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Case Report

A Case of Erythropoietic Protoporphyria with Decreased free Erythrocyte Protoporphyrin During Pregnancy

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Abstract:

Background: There have been no previous reports on tracking erythrocyte protoporphyrin levels of patients with erythropoietic protoporphyria during pregnancy, or genomic studies of mothers and their offspring.
Case presentation: We describe a Japanese woman with erythropoietic protoporphyria and compound heterozygosity of FECH, who gave birth twice (30 and 33 years old) Her symptoms and free erythrocyte protoporphyrin level improved during pregnancy. After giving birth, her erythrocyte free protoporphyrin level increased to the same as that before her pregnancy. During her pregnancy, taking iron supplement temporarily worsened her protoporphyrin level. Her 3 children were heterozygous for the FECH mutation, and showed normal levels of free erythrocyte protoporphyrin.
Conclusions: We speculate that ferrochelatase from fetal erythrocytes crossed the placenta and improved the mother's symptoms. This speculation needs to be assessed by further experimentation in the future.

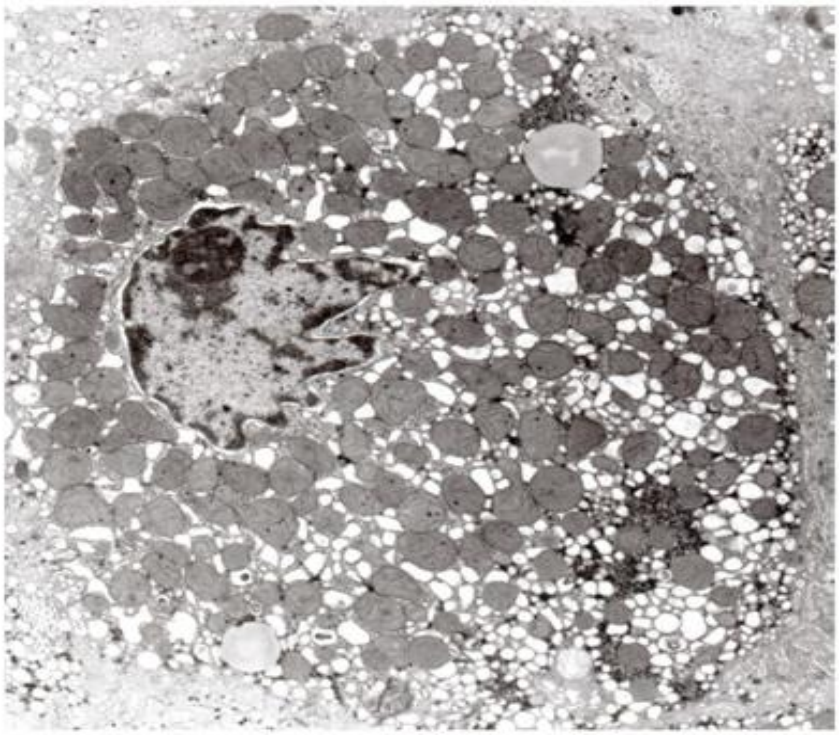
Key words: ferrochelatase, photosensitivity, liver dysfunction, fetus, iron

