The 6-year follow-up of a Japanese patient with silent erythropoietic protoporphyria

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INTRODUCTION

Erythropoietic protoporphyria (EPP) is an inherited cutaneous porphyria caused by a decreased activity of the enzyme ferrochelatase (FECH).[1,2] EPP patients are clinically characterized by painful photosensitivity of the skin, with some exhibiting liver failure.[3] The development of clinically overt EPP usually requires the inheritance of a *FECH* mutation and the existence of C at IVS3-48 in trans to a mutated *FECH* allele.[1,2] IVS3-48C polymorphism induces aberrant splicing and results in the low expression of FECH.[1,4] We describe the clinical findings and serum protoporphyrin (PP) levels of a Japanese EPP patient from the initial genetic diagnosis until the development of clinical symptoms.

Abbreviations used:

EPP:	erythropoietic protoporphyria
FECH:	ferrochelatase
iEPP:	incomplete erythropoietic protoporphyria
PP:	protoporphyrin

CASE REPORT

A 13-year-old girl presented to our clinic with painful erythema on her face after sun exposure in the summer. She had no medical history and no history of drug use. Six years previously, her elder brother had EPP diagnosed when he was 9 years old. He had initially noticed photosensitivity at 7 years of age. His case was described in our previous report.[5] This patient had never before experienced photosensitivity; however, her laboratory investigations found mild anemia (hemoglobin, 11.1 g/dL) and an increased erythrocytic PP level (4316 μg/dL; normal range, 30–86 μg/dL). No liver dysfunction was detected. Fluorocytes were also observed in the peripheral blood (Fig 1, *A*). Her parents and younger brother showed no photosensitivity and no abnormality in blood test results. A genetic analysis of the *FECH* gene was performed for all family members after written informed consent was obtained according to the ethical guidelines of the 1975 Declaration of Helsinki. This examination was approved by the Human Subjects Committee, University of Toyama. Consequently, a heterozygous mutation c.286C>T, p.R96X in the *FECH* gene and a heterozygous IVS3-48C polymorphism in trans of the *FECH* gene mutation were identified only in this patient and her elder brother (Fig 1, *B* II-1 and II-2). This result was diagnostic for EPP and suggested that she will have the clinical symptoms of EPP in the near future. We therefore proposed that she should avoid exposure to sunlight; however, she could not completely do so, and mild sunburn occasionally occurred. At 9 years of age, her PP level increased to 9503 μg/dL, which was the highest level in the last 6 years; however, she showed no photosensitivity (Fig 2). At 13 years of age, severe photosensitivity first appeared after sun exposure in the summer. In this instance, her PP level was 6439 μg/dL. She experienced her first menstruation 2 months before the development of photosensitivity. Her liver biochemical profiles have remained within the

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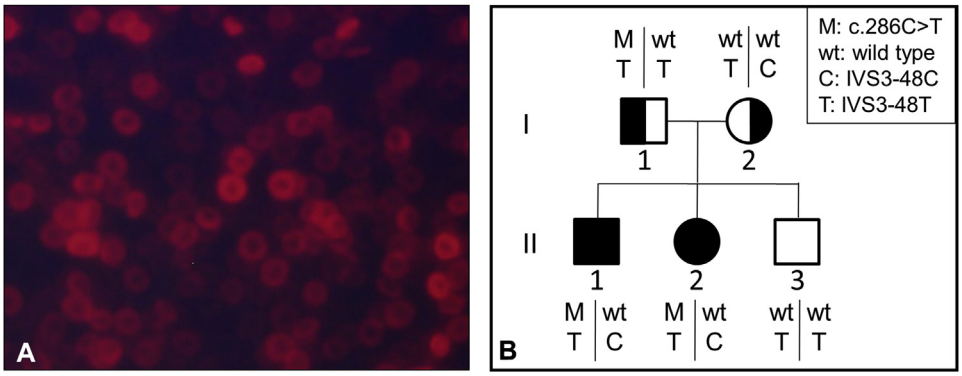

Fig 1. Fluorocytes and the pedigree of the patient. **A**, Fluorocytes were observed in the patient. **B**, The pedigree of the family with EPP. The solid symbols refer to symptomatic individuals. T and C represent wild-type IVS3-48T and IVS3-48C, respectively. *M*, c.286C>T; *WT*, wild-type.

