CASE REPORT

Secondary pseudohypoaldosteronism in an infant with pyelonephritis

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Abstract

Background: **Urinary tract infections and/or urinary tract anomalies are very frequent among children. Especiallly in newborns/infants they represent additional factors in the development of secondary pseudohypoaldosteronism.**
Case history: **We present an 8-week-old infant who developed hyponatremia and hyperkalemia secondary to acute pyelonephritis. The boy presented with non-specific signs, including poor appetite, lethargy, and hypotonia. An extended evaluation led to the diagnosis of pseudohypoaldosteronism (PHA). PHA was transient and during therapy of pyelonephritis all of abnormal laboratory parameters returned to normal. The patient had vesico-ureteric reflux grade IV.**
Conclusion: **Secondary/transient/reversible PHA occurs in patients with immature renal tubular responsiveness to aldosterone due to infancy when they have urinary tract anomalies and/or urinary tract infection.** ***(Tab. 1, Ref. 7.)***
Key words: pseudohypoaldosteronism, hyponatremia, hyperkalemia, urinary tract infection.

Disturbances of fluid and electrolyte balance are a frequent occurence in pediatric practice, and present in a wide variety of clinical scenarios, varying from an infant being previously well to a child at the intensive care unit with multiple system organ failure. The evaluation of pediatric patients with dyselectrolytemias should be primarily based on clinical examination and laboratory parameters should always be regarded as complementary.

Pseudohypoaldosteronism (PHA) is a syndrome characterized by a state of renal tubular unresponsiveness to aldosterone and is manifested by hyponatremia, hyperkalemia, and metabolic acidosis. Primary PHA is a hereditary condition that includes at least two genetically and clinically entities and involves either renal or multiple target organ defects. In secondary PHA, major contributing factors are thought to include urinary tract infection (UTI), urinary tract malformation, and infancy (1).

We describe here a case with secondary PHA due to acute UTI.

Case report

A newborn boy was delivered vaginally after 42 weeks of gestation, weighing 4.1 kg. He was the first born baby of non-consanguineous parents. He was in good condition at birth, did not need any resuscitation, and the immediate neonatal period was uneventful. He had been breast-fed and discharged on day 4. At 8 weeks of age, he was brought to our department because acute onset of poor appetite, lethargy, and hypotonia.

On admission, he was pale, without signs of dehydration, his weight was 5.0 kg, and neurological examination was unremarkable. Body temperature was 36.9 °C, pulse 140 beats/min, respirations 48, and blood pressure 85/60 mmHg. The initial laboratory evaluation revealed serum sodium (S_{Na}) 120.0 mmol/l (normal: 135.0–145.0), serum potassium (S_K) 5.7 mmol/l (normal: 3.5–5.1), serum chloride (S_{Cl}) 89.3 mmol/l (normal: 94.0–108.0), serum osmolality 258 mosmol/kg H_2O (normal: 290±5), serum C-reactive protein (CRP) 82.2 mg/l (normal: <5.0), white blood cell count 22.7×10^9/l (normal: $4.0–13.0 \times 10^9$/l) with 14.8×10^9/l neutrophils (normal: $1.5–8.5 \times 10^9$/l), and metabolic acidosis

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Tab. 1. Some laboratory parameters over time in an infant with secondary pseudohypoaldosteronism.

Day	1	2	3	8	14	27
S_{Na}	120.0	122.3	125.8	130.2	138.6	137.2
S_K	5.7	5.5	5.4	4.8	3.8	4.1
S_{Cl}	89.3	91.8	93.2	95.4	101.2	105.7
PRA		28.3		18.5	15.8	14.4
Plasma aldosterone		6.2		5.7	4.85	2.98

(pH 7.31, bicarbonate concentration 19.0 mmol/l, base excess –5.1). Urinalysis revealed 1+ protein, 1+ ketones, pH 6, random urinary sodium 38 mmol/l, and numerous white blood cells per high-power field. Abdominal ultrasonography showed increased echogenicity, loss of cortico-medullary differentiation with dilatation of the renal pelvis, and smaller left kidney. Ultrasonography of the right kidney was normal. Escherichia coli was cultured from his urine (10^7 CFU/ml).

Our initial diagnose was acute pyelonephritis (AP), and intravenous administration of antibiotic was started. The infant passed 680 ml of urine during 24h after admission. On the second hospital day his hyponatremia and mild hyperkalemia persisted (S_{Na} 122.3, S_K 5.5 mmol/l). The blood urea nitrogen concentration was 5.4 mmol/l (normal: 1.7–6.4) and serum creatinine concentration was 38.7 µmol/l (normal: 27.0–53.0). An extensive laboratory work-up revealed the following: plasma aldosterone concentration 6.2 nmol/l (normal: 0.055–3.051), plasma renin activity (PRA) 28.3 ng/ml/hod (normal: up 16.6), serum cortisol concentration 0.29 µmol/l (normal: 0.12–0.58), serum 17α-hydroxyprogesterone 1.32 nmol/l (normal: 0.5–4.7), and plasma adrenocorticotropic hormone concentration (ACTH) 19.3 pg/ml (normal: 4.5–46.0). These findings exluded congenital adrenal hyperplasia (CAH) and confirmed the diagnose of PHA.

