

## CPD

## Unusual presentation of severe photosensitivity and neurodevelopmental delay in a consanguineous family

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Variegate porphyria (VP) is a hepatic form of porphyria caused by a mutation in one allele of the gene for protoporphyrinogen oxidase (PPOX).<sup>1</sup> The resulting enzymatic activity of PPOX is lowered to 50%, with the residual activity being the product of the normal allele. Biochemical testing usually reveals increased porphyrin in the plasma, urine or faeces, but not in erythrocytes.

The clinical presentation of VP is variable, and can manifest as cutaneous photosensitivity with or without acute neurovisceral symptoms.<sup>2</sup> In most cases, the symptoms occur after puberty, and most commonly manifest as blistering and fragility of sun-exposed skin identical to those of porphyria cutanea tarda. We report the case of a young child with skin lesions, who was subsequently diagnosed with VP.

A 3-year-old girl presented with a history of recurrent blisters over sun-exposed areas from the age of 6 months, particularly involving the face and dorsa of the hands. The lesions were triggered by sun exposure, and healed with residual scarring. From the age of 2 months, the patient had also been experiencing recurrent epileptic episodes, and had delay in speech and motor development. Physical examination revealed severe scarring of the patient's face and hands with evidence of keloid scars, milia, alopecia and brachydactyly (Fig. 1a–c), along with ocular nystagmus. Neurodevelopmental delay was evident.

The patient's 16-year-old maternal uncle also had extreme photosensitivity associated with severe neurodevelopmental delay, seizures, multiple wounds and

amputation of the fingers (Fig. 1d). Several family members were reported to have had a similar condition and had died at a young age secondary to their condition (Fig. 2).

Laboratory investigations for porphyria in the proband and her uncle revealed increased levels of coproporphyrin and uroporphyrin in the urine significantly increased levels of faecal protoporphyrin and to a lesser extent coproporphyrin III. Free porphyrin was also increased in the erythrocytes, and there was a plasma fluorescence emission peak of 626 nm.

Exome sequencing in both the patient and her affected uncle revealed a novel homozygous mutation in the PPOX gene, which changes the amino acid glutamic acid into lysine at position 339 and is designated p.Glu339Lys. The patient's parents, who were second-degree relatives, were both asymptomatic carriers. The mutation was absent in 300 chromosomes screened from individuals belonging to the same population. The clinical picture, biochemistry and genetic testing suggested the diagnosis of recessive VP.

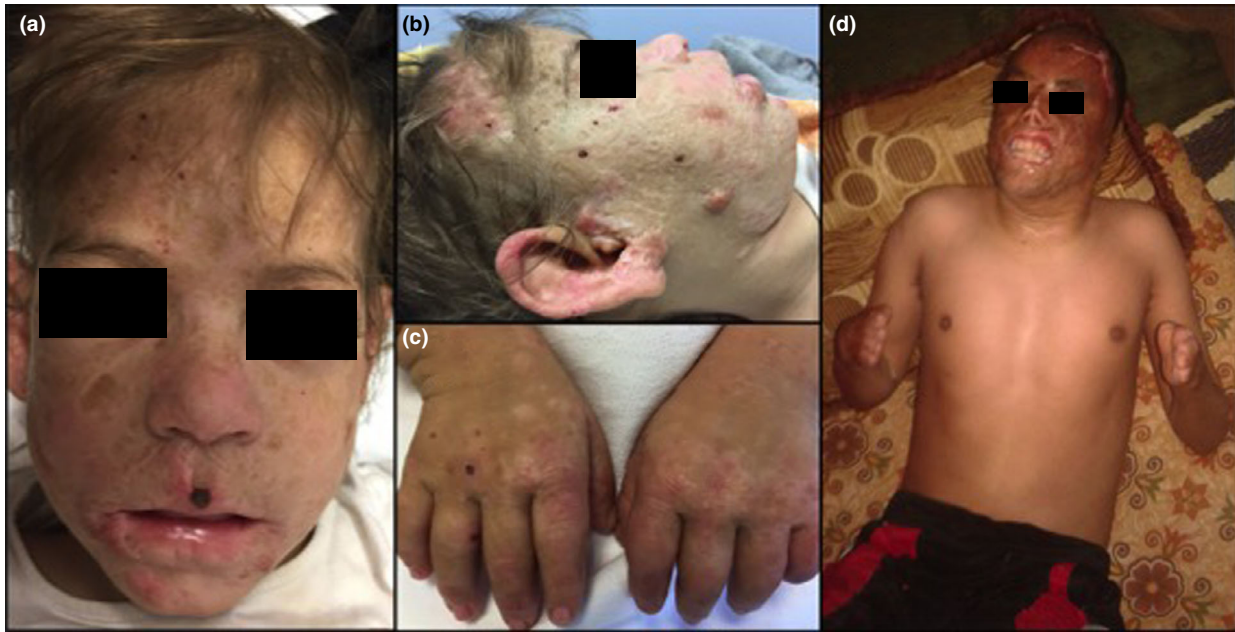
The findings in our patient were atypical in three respects: (i) the symptoms were evident very early during infancy, (ii) they progressed rapidly and (iii) they were more severe than usual for VP, resulting in mutilation of the peripheries in one of the individuals. This raised the suspicion of homozygous VP or the co-occurrence of two forms of porphyrias. Genetic testing showed a novel homozygous mutation in the PPOX gene exclusively. Few cases of homozygous VP have been described in the literature; 70% of these were compound heterozygous and almost all of them had asymptomatic carrier parents.<sup>3–6</sup> Those patients will have a very low activity level of the PPOX enzyme and may have impaired mental development, photosensitivity, dwarfism, hand deformities and nystagmus, as had our patients. Moreover, patients 'homozygous' for VP interestingly show elevated protoporphyrin levels in the erythrocytes, the explanation of which