Introduction

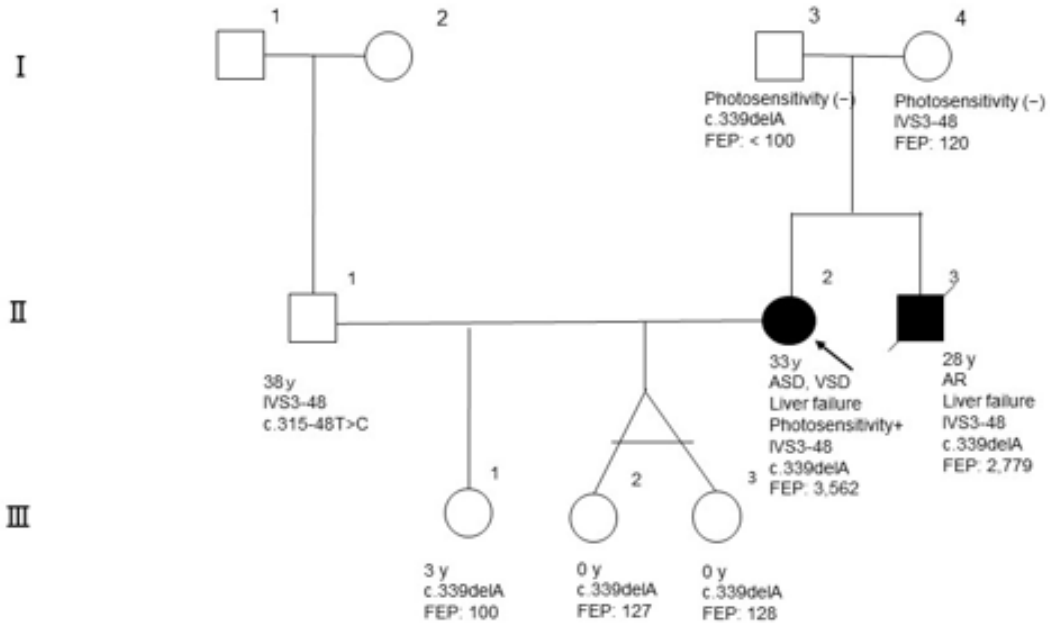
Porphyria is an inborn error of metabolism with photosensitivity caused by the accumulation of metabolic intermediates owing to the decreased activity of enzymes involved in the metabolic pathway of heme synthesis. In the present study, we encountered a rare case of a patient with erythropoietic protoporphyria (EPP, OMIM 177000), who showed a temporary decrease in free erythrocyte protoporphyrin level and normalized liver function test results during pregnancy. EPP has been reported worldwide, and its prevalence has been estimated to be approximately 1: 75,000 to 1: 200,000 [1]. We previously reported a case of siblings with liver dysfunction who had not been diagnosed as having EPP for a long time because of their mild photosensitivity [2]. There are very few studies on the effects of pregnancy in EPP patients. The present patient experienced 2 pregnancies (a single pregnancy and a twin pregnancy) without the aggravation of her disease. Moreover, an improvement in free erythrocyte protoporphyrin level was observed during her pregnancies. We also measured free erythrocyte protoporphyrin and performed genomic analyses of her children.

