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P450 oxidoreductase deficiency with maternal virilization during pregnancy

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Summary

Purpose: The authors report on a rare case of maternal virilization during pregnancy caused by autosomal recessive P450 oxidoreductase (POR) deficiency. *Materials and Methods:* A 24-year-old primigravida developed a deepening voice and hirsutism in the second trimester. Prenatal ultrasonography failed to detect any fetal abnormality and fetal growth was normal. POR deficiency was suspected, but the mother declined fetal genetic testing. A female neonate was delivered by cesarean section at 41 weeks' gestation. *Results:* The neonate had skeletal abnormalities. Mutational analysis of the POR gene demonstrated homozygosity for c.1370 G>A and p.R457H in the patient and heterozygosity in her parents. POR deficiency was confirmed in the neonate. *Conclusion:* POR deficiency should be suspected in cases of maternal virilization. Maternal urinary estriol, fetal magnetic resonance imaging, and parental genetic testing should be performed. Parental consent for fetal genetic testing should be sought to ensure prompt diagnosis and early treatment.

Key words: Congenital adrenal hyperplasia; Genetic diagnosis; Maternal virilization; P450 oxidoreductase deficiency.

Introduction

Maternal virilization during pregnancy is rare. This condition may be caused by P450 oxidoreductase (POR) deficiency [1-4], which is an autosomal recessive genetic disease classified as congenital adrenal hyperplasia. Maternal virilization is associated with skeletal malformations, disorders of adrenal steroid synthesis, abnormal sexual development, and maternal virilization during pregnancy [1, 2]. The authors describe a case of POR deficiency with maternal virilization during pregnancy.

Case Report

A 24-year-old primigravida with a spontaneous pregnancy was referred to the present hospital with a positive pregnancy test. Her personal and family histories were unremarkable. The expected delivery date was calculated from the fetal crown–rump length at ten weeks' gestation, based on transvaginal ultrasonography. The woman was followed up at our hospital. Deepening voice and hirsutism started to develop in the second trimester and were worse at 38 weeks' gestation. Maternal virilization is generally caused by POR deficiency, aromatase deficiency, luteoma, or Sertoli-stromal cell tumors. Female fetuses are more severely affected by maternal virilization than male fetuses. However, prenatal ultrasonography failed to detect any anomaly or determine the sex in the current case. The patient adopted a wait-and-see approach, but the present authors also consulted pediatricians in their hospital because of the possibility of the above-mentioned diseases. They explained the possibility of POR deficiency to the patient, but noted that it was difficult to make an accurate diagnosis based on diagnostic imaging alone. They suggested performing a genetic diagnosis by aspiration of umbilical blood and explained the potential risks of this procedure, but the patient declined and insisted that she wanted to deliver at the present hospital, even in the event of fetal anomalies. Measurement of serum androgen levels could aid diagnosis with no risk to the fetus. Although the current patient declined to undergo this blood test, it should be considered in future cases. The estimated fetal body weight was 2,795 g (+0.66 SD) at 36 weeks' gestation, which was within the normal range. No abnormalities were detected prior to birth. Delivery was induced at 41 weeks and one day of gestation because of prolonged pregnancy, but an emergency caesarean section was performed because of arrested delivery. The neonate weighed 3,245 g with Apgar scores of 8 and 9 after one and five minutes, respectively. The neonate was diagnosed as female by transabdominal ultrasonography, based on the presence of clitoromegaly and a uterus. Abnormalities including craniosynostosis, joint contractures, arachnodactyly, vesicoureteric reflux, rhinopharyngeal stenosis, an abnormal foot shape, and cephalic angioma were detected at the same time. POR deficiency was suspected from maternal virilization, as indicated by her deepening voice and hirsutism, and the physical findings of the neonate (Figure 1A, B).

Mutational analysis of the *POR* gene demonstrated heterozygosity for c.1370 G>A and p.R457H in her parents and homozygosity for c.1370 G>A and p.R457H in the patient (Figure 1C). Genetic diagnosis confirmed that the neonate suffered from POR deficiency (Figure 1C).

Discussion

Maternal virilization during pregnancy is rare but can be caused by hyperandrogenemia. Maternal virilization is

