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An Unusual Cause of Headache and Fatigue in a Division 1 Collegiate Athlete

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Abstract: Variegate porphyria (VP) is an autosomal dominant disorder of porphyrin metabolism. We report a case of a 21-year-old male collegiate athlete who complained of recurrent headache and fatigue. Extensive testing after initial presentation failed to identify a cause. Months later, his grandmother was diagnosed with VP after being hospitalized; hence, he was tested. He was positive for a heterozygous missense mutation, R168H, in one protoporphyrinogen oxidase allele. This case highlights a rare disorder of heme synthesis that should be considered in the differential diagnosis of exertional fatigue and headaches in athletes. When other more common causes of fatigue and/or headache are unable to be identified, a more focused history and examination may lead to a more unusual but crucial diagnosis. To our knowledge, there are no reported cases of this condition in Division I collegiate athletes.

Key Words: Variegate, Porphyria, Protoporphyrinogen oxidase, cutaneous, Fatigue

(*Clin J Sport Med* 2017;27:e58–e59)

INTRODUCTION

Variegate porphyria (VP) is an autosomal dominant disorder of porphyrin metabolism, resulting in deficient activity of protoporphyrinogen oxidase (PPOX), the seventh enzyme in the heme biosynthetic pathway. This condition was initially discovered and reported in South Africa in 1937 and has rarely been described in North America, with no known incidence figures as of yet. We report a very unique case of a 21-year-old male collegiate athlete who was diagnosed with VP, months after presenting with complaints of recurrent headache and fatigue and with a history of intermittent blistering cutaneous lesions in sun-exposed areas as a child.

CASE REPORT

This case highlights a 21-year-old senior male collegiate Division 1 athlete who presented to his college athletic training room with complaints of recurrent headache and generalized fatigue.

He had developed a headache for the past 2 weeks after being checked in the chest during a game. He also noted intermittent episodes of severe fatigue. He had a history of multiple previous concussions but concussion was thought to be unlikely due to a normal physical examination and cognitive testing. He improved with rest but headaches recurred with early noncontact play. Buffalo Concussion Treadmill Testing[2] was normal and physical therapy evaluation revealed poor cervical proprioception. He only had mild improvement with cervical and vestibular PT.

The patient described a history of similar fatigue episodes starting in late childhood. Evaluations for anemia, iron deficiency, and other causes had been normal. Alcohol consumption seemed to exacerbate the episodes. Initially, his symptoms were consistently related to exertion but then became sporadic and unrelated to sport. Sometimes he could hardly get through a game, yet play "the best game of his life" in the next game. He would sometimes sleep 12 to 14 hours a day during the season. He eventually had to leave the team because of severe fatigue. On review of systems, he gave a history of similar headache episodes that were occasionally associated with abdominal pain, nausea, diarrhea, lightheadedness, "spotty vision", paresthesias, and extreme generalized weakness. On further questioning, he reported a history of numerous photosensitive skin lesions consisting of pus-filled welts that scarred after draining and healing.

Physical examination on initial presentation revealed stable vitals and a normal appearing 21-year-old male. Pertinent positives included multiple scattered dark scarred lesions predominantly at previous injury sites including the left outer thigh and left forearm (Figure 1). The remainder of his examination revealed normal fundi, no lymphadenopathy, normal heart and lung findings, a normal thyroid examination, an unremarkable abdomen without hepatosplenomegaly, as well as normal musculoskeletal and neurological examinations.

Differential diagnosis: Posttraumatic headache, postconcussion syndrome, migraine headache, obstructive sleep apnea, anemia, hypothyroidism, overtraining syndrome, depression, chronic fatigue syndrome, substance abuse, somatization disorder, chronic sinusitis, polycythemia (secondary), adrenal insufficiency, brain tumor.

Initial laboratory testing was essentially normal:

Complete Blood Count: WBC 3.9×10^9/L, hemoglobin 4.95 mmol/L, hematocrit 44.4 mg/dL, platelets 172×10^9/L, mean corpuscular volume 89.7 fL, mean corpuscular hemoglobin concentration 34.5 g/dL.

Basic Metabolic Profile: Na 139 mmol/L, K 5.1 mmol/L, chloride 103 mmol/L, Ca 10.0 mg/dL, glucose 91 mg/dL, creatinine 0.89 mg/dL, blood urea nitrogen 13 mg/dL; Liver Function Testing: alkaline phosphatase 62 IU/L, aspartate aminotransferase 17 IU/L, alanine aminotransferase 17 IU/L, total protein 7.2 g/L.

Thyroid Function Testing: thyroid stimulating hormone: 1.67 mIU/L, total T4 6.0 μg/dL.

Further diagnostic testing included a nocturnal polysomnogram and brain magnetic resonance imaging with and without contrast, all of which were normal.

