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A Unique Neuropsychiatric Syndrome in Variant Hereditary Coproporphyria: Case Report and Review of the Literature

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Abstract

Hereditary coproporphyria (HCP) is the third most common of the acute porphyrias, after acute intermittent porphyria and variegate porphyria. It is caused by decreased activity of the sixth step in the heme biosynthetic pathway. Here we present a case of a woman with HCP who has experienced a wide variety of symptoms over several years. Most interesting among these is a unique neuropsychiatric syndrome marked by severe confusion, disorientation, and abnormal behavior. The literature is reviewed regarding the pathophysiology and management of neuropsychiatric manifestations of porphyria. As many other diagnoses are often considered before the diagnosis of porphyria is made, clinicians should keep in mind the highly variable neurological and psychiatric symptoms of porphyria.

Keywords: Coproporphyria; Neuropsychiatry

Introduction

Hereditary coproporphyria (HCP) is the third most common of the acute porphyrias, after acute intermittent porphyria and variegate porphyria [1, 2]. It is caused by decreased activity of coproporphyrinogen oxidase in the heme biosynthetic pathway [3]. This enzyme catalyzes the conversion of coproporphyrinogen to protoporphyrinogen [3]. HCP is an autosomal dominant disorder with variable penetrance [4]. As with other porphyrias, symptoms of HCP are numerous and variable, but can include abdominal pain, autonomic dysfunction, neuropathy, as well as cutaneous and neuropsychiatric manifestations [5-8]. These neuropsychiatric manifestations include, but are not limited to, confusion, disorientation, hallucinations, and delirium [9-11]. Similar to other porphyrias, drugs are thought to be responsible for inducing most acute attacks [4].

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Case Report

A 19-year-old woman was referred to the hematology/oncology clinic by her primary care physician due to a 7-month history of episodes of dizziness, nausea, and abdominal pain. Associated symptoms included fatigue and constipation. Approximately 1 - 2 days after these episodes, she would develop reddish orange urine, without any pain or discomfort upon urination. Upon further review of her history, she reported two similar episodes when she was a child, the most recent one occurring around age 8. During her teenage years, she was an avid exerciser and adhered to a high carbohydrate diet; she did not experience any attacks during this time. However, in the 7 months prior to presentation, her activity level decreased and she discontinued her high carbohydrate diet; she had experienced approximately six episodes in that time.

Physical examination, including skin exam, was unremarkable. Initial laboratory studies showed hemoglobin 11.3 g/dL, white blood cell count $9.8 \times 10^3/\mu L$, platelets $172 \times 10^3/\mu L$, ALT 15 IU/L, AST 16 IU/L, alkaline phosphatase 53 IU/L, total bilirubin 0.9 mg/dL, lipase 25 IU/L, and TSH 1.00 µIU/mL. The 24-h urine collection was negative for porphobilinogen, but showed a delta-aminolevulinic acid (ALA) level of 8.0 mg (normal 1.3 - 7.0 mg), uroporphyrin level of 18 µg (normal 0 - 20 µg), and a coproporphyrin level of 158 µg (normal 0 - 95 µg). She was initially managed conservatively: it was recommended to her that she resume her exercise regimen, increase her carbohydrate intake, and maintain adequate hydration. When she again presented with complaints of abdominal pain and urine discoloration, she was treated with an infusion of dextrose and water.

Over the next 4 years, the patient experienced numerous attacks which presented in a variable fashion. Almost 1 year after her initial diagnosis, she presented with a 4-week history of erythematous, pruritic, urticarial lesions involving the legs, shoulder, back, chest, face and hands. These lesions were made worse by sun exposure and were initially responsive to prednisone. Infusions of dextrose and water were also helpful in relieving her cutaneous manifestations.

