Received: 14 September 2021 | Revised: 18 December 2021 | Accepted: 4 January 2022

DOI: 10.1111/cga.12464

NOTE

Congenital Anomalies | WILEY

The first adult case of cytochrome P450 oxidoreductase deficiency with sufficient semen volume and sperm concentration

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Funding information
AMED, Grant/Award Number: 22ek0109464h0003

Cytochrome P450 oxidoreductase deficiency (PORD) is an autosomal recessive disorder and characterized by variable clinical manifestations, including adrenal insufficiency, undervirilization of an individual with the 46,XY karyotype, and bone deformity, owing to impairment of steroid synthesis and cholesterol metabolism.

Regarding androgen production capacity, male patients with PORD develop variable puberty, from delayed to spontaneous pubertal development.[1] To date, studies on spermatogenesis in PORD are scarce. One adult patient with PORD has been reported to develop azoospermia.[2] Another patient showed compromised spermatogenesis on testicular biopsy.[1] Here, we present the case of an adult PORD patient with sufficient semen volume and sperm concentration.

A Japanese male patient was 47 years old, harboring compound heterozygous *POR* pathogenic variants, p.R457H/p.L612_W620delinsR. His genetic status has been previously reported as Case 2 in Reference 1, and Case 30 in Reference 3. Since birth, he did not require hydrocortisone or testosterone supplementation. He was referred to our hospital at the age of 28 years. He presented with arachnodactyly, multiple joint contractures, and bilateral hearing loss. He had micropenis (penile length, −5.0 SD). The left testicular volume was 25 ml in the scrotum, and the right testis was located in the inguinal canal. His pubic hair was at Tanner stage III. Since the age of 35, he needed antihypertensive drugs.

At 39 years of age, our patient married a 31-year-old woman. He needed 16 mg/day of azelnidipine, and 100 mg/day of losartan to control hypertension. His wife had a history of deliveries at 18 and 23 years of age with an ex-husband. At the age of 31, she received treatment for type 2 diabetes mellitus. When our patient was 41 years old and his wife was 33 years old with hemoglobin A1c at 6.5% (reference, 4.6–6.2), they planned for pregnancy, but his wife did not become pregnant. Despite consideration of possible assisted reproductive technology, they finally divorced, when he was 44 years old.

Semen analyses were performed five times, from 36 to 47 years of age. Four of the five times, semen volumes and sperm concentrations were above the lower fifth percentile of data from men in the reference population, according to the World Health Organization laboratory manual (Table 1).[4]

The previous case with azoospermia had hypospadias and cryptorchidism,[2] while our patient had micropenis and unilateral cryptorchidism. This implied that testosterone production during fetal period was insufficient in both cases but was impaired less severely in our patient. Our patient developed puberty spontaneously, and his serum testosterone concentrations were within the normal range (Table 1). Meanwhile, his pubic hair was at Tanner stage III at the age of 28 years, and the levels of luteinizing hormone and follicle-stimulating hormone were high (Table 1), consistent with partly impaired testosterone production. No supplementation of cortisol was needed in both of our patient and the previous case.[2] Thus, despite a lack of in vitro data on the residual enzymatic activities of our patient and the previous case, we speculate that POR activity in our patient was preserved more than the previous case, and substantial residual POR activity is required for spermatogenesis in male patients with PORD.

We speculate the following three possible reasons for why his wife did not conceive naturally for more than 2 years, despite our patient showing sufficient semen volume and sperm concentration. First, his

TABLE 1 Semen analyses and endocrinological results of the patient

Laboratory examinations	References	Age (years)					
		29	36	37	39	42	47
Semen analyses							
Semen volume (mL)	≥1.4[a]	–	0.8	1.6	2.5	3.4	3.2
Sperm concentration ($\times 10^6$/mL)	≥16[a]	–	4	31	48	133	68
Endocrinological examinations							
Luteinizing hormone (mIU/L)	2.2–8.4	21.7[b]	27.2	–	–	29.4	–
Follicle-stimulating hormone (mIU/L)	1.8–12	37.7[b]	38.1	–	–	45.6	–
Testosterone (ng/mL)	1.92–8.84	3.9[b]	3.64[c]	–	–	4.89	6.01

[a]The lower fifth percentile of data from men in the reference population, according to the World Health Organization laboratory manual.
[b]At 29 years old, the patient's reference values were as follows: luteinizing hormone 0.8–5.4 mIU/L, follicle-stimulating hormone 1.1–9.7 mIU/L, testosterone 2.7–10.7 ng/mL.
[c]At 36 years old, the reference testosterone level was 2.01–7.50 ng/mL.

sperms might have low motility and malformation. Unfortunately, we did not evaluate sperm motility and morphology. Second, he could have difficulty in sexual intercourse because of micropenis. Third, he might have had erectile dysfunction caused by antihypertensive drugs. We expected his wife's reproductive capacity to be preserved for the following reasons: (a) she had two children from her previous marriage, (b) she was 33 years old at the time of planning to conceive, and (c) she had her type 2 diabetes mellitus well controlled. Therefore, we assumed that our patient could be a father through assisted reproductive technology.

In summary, we present the case of a patient with genetically confirmed PORD, whose semen volumes and sperm concentrations met the World Health Organization criteria.

ACKNOWLEDGMENTS

We thank the patient for participating in this study. This study was partly supported by a grant from AMED (22ek0109464h0003).

CONFLICT OF INTEREST

None.

ETHICS STATEMENT

This study has been approved by the Institutional Review Board at Keio University School of Medicine (Institutional Review Board number 20150104).

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How to cite this article: Sato T, Ishii T, Fukami M, Ogata T, Hasegawa T. The first adult case of cytochrome P450 oxidoreductase deficiency with sufficient semen volume and sperm concentration. *Congenit Anom*. 2022;62(3):136-137. doi:10.1111/cga.12464