On 8th hospital day the concentration of CRP was no longer elevated, SK was in normal range, mild hyponatremia persisted, and leukocyturia had resolved. The infant received a ten-day antibiotic therapy and was discharged on the 14th day after admission. The level of plasma aldosterone and PRA had returned to normal (Tab. 1). Voiding cystouretrography, performed after 1 month after the onset of AP, showed left vesico-ureteric reflux (VUR) grade IV. The patient was referred to urologists for surgical treatment.

Discussion

A variety of factors contribute to the pathogenesis of hyponatremia/hyperkalemia in neonatal and infant periods. In these children is very important to establish/exclud CAH because this is a life-threatening condition. CAH is a group of autosomal recessively inherited disorders of adrenal corticosteroid synthesis due to deficiency of one of five enzymes in the cholesterol to cortisol synthetic pathway. Thus in the commonest form of CAH (21OH deficiency) there is a potential of cortisol deficiency, aldosterone deficiency and salt loss. Plasma 17α-hydroxypro-gesterone and ACTH levels are raised. The clinical presentation of 21OH deficiency (so-called classical salt wasting form) in karyotypic females results in masculinization generally leading to ambiguous external genitalia recognized at birth but occasionally so severe that the infant is thought to be a normal male. Males usually appear normal at birth but present with penile enlargement and rapid growth. Presentation in both sexes is with vomiting within a few days/weeks after birth, severe renal wasting, and dehydration. Our patient was an infant with no abnormality during his neonatal period and with normal external genitalia. He had no episodes of vomiting or dehydration. He developed hyponatremia, hyperkalemia, metabolic acidosis, and natriuresis during AP. An extensive endocrinological work-up with elevated PRA and aldosterone established the diagnose of PHA.

Two forms of primary/congenital PHA type 1 (PHA1) exist. The autosomal recessive form (so-called multiple-organ form; gene loci 16p12, 12p13) is associated with mutation in the subunit of the epithelial sodium channel (ENaC) which the mineralocorticoid receptor gene (MLR) regulates. The autosomal dominant form (so-called renal form; gene locus 4q31.1) is due to mutations in MLR, which prevents normal receptor function and hence causes salt wasting. Low mineralocorticoid receptor binding has been found in PHA1. However, some reports describe an absence of MLR abnormality, suggesting that the low receptor binding may reflect only downregulation in response to elevated aldosterone (2). The precise mechanism responsible for the renal form of PHA1 therefore remains unclear. ENaC is an amiloride-sensitive protein composed of three subunits called α β γ. It is expressed in the apical membrane of aldosterone-responsive tissues, such as the distal part of the nephron, the distal colon, and in the duct of salivary and sweat glands. The second form of primary PHA is type 2 (so-called Gordon's syndrome or chloride shunt's syndrome; gene loci 1q31-42, 12p13.3, and 17p11-q21). It is a rare disorder with autosomal dominant mode of inheritance, the precise cellular mechanism of which is unknown beyond the hypothesis that there is unregulated chloride reabsorption (3).

Characteristic laboratory parameters for PHA1 are hyponatremia, hyperkalemia, metabolic acidosic, elevated plasma aldosterone, and natriuresis. Infants present with failure to thrive, frequent vomiting, and dehydration. During the salt-wasting episodes patients appear shocked and comatose. "Salt losing nephropathy" of renal form of PHA1 is considerable and therapy of choice is high-salt diet. Although the primary defect persists for

life, an improvement may occur beyond 1 or 2 years of age, due to maturation of proximal tubular transport. The multiple organ form of PHA1 presents with more severe salt-wasting episodes early after birth, death may ensue during the neonatal period, and has a poorer outcome than the renal form. There is a poor response to sodium supplementation alone, and rectal administration of exchange resins and dietary manipulation reducing intake of potassium are often necessary. PHA of type 2 is a familial syndrome of hyperkalemia, hyperchloremic metabolic acidosis, hypertension, and volume expansion. PRA and plasma aldosterone are supressed. Short stature, arterial hypertension, and muscle weaknes are the cardinal signs in children. These patients may also have hypercalciuria and a tendency to stone formation. The treatment is based on thiazide diuretic drugs and the long-term prognosis remains uncertain because of follow-up data being still limited.

Secondary form of PHA (PHAs) has been documented in young infants with UTI associated with congenital malformation of urinary tract (4, 5). However, literature describes PHAs in infants with congenital malformation of urinary tract but without UTI (6). Based on reviewing cases of PHAs reported previously, all patients were less than 7 months of age, 80 % suffered from urinary tract malformations and UTI, 11.7 % had urinary tract malformations without UTI, and 8.3 % had isolated UTI (7). These findings indicate that PHAs occurs in children with immature renal tubular responsiveness to aldosterone due to infancy when they have urinary tract malformation and/or suffer from UTI. Infancy is a contributing factor for the development of PHAs. After medical or surgical therapy, all abnormalities of PHAs generally disappear, although, in cases of severe obstructive uropathy, renal sodium loss may become transiently more severe during the early obstructive period.

In summary, we present a male infant with PHAs due to AP. PHA was transient and during the therapy of AP all of abnormal laboratory parameters returned to normal. It is important that renal ultrasonography and urine culture should be performed in any infant or child presenting with salt-wasting or hyperkalemia to exclude structural renal lesions or infection as the cause of the dyselectrolytemias.

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