PEDIATRIC VARIEGATE PORPHYRIA: CUTANEOUS CLUES TO A HIDDEN METABOLIC DISORDER

Milovanovic U.[1], Weimer D.S.[1], Risman S.[1], Ramadoss T.[1], Fouts A.[1], Shah S.H.[2], Ghafoor R.[2]
[1]Nova Southeastern University Dr. Kiran C. Patel College of Allopathic Medicine, Fort Lauderdale, FL, USA
[2]Jinnah Postgraduate Medical Center, Sindh, Pakistan

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Abbreviations **PPOX** = protoporphyrinogen oxidase; **VP** = variegate porphyria.

Case report. A 12-year-old boy presented to the outpatient clinic with facial erythema and diffuse burning sensations for two weeks. He also reported intermittent blistering across his hands, feet, and face, which resolved after a few days but left residual scarring. These symptoms had occurred intermittently since childhood, but a formal diagnosis had never been made. The patient noted symptomatic relief with avoidance of direct sunlight and application of cold compresses. There was a significant family history of similar manifestations, including a 16-year-old sister with milder cutaneous symptoms; his two brothers and another sister were healthy.

In addition to the cutaneous symptoms, over the preceding year the patient experienced four episodes of nausea, severe abdominal pain radiating to the thigh and lumbar region, headache, generalized weakness, loss of consciousness, and dark-colored urine. Each episode required hospitalization, with symptom resolution after three to four days.

On physical examination, the patient's vital signs were within normal limits, and his height and weight were appropriate for age. Cutaneous examination revealed pallor, multiple depressed varioliform scars, and diffuse hypertrichosis across the face (Fig. 1). Tense blisters, multiple scars, and milia were appreciated over the dorsum of the hands and feet bilaterally (Fig. 2). All other systems were within normal limits. Considering the clinical presentation, family history, and physical findings, further diagnostic testing was ordered.

Laboratory testing revealed a hemoglobin level of 8.4 g/dL (normal range 11.5 to 15.5 g/dL for age), while other blood parameters, including total leukocytes and platelets, were within normal limits. Liver and renal function were appropriate, and viral etiology tests were negative. A plasma porphyrin assay revealed increased uroporphyrin in the urine as well as protoporphyrin and coproporphyrin in the feces. Considering the cutaneous and neurovisceral symptoms, family history, physical examination, and laboratory findings, a diagnosis of variegate porphyria (VP) was made.