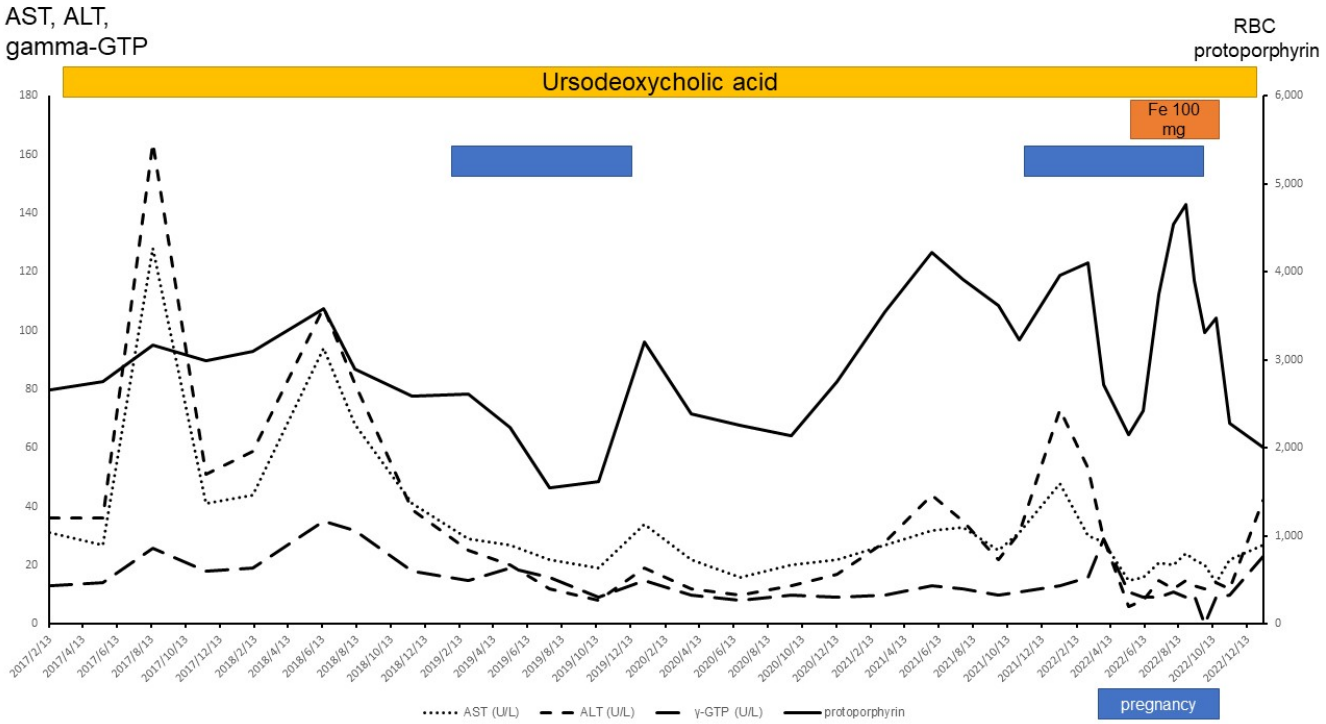
Case presentation

The Japanese girl was found to have an atrial septal defect and ventricular septal defect during the neonatal period, and underwent radical surgery at another hospital when she was 8 months old. At about 10 months old, she was found to have increased levels of liver enzymes, and was diagnosed as having post-transfusion hepatitis. At the age of 1 year, she developed redness of exposed areas of the skin. At the age of 12 years, she started taking ursodeoxycholic acid, because her data in liver function worsened. In the same year, she was referred to our hospital due to moving house. She underwent various blood, urine, and stool tests, resulting in a diagnosis of EPP. She was found to have a deletion of adenine at position 337 in exon 4 of the *FECH* gene, as the cause of her EPP. Similar mutations were also identified in her father and her brother, but her father is not affected. Genomics analysis demonstrated that she also had the IVS3-48T>C polymorphism in the *FECH* gene in her other allele. At the age of 12 years, she underwent a liver biopsy, which revealed mild liver fibrosis, lobular disruption, and brown deposits. Electron microscopy demonstrated disappearance of cristae and swollen mitochondria (Figure 1).



The patient became pregnant with her first child at the age of 30 years. Her free erythrocyte protoporphyrin level was measured and followed up during her pregnancy. The lowest value during pregnancy was 1,549 μg /dL RBC, and fluctuated between 2,000 and 4,000 μg /dL RBC, as shown in Figure 2. After delivery, *FECH* genetic analysis of the offspring was performed, and heterozygosity of the deletion of adenine at position 337 of exon 4, without IVS3-48C was identified. At the age of 33 years, she became pregnant again, and delivered twins. During pregnancy, her erythrocyte protoporphyrin level also remained low. However, when she took iron supplements for temporary anemia, her erythrocyte protoporphyrin level increased, and quit taking the supplements. All 3 children were heterozygous for the exon 4 deletion of the *FECH* gene, which was the same as the patient, but they did not have the intron mutation (Figure 3). In addition, all 3 children had low levels of erythrocyte protoporphyrin. The first child showed hyperbilirubinemia, and phototherapy was performed. There were no side effects, and bilirubin levels decreased rapidly without any side effects. The twins showed no hyperbilirubinemia.





Discussion

This is a report of an extremely rare case, as there have been no previous reports on tracking erythrocyte protoporphyrin levels of EPP patients during pregnancy, or genomic studies of mothers with EPP and their offspring. EPP is a relatively rare disease, accounting for about 181/884 cases (20.4%) of porphyria in 91 years in Japan [3]. The disease is an inherited metabolic disorder caused by a deficiency of ferrochelatase, which is the last enzyme of the heme biosynthetic pathway, catalyzing the conversion of protoporphyrin IX to heme [4]. EPP is caused by the accumulation of excess protoporphyrin IX in the skin and liver [5]. Photosensitivity is the most common symptom, which appears in early childhood [6], and hepatic involvement occurs in 10% to 20% of patients. The terminal phase, such as liver failure requiring a transplant, develops in about 2% of EPP patients [7,8]. In the present study, the patient's young brother died of liver and heart failure at the age of 28 [9]. The present study described the clinical course of a patient with EPP, including genotypes of her children, and evaluated the correlation between protoporphyrin levels and the progression of liver complications in pregnancy. In the present case, the patient tried to protect herself from light before pregnancy, but she did not protect herself from light as strictly after pregnancy. In addition, there was no change before and after pregnancy in terms of eating habits and oral medications. Her symptoms and levels of free erythrocyte protoporphyrin improved during pregnancy. After giving birth, her protoporphyrin levels increased to the same as that before her pregnancy. The 3 children were heterozygous for the *FECH* mutation, and showed normal levels of free erythrocyte protoporphyrin.