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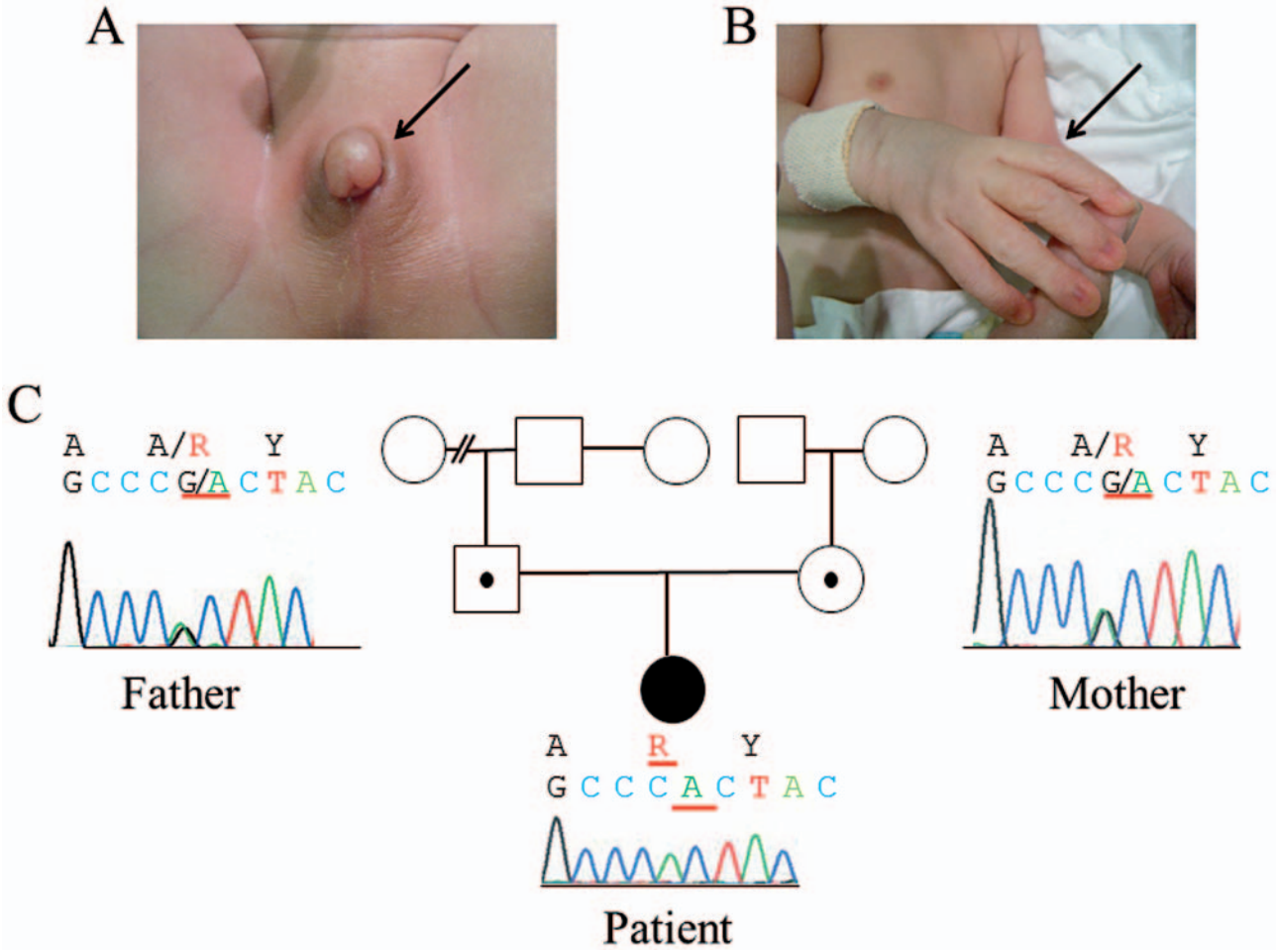

Figure 1. — The patient had a hypertrophic clitoris (A) and spider-like fingers (B). Genealogy of the patient and genetic analysis (C). Sequence analysis showed heterozygosity for c.1370 G>A and p.R457H in the *POR* gene in the patient's parents (C), but homozygosity for c.1370 G>A and p.R457H in the patient (C).

associated with several diseases, including POR deficiency, aromatase deficiency, luteoma, Sertoli-stromal cell tumors, 21-hydroxylase (CYP21A21) deficiency, and 17a-hydroxylase deficiency [4]. Based on expert clinical advice and previous reports, the presnt authors diagnosed POR deficiency in the present patient with maternal virilization during pregnancy [1, 5, 6].

POR deficiency is an autosomal recessive genetic disease classified as congenital adrenal hyperplasia [1, 2]. The general incidence of POR deficiency has not been reported, although it is known to be rare in patients with congenital adrenal hyperplasia, and only approximately 80 cases have been reported [3, 7, 8]. POR is involved in electron transfer in microsomes and is required for the activity of all microsomal P450 enzymes, including CYP21A21, 17α-hydroxylase/17,20 lyase, and aromatase, as well as some non-P450 enzymes, including squalene epoxidase. Mutation of the *POR* gene results in abnormal complex formation and subsequent deficiency of POR [1, 2]. POR deficiency was thought to be embryonically lethal, based on mouse experiments; however, POR mutations were detected in humans in 2004 [1]. Mutational analysis in 35 Japanese patients demonstrated homozygosity and heterozygosity for c.1370 G>A and p.R457H [8]. A287P is the most common mutation in Caucasian patients, while R457H is the most prevalent founder mutation in Japanese patients [8]. Genetic analysis of the current patient showed similar results, with heterozygosity for c.1370 G>A and p.R457H in the patient's parents (Figure 1C).

POR deficiency is often overlooked in patients with maternal virilization during pregnancy [9], and its prenatal diagnosis may be difficult in the absence of fetal ultrasonographic findings. However, POR deficiency should be suspected in the event of maternal virilization during pregnancy. The authors were able to diagnose POR deficiency in the present case on the basis of expert clinical

advice and descriptions in previous reports [1, 5, 6].

Ultrasonography is useful for evaluating fetal anatomy and is usually the first technique used to detect abnormalities. However, recent developments in magnetic resonance imaging technology indicate that this may also be useful for identifying equivocal prenatal cases. Because estriol is produced by aromatization of fetal androgen precursors, POR deficiency is associated with low levels of estriol during pregnancy [3], and measuring maternal urinary estriol is therefore recommended in patients with suspected POR deficiency [3]. However, the current patient declined this test. Early detection is critical for timely treatment of this condition, allowing affected fetuses to be delivered in fully-equipped hospitals.

Conclusion

The authors report a patient with POR deficiency who developed maternal virilization during pregnancy. Early treatment of this condition is associated with improved prognosis, especially in relation to skeletal malformations. When maternal virilization is detected, maternal urinary estriol, fetal magnetic resonance imaging, and genetic analysis of the parents should be performed with patient consent. Additionally, informed parental consent should be sought for fetal genetic analysis after aspiration of amniotic fluid.

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