Korean Journal of Pediatrics Vol. 52, No. 3, 2009
DOI : 10.3345/kjp.2009.52.3.376
■ Case report ■

Pseudohypoaldosteronism in a premature neonate with severe polyhydramnios in utero

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= Abstract =

We report a case of a premature newborn baby who presented with hyponatremia, hyperkalemia, and metabolic acidosis accompanied by severe polyhydramnios in utero. The baby was diagnosed with pseudohypoaldosteronism on the basis of normal 17-hydroxyprogesterone levels, elevated aldosterone, and clinical symptoms. His serum electrolyte levels were corrected with sodium chloride supplementation. Sodium supplementation was reduced gradually and discontinued at 5 months of age. At 5 months, the child was able to maintain normal serum electrolyte levels without oral sodium chloride supplementation, and showed normal physical and neurological development. This case illustrates that pseudohypoaldosteronism must be considered if a newborn infant with an antenatal history of severe polyhydramnios shows excessive salt loss with normal levels of 17-hydroxyprogesterone. (Korean J Pediatr 2009;52:376-379)

Key Words : Pseudohypoaldosteronism, Polyhydramnios

Introduction

Primary renal pseudohypoaldosteronism is an autosomal dominant disease caused by increased aldosterone secretion associated with clinical signs of hypoaldosteronism[1]. The disease is related to renal tubular unresponsiveness to aldosterone, probably due to maturational dysfunction of the aldosterone receptors[2]. Clinical signs of primary renal pseudohypoaldosteronism are polyuria, high urinary sodium excretion, hyponatremia, hyperkalemia, and metabolic acidosis[1]. Additional symptoms may include anorexia, vomiting, or salt craving. Symptoms generally improve spontaneously with age. Polyuria can begin before birth and can cause severe maternal polyhydramnios[3, 4]. Although several cases of pseudohypoaldosteronism have been reported in the literature in Korea[5-10], they were not associated with antenatal polyhydramnios. We present the first case of prenatal onset pseudohypoaldosteronism in a preterm newborn infant born to a mother with severe polyhydramnios.

Received : 25 August 2008, Revised : 9 October 2008,
Accepted : 30 October 2008
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Case report

A 27-year-old primigravida woman was transferred to Cheil General Hospital at 25 weeks of gestation because of severe polyhydramnios; amniotic fluid index was 51. Amniocentesis was performed by an obstetrician. Interestingly, it had to be repeated because of unusually rapid accumulation of amniotic fluid after the procedure. A total of seven amniocenteses were performed before delivery, and the total amount of amniotic fluid removed was about 7 liters (Table 1, Fig. 1). To evaluate the cause of the severe polyhydramnios, fetal chromosomal study and antenatal high resolution fetal sonogram were done and those results were normal. Her blood glucose level was normal. She and her husband were relatively healthy and did not have history of any past medical illness or familial disease. At 32 weeks of gestation, a male newborn baby was delivered through cesarean section due to uncontrolled preterm labor. At birth, the baby weighed 1,870 g, his initial heart rate was under 100/min, and he became less active. His heart rate and skin color came back to normal after resuscitation. His body temperature was 36.5

℃, his pulse rate was 124/min, and his respiratory rate was 51/min. On physical examination, severe subcostal retraction was observed although his body color was pinkish and he looked active. A gastric tube was inserted into the stomach very smoothly without any interruption. The laboratory data were as follows: leukocyte count 6,990/mm^3, hemoglobin 20.6 g/dL, hematocrit 56.9%, platelet 276,000/mm^3, serum sodium 130 mEq/L, potassium 6.5 mEq/L, and chloride 98 mEq/L. A small lung volume, diffuse haziness and an air bronchograms were observed on the initial chest radiogram, which was consistent with respiratory distress syndrome. Modified bovine surfactant (Newfactan®, Yuhan Co. Seoul, Korea) was administered via endotracheal tube. After surfactant replacement, respiratory distress resolved gradually.

The urine output was approximately 4.5 cc/kg/hr on the first day and the polyuria continued for several days. Hyponatremia persisted in spite of polyuria and severe weight loss (up to 21% of the birth weight). Fluids and electrolytes were actively supplemented and serum electrolyte concentrations were closely monitored. The electrolyte imbalance was severe and persisted regardless of active supplementation. On the 7th day, the baby looked ill, and his serum sodium level was 125 mEq/L with a potassium level of 7.2 mEq/L. His 17-hydroxyprogesterone level was measured to rule out congenital adrenal hyperplasia and the result was within the normal range. On the 8th day, his serum sodium level was 124 mEq/L, his potassium was 7.0 mEq/L, and his spot urine sodium concentration was 85 mEq/L. The dosage of sodium supplementation was increased to 8 mEq/kg/day, calcium to 200 mg/kg, sodium bicarbonate to 2 mEq/kg, and regular insulin injections and Kayexalate enemas were added. The possibility of pseudohypoaldosteronism was investigated after verifying normal levels of 17-hydroxyprogesterone.