There are many reports of EPP patients whose symptoms spontaneously improved temporarily during pregnancy. A typical case has been reported by Jacquemyn et al., in which the patient had experienced extremely painful skin photosensitivity since the age of 4 years. From the first trimester of pregnancy, her complaints disappeared completely, and she was relieved to be able to walk in the sun without any symptoms at the age of 21. Her course of pregnancy was uneventful, and no notable liver dysfunction was observed during pregnancy. However, within 6 weeks after delivery, her photosensitivity became apparent again. The erythrocyte protoporphyrin level in the umbilical cord was normal (1,005 μg/L) [10]. Wahlin et al. investigated symptoms during the menstrual cycle and pregnancy in 20 Swedish women older than 18 years who were diagnosed with EPP, with a total of 33 deliveries. The data showed that amelioration of photosensitivity was reported during pregnancy in 17 of the 33 (53%) deliveries, and during the breast-feeding period in 11 of the 32 (34%) deliveries. They concluded that EPP patients can go through pregnancy safely without any increased risks of pregnancy complications or adverse effects on fetal or neonatal health [11]. However, some women with EPP show no changes in their symptoms during pregnancy. Schmidt H et al. investigated 29 patients in 14 families with EPP, and reported that 5 patients (17%) showed a marked improvement in symptoms during pregnancy, but there was no change in protoporphyrin levels [12]. Poh-Fitzpatrick et al. also reported women with EPP who have increased sunlight tolerance during pregnancy. However, erythrocyte porphyrin levels were lower during pregnancy[13]. These observations suggest that a beneficial physiological effect of pregnancy in patients with EPP may be a lower circulating erythrocyte protoporphyrin burden, which leads to reduced photosensitivity. In 4 patients with EPP, erythrocyte protoporphyrin levels were reported to be reduced from 19% to 66% during 7 deliveries [14]. A total of 7 cases of EPP in pregnancy have been published by Poh-Fitzpatrick [13] and Bewley et al. [15]. Increased sunlight tolerance and lower erythrocyte protoporphyrin levels in the patients were observed with complete disappearance of symptoms without a reduction in protoporphyrin levels. Several mechanisms underlying the decrease in erythrocyte protoporphyrin levels during pregnancy have been proposed, including conversion of maternal erythrocyte protoporphyrin by the fetus, and hormonal effects on the expression of the *FECH* gene.

Todd et al. reported that symptoms of EPP develop due to low expression of the non-mutant allele when enzyme levels decrease to 10% to 30%, and

denied a simple dominant or recessive inheritance [1]. Less than 10% of carriers of the *FECH* gene mutation developed clinical disease [16]. Therefore, the genomic data and protoporphyrin levels of the patients' children are needed to reach a conclusion. There is minimal data regarding erythrocyte protoporphyrin levels and the genomic information of the patients' children. The siblings in the present study had compound heterozygosity, and showed high levels of erythrocyte protoporphyrin. However, the patient's children and father who had 1 mutation showed almost normal levels of erythrocyte protoporphyrin. In this study, free erythrocyte protoporphyrin levels were measured both before and after pregnancy and delivery, and showed a downward trend during pregnancy. At the same time, APTT (activated partial thromboplastin time) tended to be shortened, and AST (aspartate aminotransferase) and ALT (alanine aminotransferase) of hepatic enzymes showed a decreased tendency. As a reason for these observations, it is speculated that the pathology of EPP, that is, the disrupted heme synthesis pathway, was in a better state during pregnancy than before pregnancy. It is possible that the ferrochelatase enzyme required in the heme synthesis pathway was somehow recruited to the mother during pregnancy, or that porphyrins were being synthesized into heme elsewhere. The fetuses had heterozygous for the *FECH* gene mutation on postnatal testing. In addition, the free erythrocyte porphyrin levels of the fetuses were within the normal range. Therefore, it was concluded that the children do not show any signs of EPP. One possibility is that fetal ferrochelatase entered the mother's body and assisted in the heme synthesis pathway. However, ferrochelatase has a molecular weight of 40,900 g/mol and is unlikely to cross the placenta. Alternatively, maternal protoporphyrin IX may have crossed the placenta and synthesized heme in the fetus. Protoporphyrin IX has a molecular weight of 562.66 g/mol, and may hence cross the placenta. It is possible that the placenta adsorbed protoporphyrin IX, but it is unlikely because no abnormalities were identified in pathological analysis of the placenta. Therefore, it is highly likely that normal erythrocytes of the fetus passed through the placenta to metabolize protoporphyrin in the mother. Increased erythrocyte protoporphyrin levels improved during pregnancy, and worsened after giving birth in most previously reported patients, as in our present patient. The children of the present patient had a heterozygous mutation (deletion of adenine at position 337 in exon 4) of *FECH*, and did not have the IVS3-48C polymorphism.

