Acute Variegate Porphyria in a Professional Bodybuilder after Starting a High-protein Diet and Treatment with Testosterone

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Variegate porphyria (VP) is a rare inherited disorder caused by a deficiency of protoporphyrinogen oxidase (PROX). Clinical symptoms include viscer-neurological symptoms or light-triggered cutaneous manifestations, such as blister formation and erosions. Diagnosis of VP is based on clinical features, urine and stool diagnostics, and plasma fluorescence scan with a specific emission maximum, and may be complemented by molecular genetic testing. We report the first onset of symptoms of VP in a man undergoing a strict high-protein diet and anabolic steroid abuse.

CASE REPORT

A 24-year-old man presented to our outpatient clinic with a 2-week history of strong itching on his arms, shoulders and face. A burning sensation, skin erosions and painful blisters had occurred in light-exposed areas on the back of his hands, dorsal forearms and face within the last 3 days. Recently, he had had muscle cramps and a reddish-brown urine. The patient reported being a professional competitive bodybuilder, having had testosterone and steroid injections for a bodybuilding contest. Six weeks prior to presentation he had initiated a high-protein, low-carbohydrate diet, including daily intake of 400 g protein and nutritional supplements. His family history was unremarkable for chronic diseases.

Skin examination revealed erythematous plaques and crusty-coated erosions on the cheeks, nasal bridge, dorsal hands and extensor side of the forearms (Fig. 1A). Single bulging blisters were visible on the back of the hands and on the fingers (Fig. 1B). Mucosal sites were unremarkable. A urine sample showed reddish-brown discoloration after sunlight exposure (Fig. 1C and D).

Histopathology from the right index finger revealed subepidermal blister formation with scarce inflammation (Fig. 2). This is consistent with VP, but also occurring in other blistering (pseudo-)porphyrias. Direct immunofluorescence staining revealed a broad deposition of IgG along the basement membrane, broad perivascular deposition of IgG and IgA, weak perivascular deposition of IgM, and granular perivascular deposition of C3c. Elevated total porphyrin (2,564 µg/24 h, cut-off < 145.0 µg/24 h) with predominance of coproporphyrin (2,236 µg/24 h) was found in a 24-h urine collection. Faecal examination showed a significant elevation of porphyrins (383.5 µg/g, cut-off < 85) with predominance of protoporphyrin (272.2 µg/g, cut-off < 80). In addition, coproporphyrin level was elevated (108.2 µg/l, cut-off 24 µg/l) mainly isomer III (88.7%, range 25–35%) compared with isomer I (11.3%, range 65–75%). Plasma fluorescence scan provided an emission maximum at a wavelength of 624 nm, characteristic for VP.

On the basis of clinical presentation, serological, urine, stool and histological findings VP was diagnosed. Characteristic plasma...
florescence scan also confirmed the diagnosis of VP in the patient’s younger, asymptomatic brother. While no further attack of VP has occurred, the patient still has residual scarring, dysesthesia, increased photosensitivity and friable skin in light-exposed areas.

**DISCUSSION**

Porphyrias comprise a group of clinically heterogeneous metabolic disorders, mostly caused by inherited defects in enzymes involved in heme biosynthesis (1–4) and subsequent accumulation of biosynthetic intermediates, predominantly in the liver (hepatic porphyrias) or erythrocytes (erythropoietic porphyrias) (1, 4). Acute and non-acute porphyrias can be distinguished (4). There are 4 different types of acute hepatic porphyrias (AHPs): acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), 5-aminolevulinic acid-dehydratase porphyrin and VP (2). Common triggers of an acute attack include smoking, alcohol, infection, diet, stress or porphyrinogenic drugs, increasing heme biosynthesis by upregulating aminolevulinic acid synthase 1 (ALAS1), the rate-limiting enzyme for heme biosynthesis (5). AHPs commonly cause acute visceroneurological symptoms (3) while HCP and VP may feature additional or exclusive characteristic cutaneous reactions in light-exposed skin (3, 5, 6). VP is caused by a deficiency of the mitochondrial enzyme protoporphyrinogen oxidase (PPOX) due to a mutation in the encoding PPOX gene, located on chromosome 1q22-23 (2, 7, 8), leading to reduced oxidation of protoporphyrinogen to protoporphyrin (8, 9). At least 177 different PPOX mutations resulting in VP have been described (9). The prevalence of this autosomal dominant inherited disease is reportedly 0.5–2 per 100,000 (7), with variable penetrance (3, 10). While most heterozygotes remain asymptomatic throughout life, a minority develops one or more attacks (8). Attacks occur typically after puberty, more frequently in women than in men, and may be precipitated by drugs, dieting or other triggers (9).