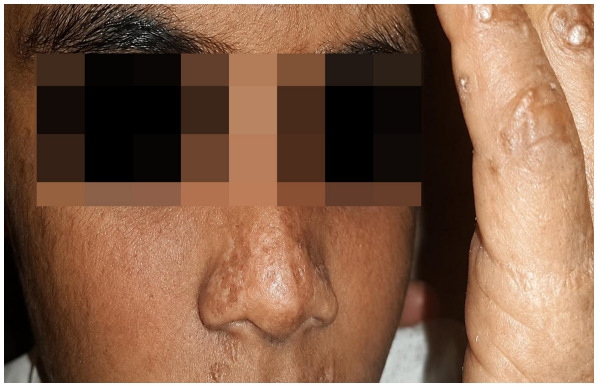


Fig. 1

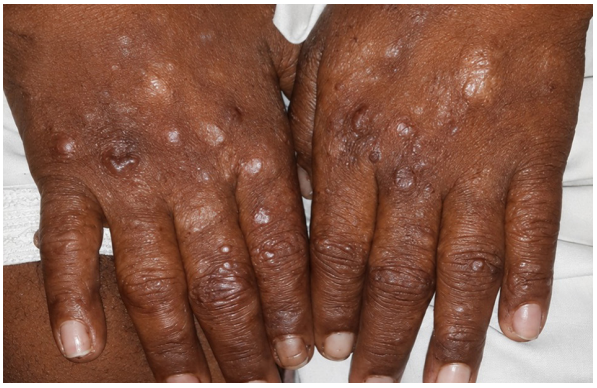


Fig. 2

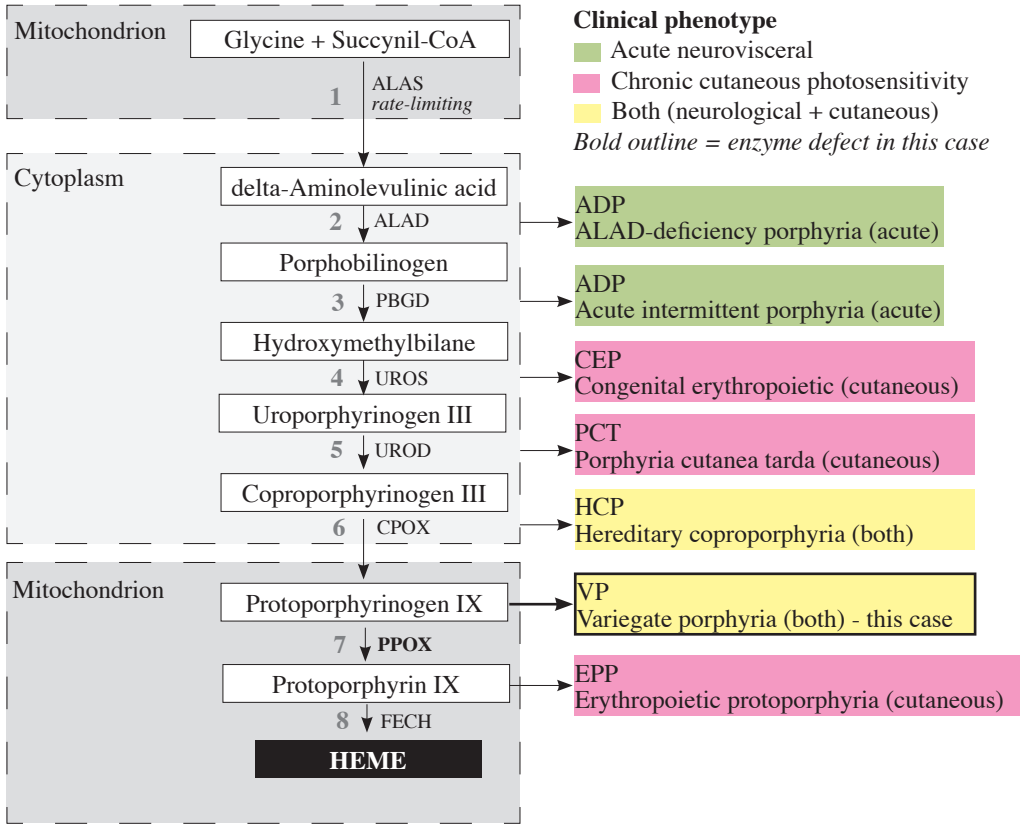
Fig. 1, 2: Variegate porphyria in a 12-year-old boy: scars on the face (Fig. 1) and on the back of the hands (Fig. 2).

Discussion. Hereditary porphyrias are inherited metabolic disorders affecting critical enzymes of the heme biosynthesis pathway (Scheme). These diseases interfere with the production of hemoglobin and cytochrome P450 enzymes in the bone marrow and liver, respectively (9, 10). The accumulation of toxic intermediates, such as porphyrins, secondary to enzyme deficiencies, leads to the symptoms found in porphyria (9,10).

Recognized as the most common neurocutaneous porphyria, variegate porphyria (VP) is an inherited autosomal dominant disorder, though it exhibits low penetrance with variable expressivity (5, 6). VP has been extensively studied in Dutch descendants in South Africa, where incidence is higher due to a founder effect (8). The prevalence in these populations is estimated at approximately three per 1,000 individuals (8).

The pathophysiology of VP involves dysfunction of the protoporphyrinogen oxidase (PPOX) enzyme, leading to impaired conversion of protoporphyrinogen to protoporphyrin (Scheme) (5, 6, 11). This results in the accumulation of protoporphyrinogen and other upstream metabolites (10, 11). In normal metabolism, excess protoporphyrinogen within hepatocytes is oxidized to protoporphyrin and eventually excreted in feces (10). In VP, however, protoporphyrinogen levels are elevated, accompanied by increased concentrations of uroporphyrin in urine and protoporphyrin, uroporphyrin, and coproporphyrin in both feces and urine (12). Exacerbating factors, such as cytochrome P450-inducing drugs, steroid hormones (e.g., progesterone), alcohol, tobacco, fasting, metabolic stress, and infections, can trigger acute attacks (13, 14). These factors contribute to symptomatic episodes through increased activity of aminolevulinic acid synthase (ALAS) (Scheme), the rate-limiting enzyme in heme synthesis (13, 14).

The cutaneous manifestations of VP include blistering in sun-exposed areas, such as the hands and feet, and diffuse hypertrichosis. These symptoms occur due to photoactivation of porphyrins, specifi-



cally on exposure to Soret bands in UV light, at wavelengths of approximately 408 nm (15). Upon activation, porphyrins undergo a transition to an excited triplet state, generating reactive oxygen species that contribute to cell membrane destruction (6, 14).

Neurovisceral symptoms in VP include abdominal pain, vomiting, autonomic dysfunction, alterations of consciousness, and generalized weakness with back and extremity pain (5, 6). These are thought to result from neurotoxic metabolites such as aminolevulinic acid and from electrolyte imbalances, such as hyponatremia. Aminolevulinic acid-induced demyelination of neuronal axons can lead to neuropathy and weakness, while hyponatremia may contribute to altered consciousness (2, 16).