Approximately 4 years after her initial presentation, during a pregnancy, she began to experience worsening cogni-

Table 1. Summary of the Course of the Patient's Symptoms Since Her Presentation to Our Clinic

Date	Presenting symptoms	Treatment
2005 - 2008	Lethargy, abdominal pain, ileus, frequent UTIs, red urine, poor school performance	Sought treatment out of state
May 2008 (age 19)	Nausea, dizziness, abdominal pain, red urine, frequent UTIs (first presentation to our clinic)	Recommended increased carbohydrate intake, increased exercise
August 2008 - May 2009	Recurrent attacks of abdominal pain, nausea, red urine	Dextrose 5% in water
June 2009	Abdominal pain; diffuse erythematous, pruritic, urticarial lesions	Hematin 4 mg/kg × 2 doses
December 2009	Admitted to the hospital for severe abdominal pain, dysuria, red urine	Hematin 4 mg/kg × 2 doses; Ciprofloxacin
February 2011	Admitted to the hospital for arthralgias, abdominal pain, fever while 18 weeks pregnant (otherwise, symptoms had been very mild during pregnancy)	Hematin 4 mg/kg × 2 doses
June 2011	1 - 2 days after cesarean section delivery of daughter, experienced abdominal pain, headache, and difficulty with concentration and memory, including being unable to recall when her daughter had last fed	Hematin 4 mg/kg × 1 dose
December 2011	Admitted for generalized weakness, malaise, dizziness, headache, shortness of breath, and confusion while 7 weeks pregnant	Hematin 4 mg/kg × 3 doses
June - July 2012	Word-finding difficulties, trouble concentrating, performing tasks out of normal order (e.g., drying dishes before rinsing them), get lost while driving to familiar places, initiating tasks but then forgetting to complete them (e.g., only cleaning half of a surface at home)	Hematin 4 mg/kg × 5 doses
October 2012	Continued confusion as above; pruritic, urticarial lesions; arm pain	Hematin 4 mg/kg 5 days per week × 3 weeks, resulting in total clearing of her cognitive symptoms
November 2012	Confusion, difficulty concentrating, abdominal pain, paresthesias in upper extremities	Hematin 4 mg/kg × 7 doses
December 2012 - January 2014	Confusion, difficulty concentrating, paresthesias in upper extremities	Hematin 4 mg/kg twice weekly, then once weekly beginning in May 2013, then tapered to PRN-basis
March 2014	Fatigue, ileus, nausea, vomiting	Hematin 4 mg/kg × 1 dose
June 2014	Fatigue, myalgias while 26 weeks pregnant	Hematin 4 mg/kg × 2 doses
September 2014	Fatigue, myalgias, arthralgias, headache	Hematin 4 mg/kg × 1 dose
January 2015	Abdominal pain, right arm pain	Hematin 4 mg/kg × 2 doses
March 2015	Abdominal pain, dysuria, generalized numbness and tingling	Hematin 4 mg/kg × 1 dose

Note the evolution from primarily abdominal and genitourinary symptoms, then to neuropsychiatric symptoms, and back again to abdominal and other physical manifestations.

tive functioning. She endorsed word-finding difficulties, inability to tell stories in appropriate chronological order, and occasionally becoming lost while driving to familiar places. She denied any other porphyria-related symptoms at this time, with the exception of occasional tingling and paresthesias in her upper extremities. She was treated with a 5-day course of hematin and responded well to it. Upon further questioning, she recalled similar episodes of cognitive dysfunction in her teenage years, but thought nothing of them at the time. Repeat laboratory analysis at this time was significant for a plasma coproporphyrin level of 1.1 µg/L (normal < 0.8 µg/L) and a 24-h delta-ALA level of 1.3 mg. Lead level was 1.0 µg/dL. Upon completing 5-day infusions of hemin during acute attacks, she was treated with biweekly hematin, then with hematin on a PRN-basis. A summary of her symptoms and clinical course is given in Table 1.

