CASE REPORT

Perinatal manifestation of pseudohypoaldosteronism type 2 in a mother and her children

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Pseudohypoaldosteronism type 2 (PHA2) is an extremely rare autosomal dominant disease characterized by salt-sensitive hypertension with hyperkalemia which develops at a young age. This report describes for the first time the perinatal course and outcome of pregnancy in a woman and her children with PHA2. A 33-year-old woman with PHA2 presented with exacerbated hypertension and hyperkalemia from mid-pregnancy and was treated with thiazide diuretics in her two pregnancies. She developed superimposed pre-eclampsia only during her first pregnancy; fetal growth restriction was observed in both pregnancies. Both of her neonates developed hypertension and electrolyte imbalances and were diagnosed with PHA2 by genomic analysis. If a pregnant woman develops hypertension with hyperkalemia, PHA2 should be suspected, and both the mother and her infant should be managed carefully.

Introduction

Pseudohypoaldosteronism type 2 (PHA2) is an extremely rare autosomal dominant disease which develops at a young age and is characterized by salt-sensitive hypertension with accompanying hyperkalemia and hyperchloremic metabolic acidosis. Effective treatments include the administration of thiazide diuretics (TD) and sodium intake restriction. To date, no report has described in detail the pregnancy course of patients with PHA2. Here we report for the first time a patient with PHA2 whose symptoms became exacerbated during her two pregnancies and deliveries, as well as the clinical course of her children.

Case presentation

The patient was a 33-year-old primigravida Japanese woman with PHA2. She was born at 38 weeks of gestation with a weight of 2,200 g (−1.6 SD). She had a convulsive seizure due to electrolyte imbalance at age 6 months, developed hypertension at age 4 years, and was clinically diagnosed with PHA2 at age 7 years. She had no known family history of PHA2 (Figure 1), and no genetic testing had been performed. She had been treated with oral administration of TD, sodium bicarbonate...
PHA2 in pregnancy

(SB), and an angiotensin-converting enzyme since the diagnosis of PHA2. At age 25 years, all medications were discontinued, as her symptoms and electrolyte levels stabilized; however, she resumed TD treatment at age 30 years.

She was undergoing a cycle of controlled ovarian stimulation due to ovulation disorder when she conceived her first child at age 33 years. Prenatal checkups were performed at a local clinic. TD administration was discontinued due to her pregnancy but was resumed at 16 weeks of gestation as she developed hyperkalemia (4.9 mmol/L). She was referred to Kumamoto University Hospital. She first visited the hospital at 29 weeks and 0 days of gestation for the management of her perinatal course.

On her first visit, she was 153.0 cm in height, weighed 48.0 kg (BMI: 20.5 kg/m²), and presented with uncontrolled hypertension with blood pressure 160/95 mmHg. Laboratory test results were as follows: white blood cell count, 10,200/mm³; hemoglobin, 12.0 g/dl; platelet count, 263 × 10³/mm³; albumin, 3.3 g/dl; sodium, 136 mmol/L; potassium, 4.6 mmol/L; chloride, 110 mmol/L; calcium, 8.8 mg/dl; magnesium, 1.8 mg/dl; blood urea nitrogen, 11.6 mg/dl; creatinine, 0.51 mg/dl; and glucose, 79 mg/dl. Urinalysis revealed a urine pH of 5.5 and negative urine protein and glucose results. Fetal biometry revealed symmetrical fetal growth restriction (FGR), with an estimated fetal weight of 921 g (−2.3 SD). Fetal structural anomaly was not evident, TORCH infections were negative, and uterine artery and umbilical artery Doppler measurements were normal.

She was admitted for the assessment and management of hypertension and fetal condition. Sodium chloride (NaCl) restriction, administration of 1.5 g SB daily, and oral administration of TD at an increased dosage (2.0 mg) and nifedipine (NF; 20 mg) were initiated. Despite the manifestation of FGR, fetal monitoring confirmed reassuring fetal status and continuous fetal growth, and the patient was discharged at 33 weeks of gestation. At discharge, doses of NF and SB were increased to 20 mg twice daily and 2.0 g thrice daily, respectively, with continued oral TD for hyperkalemia and acidosis.

At 35 weeks and 6 days of gestation, she developed superimposed pre-eclampsia (SPE), and cesarean section was performed on the day of diagnosis as her cervical ripening was insufficient for induction. She gave birth to a female infant weighing 1,430 g (−4.3 SD), with Apgar scores of 8 and 9 at 1 and 5 min, respectively. Her puerperal course was uneventful, and the amount of oral medication was reduced (Figure 2).

The newborn infant required no support immediately after birth, except for the administration of intravenous glucose solution for hypoglycemia (42 mg/dl). Hyperkalemia (7.3 mmol/L) and hyperchloremic metabolic acidosis (chloride 124 mmol/L, base excess −9.5) developed on day 13; the administration of TD corrected these electrolyte imbalances. The infant was diagnosed with PHA2 by genetic analysis.

One year later, the patient became pregnant for the second time. Regular prenatal checkups were performed at our facility as well as at a local clinic. She was taking 1.0 mg of TD, 0.5 g of SB, and 20 mg of NF for PHA2...
when she became aware of her pregnancy. Both blood pressure and electrolyte balance were almost stable. She required no additional intervention, except that SB and NF doses were increased to 1.5 g and 40 mg (daily), respectively, at 35 weeks of gestation. Fetal biometry revealed symmetrical FGR. Fetal structural anomaly and TORCH infections were negative, and uteroplacental blood flow was not impaired. She did not develop pre-eclampsia throughout the course of pregnancy.