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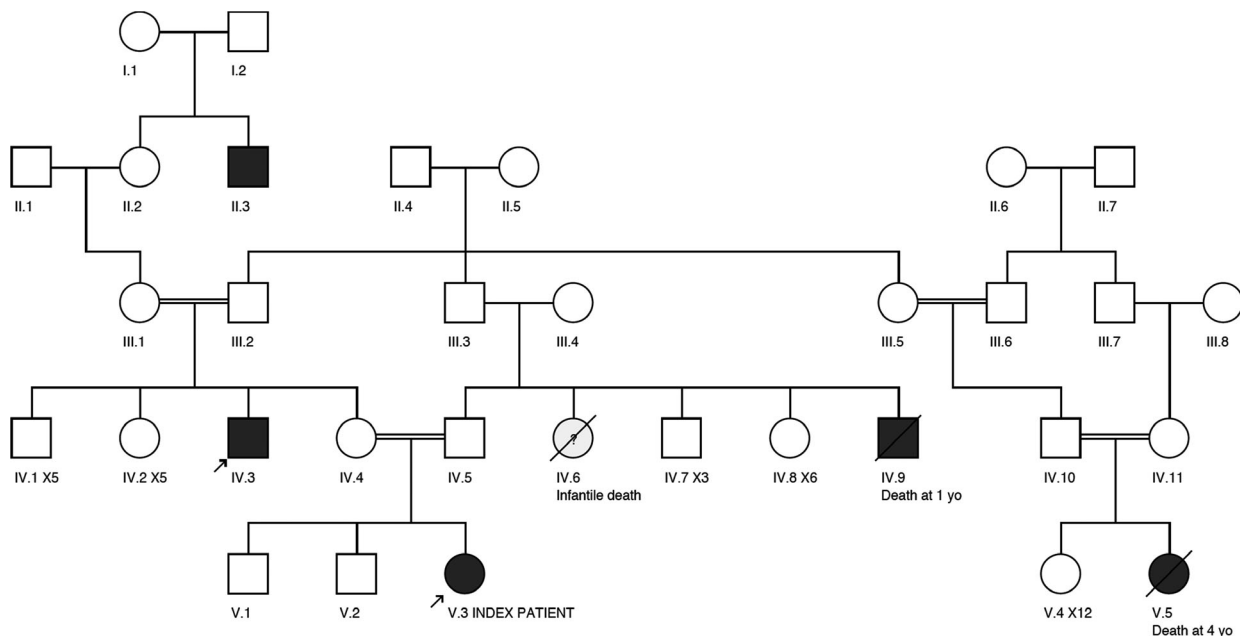
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**Figure 1** Two related patients with the recessive form of variegate porphyria. (a–c) The index patient had (a,b) severe scarring affecting sun-exposed areas with atrophic and hypertrophic scars, and (c) milia and brachydactyly. Her maternal uncle had severe mutilation of the digits).



**Figure 2** Pedigree showing several affected members in a multigenerational consanguineous family, causing death at a young age. The reported patients are indicated by arrows; the index patient was a 3-year-old girl.

remains unknown. This finding has also been reported in cases of homozygous porphyria cutanea tarda and homozygous hereditary coproporphyria and thus appears to be a general consequence of severe

enzymatic defect in the porphyrin–haem biosynthetic pathway. We speculate that this may be due to an alteration of the activity of the mitochondrial ferrochelatase secondary to the toxic milieu, resulting in

the upstream accumulation of protoporphyrin in the red blood cells. Further studies are needed to confirm this mechanism.

In conclusion, homozygous VP presents in a more exaggerated form than the heterozygous condition, and should raise awareness among clinicians to strictly eliminate factors that may precipitate the acute attacks such as porphyrinogenic drugs or alcohol.

## References

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## CPD questions

### Learning objective

To learn about the differences in phenotypes and severity seen in the rare homozygous form of variegate porphyria compared with the usual autosomal dominant heterozygous form.

### Question 1

Which of the following statements about variegate porphyria (VP) is correct?

- (a) VP is considered a cutaneous form of porphyria.

- (b) VP is caused by a defect in the activity of a cytosolic enzyme.
- (c) One inherited mutation in the protoporphyrinogen oxidase gene is sufficient to cause VP.
- (d) VP mainly presents in early childhood.
- (e) Cutaneous manifestations of VP are usually severe photosensitivity with no blistering.

### Question 2

Which one of the following options best describes the distinguishing characteristics of the homozygous form of variegate porphyria (HVP)?

- (a) HVP usually presents later in adulthood with a milder clinical presentation than heterozygous VP.
- (b) Parents of patients with HVP are usually affected.
- (c) Patients with HVP usually have impaired mental development, photosensitivity, dwarfism, hand deformities and nystagmus.
- (d) HVP is associated with elevated protoporphyrin levels in the erythrocytes, similar to the autosomal dominant heterozygous form of VP.
- (e) 30% of the HVP cases reported are compound heterozygous.

## Instructions for answering questions

This learning activity is freely available online at <http://www.wileyhealthlearning.com/ced>

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at <http://www.wileyhealthlearning.com/ced> and answer the CPD questions
- Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

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