Urinary changes, including dark- or tea-colored urine, are a hallmark of hereditary porphyrias, though not limited to VP. This is due to the oxidation of porphobilinogen to porphobilin upon exposure to air and light (2, 15). Although nonspecific, this finding is valuable in narrowing the differential diagnosis.

Two primary factors contribute to the variability in clinical presentation between porphyria subtypes. There are over 200 pathological variants of the *PPOX* gene, many with unknown consequences. In addition, porphyrias present with variable expressivity, so individuals who are genetically predisposed may develop mild to severe disease (17, 18, 19, 20).

Although porphyrias are rare in childhood, presenting primarily in homozygous females between 15 and 45 years of age, VP can present in pediatric populations (21). In particular, pediatric disease with onset before puberty is often associated with homozygous or heteroallelic *PPOX* mutations. These patients often present with mental and/or growth developmental delays in addition to the characteristic symptoms of VP (17, 22). Erythropoietic protoporphyria remains the most common porphyria type in children (6). Diagnosis in children is challenging due to the rarity of the disease, limited research, and its variable presentation, which often leads to misdiagnosis. Differential diagnoses for a VP presentation can include seizure disorders, autoimmune disorders, blistering skin conditions, and tyrosinemia (2).

Although VP should be considered based on clinical presentation, laboratory testing helps narrow the differential diagnosis. In this patient, initial serological testing demonstrated anemia without leukocytosis or evidence of infection. While anemia is not a hallmark of VP, it may reflect a concurrent process or an alternative explanation warranting further investigation (12). Urine testing during an acute attack typically reveals elevated porphyrin precursors, including porphobilinogen, while fecal analysis characteristically demonstrates markedly elevated porphyrins with roughly equal proportions of coproporphyrin III and protoporphyrin, a pattern that distinguishes VP from hereditary coproporphyria, in which coproporphyrin III predominates (12). Plasma fluorescence scanning revealing a peak at approximately 626 nm is highly sensitive and specific for VP and represents the most sensitive method for establishing the diagnosis, particularly in asymptomatic patients (12). Imaging, such as ultrasound, can help rule out other pathologies, though findings are typically unremarkable in VP unless the disease has progressed. Lastly, genetic testing for *PPOX* mutations, along with measurement of residual PPOX activity, can narrow the diagnosis, though these tests may be limited by economic and accessibility factors.

The International Porphyria Network has established guidelines for the management of acute attacks and preventive measures in VP (6, 23). Prevention is critical due to the life-threatening nature of acute attacks. Conservative measures include avoiding porphyrinogenic triggers, minimizing metabolic stress, reducing sun exposure, and maintaining an appropriate diet with adequate carbohydrates and sodium. Patients should avoid drugs that induce cytochrome P450 enzymes, such as barbiturates and sulfonamide antibiotics, as these can exacerbate the condition (5, 6). Sun protection measures, such as zinc oxide sunscreen and protective clothing, are essential. In our case, the patient was prescribed oral beta-carotene 90 mg daily to mitigate phototoxic reactions and protect against further photodamage (24).

Notable limitations of this case include failure to execute genetic testing due to limited accessibility. Genetic testing for the extended family could have provided a more in-depth analysis of the disease process, though it is not required for diagnosis. Future research should focus on the development of predictive biomarkers and targeted therapies to enhance disease monitoring and treatment efficacy.

This case is distinguished by the combination of prolonged diagnostic delay and recurrent neurovisceral predominance in a pediatric patient, despite longstanding cutaneous manifestations. While neurovisceral symptoms are common in VP, diagnostic delay is also common, as demonstrated in our patient, who underwent multiple hospitalizations before a diagnosis was established. From this case, the authors aim to emphasize the importance of considering porphyria in photosensitive blistering disorders in pediatric patients, particularly when accompanied by unexplained abdominal or neurologic symptoms. Earlier recognition may significantly reduce morbidity by preventing recurrent acute attacks and avoiding unnecessary testing and interventions.

Conclusion. This case of variegate porphyria in a 12-year-old patient exemplifies the diagnostic challenges posed by its overlapping cutaneous and neurovisceral features. Accurate diagnosis requires integrating family history, clinical suspicion, and targeted biochemical testing. Greater clinical awareness and timely intervention remain essential to prevent complications and improve outcomes for patients with VP.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Address to:
Dr. Una Milovanovic
Nova Southeastern University Dr. Kiran C. Patel College of Allopathic Medicine
30 SW 12th St, Dania Beach, Florida 33004, USA
e-mail: unamilov@yahoo.com

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