About 8 months after his initial presentation, the patient's grandmother was hospitalized for several weeks secondary to

Submitted for publication July 28, 2015; accepted March 16, 2016.
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The authors report no conflicts of interest.
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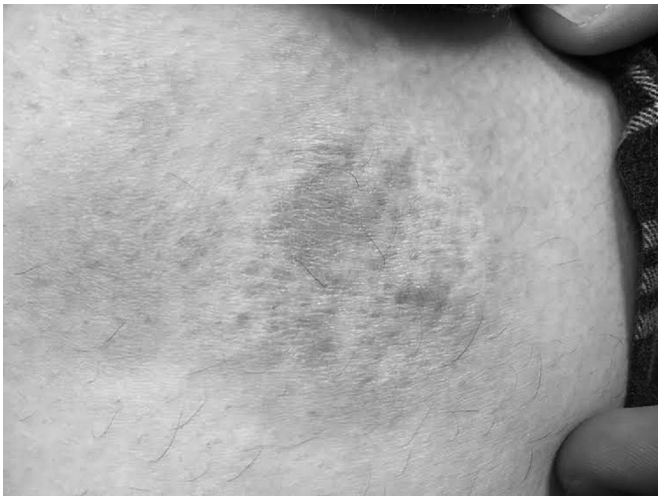

FIGURE 1. Scarred, hypopigmented skin lesion from previous welt/blister formation.

abdominal pain and what seemed to be a severe reaction to a sulfa medication. An astute physician made the diagnosis of a rare form of porphyria and so the patient and his extended family were tested for this genetic disorder. He tested positive for a heterozygous missense mutation, R168H, in one PPOX allele that established the diagnosis of VP. The mutation was positive in all 3 siblings, his mother and all 4 of his maternal aunts (Figure 2).

The patient was counseled and educated about the nature of the diagnosis. His treatment protocol included avoidance of specific triggers, including alcohol and extreme exertion. He was also given a list of specific medications that could precipitate acute porphyria attacks.

Since avoiding triggers, the patient has been doing very well. He has not required any hospitalizations for acute porphyria attacks. He is currently not participating in competitive sports.

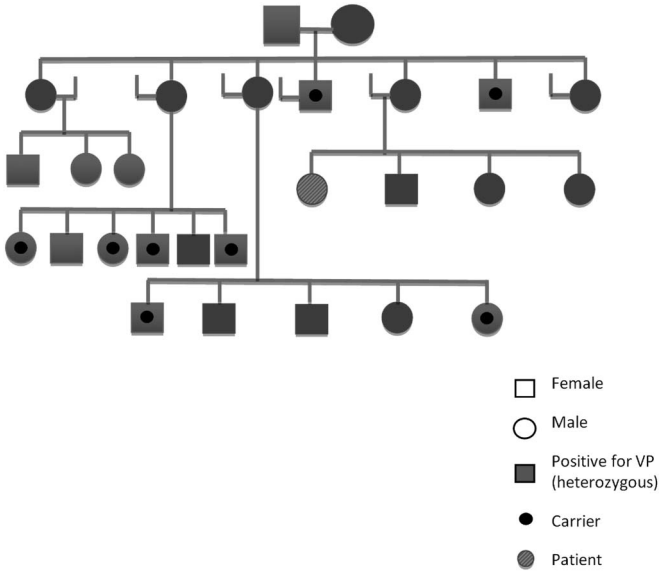

FIGURE 2. Patient family tree.

DISCUSSION

The porphyrias are a group of hereditary disturbances of porphyrin metabolism characterized by an increase in formation and excretion of porphyrins or their precursors. Variegate porphyria is an autosomal dominant disorder of porphyrin metabolism as a result of a mutation in one or both PPOX oxidase alleles. This affects production of the seventh enzyme in the heme biosynthetic pathway, leading to inability in converting protoporphyrinogen IX to protoporhyrin IX, and in turn decreased heme synthesis.[1] As heme breaks down, the body attempts to compensate by accelerating the rate of heme production, which again results in heme breakdown and a vicious cycle of incomplete heme synthesis. Most commonly, patients inherit a heterozygous mutation that reduces PPOX activity by 50%, and they therefore do not typically suffer acute porphyria attacks.[1] Homozygous carriers experience more life-threatening manifestations because of near-complete enzyme deficiency. Certain triggers may provoke symptoms in the form of either acute neurovisceral manifestations (abdominal pain, fatigue, headache, nausea, and diarrhea) or chronic blistering skin lesions, or both.[1,3]

Triggers include drugs (ie sulfonamides, antifungals, anticonvulsants, etc.), alcohol, physical exertion, metabolic stress, steroids, and infection.[1] In the case of our patient, severe exertion during sport activity provoked symptoms of fatigue because of decreased oxygen carrying capacity during periods of increased tissue demand. The skin manifestations are a result of porphyrins being transported in the plasma, from the liver to skin, where photoactivation by long wave ultraviolet light causes release of tissue-damaging oxygen species.[1] As was made evident by this case, patients with VP can present with a variety of vague symptoms, such as headache and fatigue, which may mimic other more common conditions.

Treatment of VP involves avoiding specific triggers and supportive care for individual acute symptoms and laboratory findings (ie electrolyte and fluid replacement). Hemin, an iron containing porphyrin IX, and/or glucose loading are often used for more severe acute attacks that require hospitalization to prevent life-threatening manifestations such as renal impairment, hyponatremia, and seizures.[3] Glucose therapy reduces porphyrin biosynthesis in the liver and therefore excess excretion of heme precursors. This is why patients are advised to avoid carbohydrate restriction or fasting. Patients typically recover from acute attacks and long-term prognosis and outcome are quite favorable. Morbidity and mortality have both decreased over the past few decades thanks to improve management of acute and chronic symptoms, as well as identification of exacerbating factors.[1,3]

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