+), pyuria (4+), urine culture was found to be positive (> 100 000 colonies/mm^3 of *Escherichia coli*). Blood and cerebrospinal fluid cultures were negative. Cortisol and 17-OH progesterone levels were normal, as well as a sweat-chloride test. On abdominal ultrasound, right kidney 'pyelon' diameter was 12 x 8 mm with calices up to 5 mm. The left kidney presented with a slightly accentuated canalicular system with calices of up to 5 mm. Chest X-ray, brain ultrasound, echocardiography and electroencephalogram were normal.

On admission, parenteral rehydration, salt supplementation and parenteral antibiotic therapy were introduced. Hyperkalaemia was treated with salbutamol inhalations, sodium bicarbonate and continuous insulin infusion. Peritoneal dialysis was started because of persistence of electrolyte imbalance and anuria. On the second day of treatment electrolyte homeostasis was achieved, followed by gradual improvement of renal function and normalisation of diuresis. Peritoneal dialysis was stopped on the fifth day of treatment. A second urine culture was negative. Although antibiotic prophylaxis was introduced on hospital discharge, the patient subsequently had two episodes of urinary tract infections. During these episodes, blood electrolytes including potassium level remained in reference ranges without salt supplementation. However, renal function remained slightly impaired and at the age of two months first-grade chronic renal failure with CCr 37 ml/min was diagnosed. Voiding cistourethrography was performed and bilateral fifth-grade vesicoureteral reflux was diagnosed. By the age of three years, endoscopic treatment of bilateral vesicoureteral reflux with Deflux® had been performed. Control values of aldosterone and PRA were within reference values (Table 2).

Discussion

Differential diagnosis between PHA and other diseases based on serum electrolyte values includes hypoaldosteronism, adrenal hypoplasia and congenital adrenal hyperplasia (CAH). Normal hormone values, ACTH, 17-OH progesterone and cortisol rule out adrenal insufficiency. High values of aldosterone and cortisol are crucial for PHA diagnosis.[2]

Clinical signs of PHA, caused by electrolyte disturbance, are mainly non-specific and include poor feeding, vomiting, dehydration and electrolyte values similar to those in congenital adrenal hyperplasia.[2,4,12]

Treatment of renal PHA-1 includes sodium-chloride supplementation with gradual reduction of daily doses. Hyperkalaemia is usually moderate. Treatment of multiple PHA-1 is more complex, and includes sodium supplementation (with sodium chloride or sodium bicarbonate) as well as early hyperkalaemia treatment (usually with ion exchange resins—calcium resonium or sodium resonium). If this treatment is ineffective, indomethacin introduction should be considered. This inhibits prostaglandin synthesis, which results in decreased urine output and renal sodium losses. As recurrent respiratory infections can frequently occur, prophylactic use of antibiotics is sometimes recommended. In the case of feeding difficulties caused by severe gastro-oesophageal reflux, fundoplication with gastro- or jejunostomy should be performed.[4] In secondary PHA-1, the resolution of clinical signs and normalisation of serum electrolyte levels is achieved after resolution of urinary tract infection or surgical treatment of urinary tract anomaly. However, partial reduction of distal tubule sensitivity to aldosterone can persist for some time (according to some studies 3–13 months) after surgical treatment. Therefore, tight control of weight gain and serum electrolyte levels is recommended for at least one year.[7–9]

Amin *et al.* showed follow-up results of five cases of renal PHA-1 and two cases of multiple PHA-1. Patients with renal PHA-1 underwent regular check-ups for up to 62 months and required a small amount of sodium supplementation in four cases. On the other hand, patients with multiple PHA-1, regularly followed up to 3.5 years of age, remained on sodium supplementation and indomethacin treatment.[13]

In our study, the first two cases described were diagnosed with renal PHA-1. Interestingly, in one case salt supplementation was performed for a short period (for 24 h) but in the second patient it was performed for 1.5 years. Also, in the first case severe respiratory acidosis as a result of pulmonary infection and not metabolic acidosis was observed.

Since Rodriguez-Soriano *et al.*[14] established the entity of transient PHA-1 associated with obstructive uropathy in 1983, 60 cases have been described. A higher incidence of this entity is presumed, but this condition remains frequently undiagnosed because potassium levels are often only slightly elevated and aldosterone and renin levels are not routinely determined. Watanabe showed that all patients with this condition were younger than seven months, 80% had urinary tract malformations with urinary tract infection, 11.7% had a urinary tract malformation without urinary tract infection and 8.3% had only urinary tract infection. Transient PHA-1 probably occurs as a result of immature response of renal tubules to aldosterone. The incidence of transient PHA-1 decreases sharply after the third month of life. Prompt treatment of urinary tract infection is crucial in the prevention of kidney damage and possible complications of its delay are sepsis and septic shock. Therefore, in all cases of salt-wasting, urinalysis, urine culture and abdominal ultrasound should be performed.[7,8,15]

Because of oliguria and severe electrolyte disturbance, peritoneal dialysis was performed for five days in our patient with transient PHA-1. Unfortunately, after acute renal impairment, full renal function recovery was not achieved and first-grade chronic renal insufficiency developed. After that, this patient had two subsequent episodes of urinary tract infection without electrolyte disturbance, i.e. without clinical and laboratory parameters related to PHA.

All three patients showed improvements in appetite and adequate weight gain after discharge.

For technical reasons, we were not able to perform genetic analysis for any of our three patients.

In conclusion, in all patients with salt-wasting and dehydration differentiation between CAH and PHA should be performed. Also, in cases with hyperkalaemia, hyponatremia and metabolic acidosis, urinary tract infection and obstructive uropathy should be excluded. In some cases of PHA, long-term salt supplementation is required. Further studies are needed to improve our knowledge of this complex condition.

Conflicts of interest – The authors report no conflicts of interest.

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