Discussion

With an estimated prevalence of 1 - 2 cases per million, HCP is the third most common of the acute porphyrias, after acute intermittent porphyria and variegate porphyria [1, 2]. It is caused by decreased activity of coproporphyrinogen oxidase, the sixth enzyme in the heme biosynthetic pathway [3]. The primary clinical manifestations of HCP are abdominal pain, autonomic

dysfunction (hypertension, tachycardia, ileus, etc.), and motor neuropathy, although confusion and psychosis have also been reported [4-6]. Dermatologic symptoms are also possible, but are much less common than in the other acute porphyrias: less than 10% of patients with HCP present with skin lesions alone, and 29% present with any skin involvement at all [7, 8]. Diagnosis of HCP is based on increased urinary excretion of delta-ALA, porphobilinogen, and coproporphyrin during an acute attack, as well as fecal excretion of coproporphyrin [12]. However, levels of delta-ALA and porphobilinogen may be less markedly increased than in other acute porphyrias, particularly acute intermittent porphyria [9].

In the case discussed, the patient initially presented with typical porphyric symptoms, including abdominal pain, nausea, constipation, and fatigue. Later in her disease course, she developed peculiar neuropsychiatric symptoms that were severely debilitating. Her confusion was, at times, so severe that she would become lost while moving from room to room in her own house. We also found her dyspraxia, including performing tasks (such as loading the dishwasher) out of order, to be particularly intriguing and a symptom rarely described in the literature. For periods of time, she had disabling central nervous system attacks always responsive to hematin treatments over different time courses and eventually the neurologic crises resolved, but episodes characterized by fatigue, gastrointestinal symptoms and myalgias became predominant. She also occasionally has presented with cutaneous manifestations, which are somewhat atypical in HCP. Diagnosing her condition has proven somewhat challenging. She has never had a urine sample test positive for porphobilinogen, which is typically recommended as a first line test to establish the diagnosis of an acute porphyria [9]. However, both her urine and plasma have shown elevated levels of coproporphyrin during multiple acute attacks. Her urine has also shown elevated excretion of delta-ALA during an attack. We therefore describe her case as a unique neuropsychiatric syndrome of a variant HCP.

Estimates of the prevalence of neuropsychiatric symptoms in patients with HCP vary from approximately 25% to 60% [8-10]. A wide variety of symptoms have been reported, ranging from minor behavioral changes to insomnia, agitation, disorientation, confusion, hallucinations, phobias, delirium, and depression [9-11]. Less commonly, seizures, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and focal CNS deficits can be present [10]. The same patient may experience different neuropsychiatric symptoms during each attack [13]. Abdominal pain and other typical porphyric symptoms are present in most patients, but case reports have been described in which psychiatric manifestations were the presenting symptom [14]. Given these myriad neuropsychiatric manifestations, several other conditions are often considered before the diagnosis of HCP is made. These can include depression, anxiety, schizophrenia, conduct disorder, conversion disorder, somatization, and chronic fatigue syndrome [15].

Various imaging modalities have demonstrated several changes during an acute porphyria attack. MRI has shown reversible cortical changes consistent with posterior reversible encephalopathy syndrome (PRES), and angiographic/Doppler studies have demonstrated various evidence of cerebral vascular dysregulation [13]. Several pathogenic mechanisms have been proposed to explain the neurological manifestations of HCP. These include neurotoxicity of delta-ALA, altered tryptophan metabolism, and heme depletion in nerve cells [16]. Recent evidence suggests neurotoxic effects of ALA as the primary cause of acute attacks [17]. ALA may have several neurotoxic effects, including formation of oxygen free radicals, alteration of GABA/glutamate binding, and reversible inhibition of the Na^+/K^+ ATPase in brain tissue [13, 15, 17].