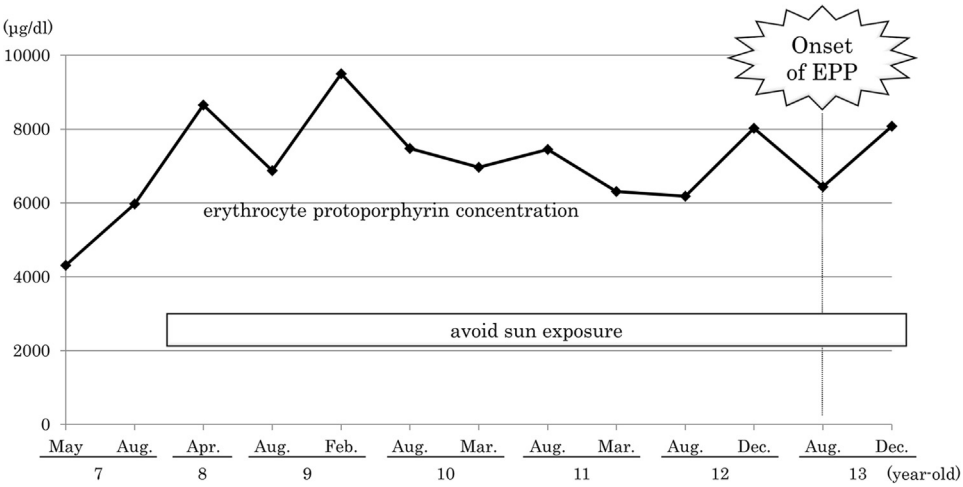

Fig 2. The clinical course of EPP development.

normal limits for the last 6 years. She currently maintains strict avoidance of sun exposure.

DISCUSSION

This patient had fluorocytes, an increased PP level, and a *FECH* gene mutation when she was 7 years old; however, the patient's photosensitivity initially appeared at 13 years of age. We refer to this condition without any clinical symptoms of EPP as *silent EPP*. We examined the PP level during the period of silent EPP. Interestingly, the PP level was the highest at 9 years of age, although the patient's photosensitivity did not appear at the time. This finding suggests that the onset of EPP symptoms may not necessarily depend on the PP level as evidenced by the progress of this patient and her PP levels. Although the exact mechanism underlying the onset of EPP symptoms remains unclear, there have been only a few reported adult-onset EPP cases with the *FECH* gene mutation.[6,7] These reports showed that the late-onset EPP patients developed photosensitivity after strong sun exposure in tropical climate in middle age, although such symptoms had not been experienced when they were in Northern Europe and were only exposed weak sunlight.[6,7] Thus, the dose of sun exposure may play an important role in the induction of EPP symptoms. In this patient, the avoidance of sun exposure may have delayed the onset of EPP. Additionally, menstruation is reported to occasionally be associated with a worsening of EPP symptoms.[8] This patient experienced her first menstruation at 13 years of age; therefore, this may have been associated with the onset of EPP.

The onset of EPP in this patient and her brother seems to be late in comparison with that of the white population, because a previous review of 223 EPP cases in the United Kingdom found the median age of onset to be 1 year (range, 0–12 years).[9] We therefore reviewed the literature of 72 Japanese EPP cases that were reported from 1980 to 2015. Consequently, the median age of onset was 6 years

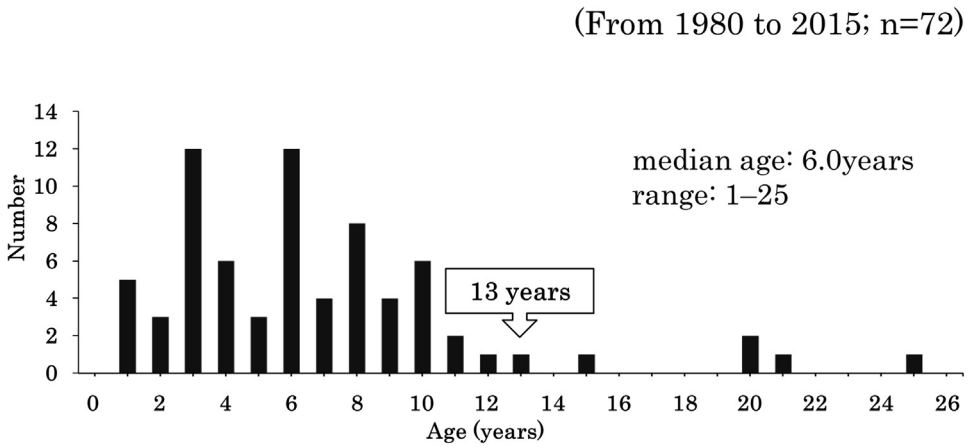

Fig 3. The age at the onset of symptoms of 72 EPP patients reported in Japan.

(range, 1−25 years; Fig 3). Surprisingly, approximately 20% of all patients recognized the symptoms of EPP after 10 years of age. We hypothesize that the onset of EPP in the Japanese population appears to be later than that in the white population.

We recently reported that the homozygous IVS3-48C polymorphism can induce a slight increase in the PP level and the formation of a small number of fluorocytes in the absence of any known *FECH* mutation, thereby resulting in the development of a mild phenotype of EPP, which is referred to as *incomplete EPP* (iEPP).[10] The frequency of the homozygous IVS3-48C polymorphism in the Japanese population is more than 10 times higher than that observed in individuals from European countries.[4] The high frequency of iEPP may be associated with the late onset of EPP in the Japanese population.

Further study is required to clarify the exact mechanism of the onset of EPP. Nevertheless, these findings are considered helpful for extending our knowledge in the pathogenesis of EPP.

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