She went into labor spontaneously at 37 weeks and 6 days of gestation and gave birth vaginally to a 1,775 g (~2.9 SD) female infant with Apgar scores of 8 and 9 at 1 and 5 min, respectively. She was discharged from the hospital with a good postpartum course, with reduced doses of TD and SB.

The neonate was carefully monitored during the postnatal period. Hypertension (100/65 mmHg), hyperkalemia (6.4 mmol/L), and hyperchloremic metabolic acidosis (chloride 113 mmol/L, base excess −10.0) developed on day 9, but were corrected with the administration of TD. She was also diagnosed with PHA2 by genetic analysis.

**Discussion**

PHA2, also known as Gordon’s syndrome, is an extremely rare disease that reportedly affects about 180 individuals and families worldwide. It is an autosomal dominant disease featuring hypertension in adolescents and young adults, and is accompanied by hyperkalemia and hyperchloremic metabolic acidosis despite a normal glomerular filtration rate. The condition is the “mirror image” of Gitelman syndrome, which is characterized by normotension with hypokalemia, hypochloremia, and metabolic alkalosis. In PHA2, these conditions can be corrected with sodium restriction and/or administration of TD, i.e., specific antagonists of the NaCl cotransporter (NCC) of the distal convoluted tubule.

PHA2 is caused by gene mutations in the region that encodes either with-no-lysine kinase (WNK)1 or WNK4, enzymes that play a key role in regulating sodium, potassium, and pH homeostasis or their related proteins (e.g., KLHL3, CUL3). These gene products interact with each other, and individuals with mutations express similar phenotypes to varying degree. Levels of WNK proteins in the distal convoluted tubules are generally maintained by degradation through ubiquitination by the KLHL3-CUL3 E3 ligase complex. However, mutant WNK or loss of function of related proteins increases WNK levels due to impaired ubiquitination, resulting in persistent cascade activation that involves a thiazide-sensitive NCC. The activated NCC increases serum sodium levels, thereby inhibiting the aldosterone-sensitive renal outer medullary potassium (ROMK) channels present on the apical membrane of the distal renal tubule. This decreases the secretion of potassium and hydrogen ions and leads to the development of hyperkalemia and metabolic acidosis.

PHA2 is often diagnosed during childhood or adolescence based on convulsive seizures (as in the present case), periodic paralysis, and hypertension with electrolyte imbalances. In its most severe form, PHA2 may be associated with muscle weakness, short stature, and intellectual impairment. Since PHA2 is an extremely rare disease with varying phenotypes, patients with mild/partial PHA2 may be underdiagnosed. Proper diagnosis is important because clinical conditions are effectively improved with TD. TD, however, is not primarily used during pregnancy due to the risk of fetal or neonatal electrolyte imbalance, jaundice, and thrombocytopenia.

This report is the first to describe the clinical manifestations of PHA2 in both a pregnant woman and her newborns. Hyperkalemia and metabolic acidosis worsened during her two pregnancies, possibly due to increased serum progesterone concentrations with the progression of pregnancy, resulting in an anti-aldosterone effect. Although aldosterone stimulates potassium and hydrogen ion secretion into the tubular lumen through the ROMK channel, progesterone has a similar affinity for the mineralocorticoid receptor to aldosterone and thus acts as a competitive antagonist. In addition, WNK4 may be activated by hyperinsulinemia due to increased insulin resistance during pregnancy. In the present case, the patient’s symptoms subsided at the end of pregnancy, suggesting that the endocrine environment may be involved in the exacerbation of PHA2 during pregnancy.

Our patient developed SPE in her first pregnancy and delivered a severely small-for-gestational age (SGA) infant. It is interesting that her second pregnancy was also complicated with mild SGA despite the absence of obvious pre-eclampsia. Various factors, such as HDP-related placental dysfunction, familial trend in SGA, TD administration, and maternal and fetal acidosis may have been involved in the development of SGA. The patient herself was born SGA, although her mother (1-4, Figure 1) was not affected by PHA2 or HDP. This suggests that fetal PHA2 was a causative factor for SGA and was additively affected with maternal SPE in her first pregnancy.

Maternal metabolic acidosis may impair fetal bone growth and development, and even lead to fetal loss in patients with renal tubular acidosis type 4, a more frequently observed disease showing hyperchloremic metabolic acidosis similar to PHA2. In pregnancies with PHA2-related complications, serum potassium concentration and pH should be carefully monitored, given the risk of fetal complications related to acidosis as well as lethal cardiac arrhythmias associated with
In conclusion, this report described for the first time a woman and her infants affected by PHA2. If a pregnant woman develops hypertension with unexplained hyperkalemia, PHA2 and its related conditions should be considered as differential diagnoses, and careful management including electrolyte monitoring with a nephrologist should be provided for both the mother and infant.

Acknowledgments

The authors wish to thank the patient and her family for their cooperation in this investigation.

Conflict of interests

The authors declare no conflict of interests.

Informed consent

A signed consent form in Japanese was obtained from the patient.

Funding statement

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors’ contributions

Chisato Kodera drafted the manuscript. Takashi Ohba, Takashige Kuwabara, and Hidetaka Katabuchi revised the manuscript. All authors have read and approved the final version of the manuscript.

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