His serum renin activity was 4.2 and 73 ng/mL/hr on the 12th and 34th day respectively (normal range for 0-3 years old is less than 16.6 ng/mL/hr).

His plasma aldosterone levels were 1,630 pg/mL on the 12th day and 3,710 pg/mL on the 34th day (normal range of 190-1,410 pg/mL for a preterm infant of 31-35 weeks). We continued to monitor electrolytes and supplement sodium. From the 50th hospital day, electrolyte levels were maintained within normal range with 2 mEq/kg/day of oral sodi-

Table 1. Volume of Amnioreductions and the Changes of the Amniotic Fluid Index after Amnioreductions

Gestational age (wks)	Volume of amnioreduction (mL)	Change of amniotic fluid index after amnioreduction
25	1,000	52→44
25+1	1,000	44→35
25+6	810	39→35
26+3	1,000	42→36
27+6	1,200	51→33
28+6	1,000	50→41
30+1	1,000	47→42

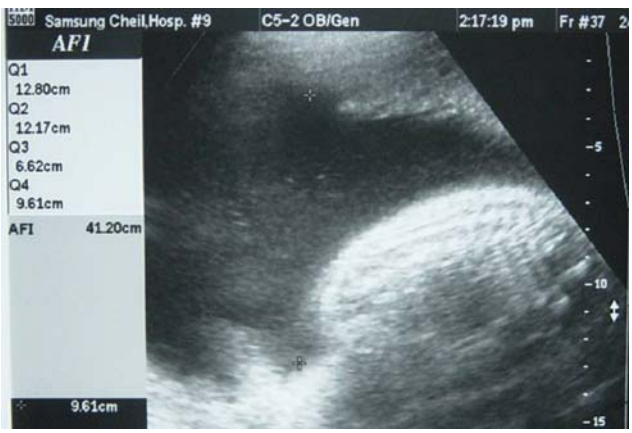

Fig. 1. Antenatal fetal ultrasonogram performed at 25+3 weeks of gestational age reveals polyhydramnios, showing amniotic fluid index of 41.

Table 2. Changes of Electrolyte and Hormones Levels in the Serum and Urine related to Sodium Chloride Supplementation

Age (days)	Na (mEq/L)	K (mEq/L)	Urine sodium (mEq/L)	Plasma renin activity (ng/mL/hr)*	Plasma aldosterone (pg/mL)†	17hydroxy progesterone (ng/mL)	Supplemented NaCl (mEq/kg/day)
1	130	6.5					
3	138	4.5					3
8	125	7.0	85			14.1	8
12	134	3.0	107	4.2	1,630		15
28	132	6.4				4.7	8
34	134	4.9	12	73	3,710		3.4
61	133	4.6					3.4

*Normal range for 03 years old : <16.6 ng/mL/hr
†Normal range for preterm infant 31-35 weeks, 190-1,410 pg/mL

um supplements(Table 2). Renal ultrasonography was done on the 49th and 62nd hospital day, and showed medullary nephrocalcinoses in both kidneys. The baby was discharged with sodium chloride supplementation in a powdered form at a dosage of 2 mEq/kg/day. After discharge, he was followed up through the outpatient clinic at one month of his corrected age. His sodium level was 136 mEq/L and his potassium level was 4.4 mEq/L. The dosage of the sodium chloride supplement was then reduced to 1.5 mEq/kg/day. His electrolyte levels were within normal range in the following months. The sodium chloride supplement was tapered down with monitoring of electrolytes, and discontinued at three months of his corrected age. Thereafter, his electrolyte levels were maintained at normal levels without any oral sodium chloride supplement. The childs length and weight increased satisfactorily and he showed normal neurological development.

Discussion

Type 1 pseudohypoaldosteronism (PHA-1) was first reported by Cheek and Perry in 1958[11]. This rare syndrome has a wide spectrum. There are two primary genetic forms: a renal form of autosomal dominant inheritance involving a mutation of the mineralocorticoid receptor, and more severe systemic multiple target organ defective form of autosomal recessive inheritance involving a mutation of the epithelial sodium channel gene. There is also a secondary form that is usually associated with urinary tract malformation and infection[1].

PHA-1 is characterized by salt wasting and failure to thrive in the newborn. Diagnosis is based on dehydration, hyponatremia, hyperkalemia, high urinary sodium, and high serum concentrations of aldosterone and rennin[12]. The underlying abnormality in renal type PHA-1 is a maturational dysfunction of aldosterone receptors caused by a mutation of the mineralocorticoid receptor gene[13]. Cases have been reported of newborn infants suffering from unknown dehydration and metabolic acidosis with abnormal electrolyte levels, hyponatremia, and hyperkalemia[14, 15]. Those patients showed polyuria, and high urinary sodium in spite of dehydration. Therefore, a first impression might congenital adrenal hyperplasia, but pseudohypoaldosteronism could be considered based on unresponsiveness to steroid therapy and normal levels of 17-hydroxyprogesterone, even before identifying elevated plasma rennin activity and aldosterone levels[1].