Early studies indicated the autosomal dominant inheritance of EPP, and noted that some people who are obligate carriers and have lifelong increased protoporphyrin levels may never develop photosensitivity, such as the father of the present patient [17,18,19]. In an exhaustive study in the Netherlands, Went and Klasen (1984) identified 200 EPP patients in 91 families. In 46 of these families, only a single patient was identified. The presence of an occasional fluorescent red blood cell combined with normal protoporphyrin levels was observed in half of the children and siblings of patients and in 1 of their parents. Thus, they concluded that this trait appeared to be autosomal recessive [20].

Gouya et al. (2002) identified an intronic polymorphism, IVS3-48T-C, that modulates the use of a constitutive aberrant acceptor splice site 63-bp upstream of exon 3. The aberrantly spliced mRNA is degraded by a nonsense-mediated decay mechanism, producing a decreased steady-state level of mRNA[21]. Moreover, Gouya (2006) studied a cohort of 173 white French EPP families. In 97.9% of dominant cases, the IVS3-48C allele was coinherited with the deleterious mutation in trans [22]. Therefore, the ferrochelatase activity of these patients is impaired by a combination of a mutated *FECH* allele leading to markedly decreased enzyme activity, and a common hypomorphic allele (IVS3-48C), which is called "pseudodominant" inheritance [23,24]. The incidence of IVS3-48C, which is a low expression allele, is 11.3% or less in Caucasians, whereas it is as high as 43.3% to 45.2% in the Japanese population, indicating that the incidence is higher in the Japanese population than in Caucasians [22,25].

In the present case, a pedigree study identified the *FECH* gene mutation with IVS3-48C in the patient, suggesting that her EPP was hereditary. Therefore, regular follow-up of liver function and free erythrocyte protoporphyrin levels is recommended for the patient. Moreover, the possibility of EPP in her grandchildren will depend on her partner, particularly whether he has the IVS3-48C polymorphism. Symptoms develop only when the levels of the enzyme are as low as 10% to 30% of normal, as a result of low expression of the nonmutant allele [26].

In the present patient, her liver function test and levels of erythrocyte protoporphyrin worsened upon the use of iron supplements. EPP is caused by partial deficiency of ferrochelatase, which is the enzyme that catalyzes the final step of insertion of the Fe^{2+} ion into protoporphyrin IX to form heme. Iron drugs might be an aggravating factor owing to the differentiation of erythrocytes. At present, iron therapy remains controversial. A patient with EPP and abnormal liver function test results in whom oral iron therapy led to a substantial decrease in free erythrocytes and the return of liver function to normal has been reported [27]. On the other hand, 4 patients with EPP in whom oral iron treatment resulted in clear clinical and biochemical deterioration have been reported [28]. This suggests that there are 2 biochemically and genetically distinct subgroups of EPP patients, distinguished by their completely different responses to oral iron. There have been no genomic studies to date regarding the response of EPP patients to oral iron supplements. This information is needed to conclude the results of genomic data analyses. The speculation that ferrochelatase from fetal erythrocytes actually crossed the placenta and improved the mother's symptoms needs to be assessed by further experimentation in the future.

Conclusions

It was been speculated that ferrochelatase from fetal erythrocytes crossed the placenta and improved the mother's symptoms, and that iron, which accelerates the differentiation of erythrocytes, is an aggravating factor for protoporphyria.

Authors contributions

N.S. and H.K. designed the study; N.R. and S.S. analyzed the genomic data; and N.S. wrote the manuscript; H.K. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

o Ethics Approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must include a statement on ethics approval and consent (even where the need for approval was waived) and include the name of the ethics committee that approved the study and the committee's reference number if appropriate.

o Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

o Availability of supporting data.

Not applicable

o Funding

Not applicable

o Acknowledgements

Not applicable

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