Management of HCP is primarily based on two principles: avoidance of pharmacological and hormonal porphyrinogenic substances, and down-regulation of the heme biosynthetic pathway. These porphyrinogenic substances increase the demand for heme and induce ALA synthase, thus precipitating an attack [10]. Commonly implicated drugs include alcohol, antiepileptic drugs, sulfonamide antibiotics, and rifampicin, although many other drugs are considered unsafe in porphyria [13]. Progesterone, cigarette smoking, and metabolic stress, such as that caused by fasting, infection, or surgery, can also promote attacks [9]. Two treatments have commonly been used for down-regulation of heme synthesis. Carbohydrates, such as sucrose or dextrose, have a non-specific repressive effect on ALA synthase and are often sufficient for mild attacks [9]. More severe attacks require treatment with hemin, which replenishes the body's heme pool and thus decreases the activity of ALA synthase [9]. Few recommendations have been made about specific treatment for the neuropsychiatric symptoms of HCP. However, psychosis is considered to be an indication for hemin therapy during an acute attack [18]. Insomnia and restlessness can be treated with chloral hydrate or low doses of benzodiazepines [17]. For depression, fluoxetine is considered safe, while tricyclic antidepressants are not [18].

References

1. With TK. Hereditary coproporphyria and variegate porphyria in Denmark. Dan Med Bull. 1983;30(2):106-112.
2. Elder G, Harper P, Badminton M, Sandberg S, Deybach JC. The incidence of inherited porphyrias in Europe. J Inherit Metab Dis. 2013;36(5):849-857.
3. Elder GH, Evans JO, Thomas N. The primary enzyme defect in hereditary coproporphyria. Lancet. 1976;2(7997):1217-1219.
4. Tracy JA, Dyck PJ. Porphyria and its neurologic manifestations. Handb Clin Neurol. 2014;120:839-849.
5. Hift RJ, Meissner PN. An analysis of 112 acute porphyric attacks in Cape Town, South Africa: Evidence that acute intermittent porphyria and variegate porphyria differ in susceptibility and severity. Medicine (Baltimore). 2005;84(1):48-60.
6. Elder GH, Hift RJ, Meissner PN. The acute porphyrias. Lancet. 1997;349:613-617.
7. Schulenburg-Brand D, Katugampola R, Anstey AV, Badminton MN. The cutaneous porphyrias. Dermatol Clin. 2014;32(3):369-384, ix.
8. Brodie MJ, Thompson GG, Moore MR, Beattie AD, Goldberg A. Hereditary coproporphyria. Demonstration of the abnormalities in haem biosynthesis in peripheral

blood. Q J Med. 1977;46(182):229-241.
9. Anderson KE, Bloomer JR, Bonkovsky HL, Kushner JP, Pierach CA, Pimstone NR, Desnick RJ. Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med. 2005;142(6):439-450.
10. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet. 2010;375(9718):924-937.
11. Siegesmund M, van Tuyll van Serooskerken AM, Poblete-Gutierrez P, Frank J. The acute hepatic porphyrias: current status and future challenges. Best Pract Res Clin Gastroenterol. 2010;24(5):593-605.
12. Kuhnel A, Gross U, Doss MO. Hereditary coproporphyria in Germany: clinical-biochemical studies in 53 patients. Clin Biochem. 2000;33(6):465-473.
13. Simon NG, Herkes GK. The neurologic manifestations of the acute porphyrias. J Clin Neurosci. 2011;18(9):1147-1153.
14. Mandoki MW, Sumner GS. Psychiatric manifestations of hereditary coproporphyria in a child. J Nerv Ment Dis. 1994;182(2):117-118.
15. Crimlisk HL. The little imitator - porphyria: a neuropsychiatric disorder. J Neurol Neurosurg Psychiatry. 1997;62(4):319-328.
16. Meyer UA, Schuurmans MM, Lindberg RL. Acute porphyrias: pathogenesis of neurological manifestations. Semin Liver Dis. 1998;18(1):43-52.
17. Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. Blood. 2012;120(23):4496-4504.
18. Stein P, Badminton M, Barth J, Rees D, Stewart MF. Best practice guidelines on clinical management of acute attacks of porphyria and their complications. Ann Clin Biochem. 2013;50(Pt 3):217-223.