Clinical manifestations of the disease vary from asymptomatic cases to death in infancy[2]. In the multiple target organ defective form of autosomal recessive inheritance, patients have salt wasting from the kidney, colon, sweat and salivary glands. Because of dramatic volume depletion, patients require massive sodium supplementation throughout life. In contrast, renal form of autosomal dominant or sporadic inheritance is considered a mild disease[16, 17].

Patients of renal form PHA-1 may be asymptomatic or ill at birth from renal salt wasting, and sodium supplementation can be discontinued after a variable period of time. However, high aldosterone levels may persist even after normalization of the clinical picture. The mechanisms that restore sodium homeostasis in these patients are not clear. But, kidney maturation or replacement of distal sodium reabsorption by proximal parts of the nephron have been suggested and chronic upregulation of the reninangiotensinaldosterone system is also important, too. In contrast, in the recessive form of PHA1, life-long supplementation with high doses of salt is required, and patients are subject to recurrent life-threatening episodes of salt loss[16, 18].

The patient in our case was born prematurely with antenatal history of polyhydramnios. At first, it appeared that the electrolyte imbalance was due to immature function of the premature kidneys. Premature babies usually experience excessive weight loss following hypernatremia for several days after birth. However, instead of the hypernatremia typical in such cases, this patient had normal or low sodium levels despite polyuria greater than 5.9 cc/kg/hr, and the hyponatremia persisted despite 21% weight loss and supplementation of sodium chloride, prompting us to consider a disorder causing salt wasting. The disease in question would be one that causes salt wasting as well as antenatal polyhydroamnios. Among the possible etiologies of antenatal maternal polyhydramnios, no chromosomal anomalies, congenital malformations or intestinal obstructions were apparent in this case. Polyhydramnios is one of the prenatal signs of pseudohypoaldosteronism, as fetal polyuria is a probable cause of polyhydramnios[3, 4]. Therefore, either congenital adrenal hyperplasia or PHA would be the most likely cause. Since the 17-OHP level turned out to be normal, the patient was diagnosed with PHA-1. The patient was a firstborn, with no family histories, and no genetic studies were done. Therefore, no genetic mutations or inheritance patterns could be verified. However, as the patient shows spontaneous resolution of symptoms and relatively short clinical course,

and he had no evidence of any obstructive uropathy and urinary tract infection, clinical manifestations and laboratory findings in this case are consistent with renal type PHA-1. Of the laboratory values, rennin activity was in the normal range in one of the measurements, but it could be attributed to aggressive volume replacement in the NICU. Also, in some cases in the literature, plasma rennin activity was in normal range in spite of high aldosterone level[19].

With early screening of 17-hydroxyprogesterone, it was possible to diagnose PHA-1 early and prevent unnecessary use of steroids, allowing early and proper treatment.

In conclusion, pseudohypoaldosteronism must be suspected if a newborn infant who has an antenatal history of severe polyhydramnios shows excessive salt loss and normal levels of 17-hydroxyprogesterone.

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가성 저알도스테론혈증은 신장 세뇨관의 알도스테론 수용체의 이상으로 알도스테론의 분비는 증가되지만 반응성은 감소되어 저알도스테론혈증의 증상을 보이는 질병이다. 가성 저알도스테론혈증은 다뇨증, 과도한 소변 내 염분소실, 저나트륨혈증, 고칼륨혈증, 대사성 산증을 특징으로 하며, 산전부터 다뇨 증상이 시작되면 양수과다증을 초래할 수 있다. 미숙아에서는 생후 초기 불감 수분 손실량이 많으며, 폐 기능과 신장 기능이 미숙하여 전해질 이상을 흔히 동반하는데, 몸무게의 소실에도 불구하고 지속적인 다뇨와 저나트륨혈증, 고칼륨혈증의 증상이 있다면 전해질 불균형을 초래하는 기저질환을 확인하여야 한다. 저자들은 양수 과다증의 산전력이 있는 산모에게서 출생한 재태주령 32주 미숙아에서 지속적인 몸무게 감소에도 불구하고 계속되는 다뇨와 저나트륨혈증, 고칼륨혈증이 있어 17수산화프로게스테론을 조기에 선별 검사하여 선천성 부신 과형성증의 가능성을 배제함으로써 불필요한 스테로이드 치료를 피하고, 지속적인 전해질 보충으로 점차 전해질 이상의 호전을 보인 가성 저알도스테론혈증 1예를 경험하였기에 문헌 고찰과 함께 보고하는 바이다.

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