Diagnosis of VP is based on clinicopathological features, analysis of porphyrin metabolites in urine, stool and plasma fluorescence diagnostics (9). The biochemical diagnosis of VP should be complemented by confirmatory mutation analysis in order to identify the pathogenic PPOX variant and to offer appropriate counselling to patients with VP (2, 3, 4, 9). As the current patient and his brother declined genetic counselling, information on the underlying pathogenic variant in PPOX by molecular genetic testing is not available.

It is assumed that epidermal blistering in VP is caused by an overproduction of intermediate products of heme biosynthesis (5) and subsequent release of reactive oxygen species during light exposure (8). The reddish-brown urine, associated with VP, results from porphyrins and oxidation of porphobilinogen to porphobilin (6). Increased plasma and urinary level of porphobilinogen are seen during acute episode, whereas during remission values may normalize (3, 8). Faecal porphyrin, predominantly protoporphyrin and coproporphyrin III, are elevated in VP (8). Fluorescence scanning shows a specific plasma porphyrin emission peak at a wavelength of 626 ± 1 nm (3, 9, 11). Guidelines for the clinical management of AHPs are available (1, 6). Therapy of acute attacks of porphyria includes carbohydrate intake (1, 10) or intravenous blood-derived heme (4, 6). In a recently published phase 3 clinical study, givosiran, a subcutaneously administered small RNA therapeutic targeting ALAS1, mediated at 74% reduction in the rate of porphyria attacks in patients with AIP (12) and is now US Food and Drug Administration-approved for the treatment of AHPs, including VP.

Long-term complications include hepato cellular carcinoma (HCC), nephropathy and renal dysfunction (3). All patients with VP aged 50 years or older should undergo liver sonography every 6 months to detect HCC as early as possible (9). Annual monitoring of serum creatinine is recommended in symptomatic patients (13). Neurological symptoms are associated with elevations in aminolevulinic acid and porphobilinogen (2).

The current patient’s high-protein/low-carbohydrate diet and anabolic steroid abuse are a probable cause of his symptomatic porphyria. Di Pierro et al. recommend high carbohydrate and antioxidants intake for patients with porphyria. Vitamin D monitoring and supplementation is advisable for porphyria patients with cutaneous symptoms, as they may follow strict sun-protection measures (14). According to Handschin et al. (10), low-carbohydrate diet or fasting promotes acute attacks of hepatic porphyria by inducing ALAS1 through peroxisome proliferator-activated receptor gamma coactivator 1-α. Thus, patients should be encouraged to eat regularly, especially carbohydrate-rich food and normal amounts of protein (4). Steroidal hormones, such as progestins or androgens and hormone-like drugs, are known inducers of hepatic ALAS1 with an aggravating effect on AHPs. VP has been reported after intake of lynestrenol, a synthetic progestin (11). While to the best of our knowledge, misuse of exogenous testosterone has not been previously described as a trigger of the first manifestation of VP symptoms, induction of acute HCP by the androgenic anabolic steroid methandrostrotenolone has been reported (15).

This case highlights the importance of patient education regarding sun-protection measures, triggers of acute attacks and genetic counselling for patients with VP (3, 6, 9).

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