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CLINICOPATHOLOGIC CONFERENCE

A 22-Year-Old Woman With Severe Headaches, Vomiting, and Tonic–Clonic Seizures

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CASE PRESENTATION

Chief symptom

A 22-year-old woman with severe headaches, vomiting, and multiple tonic–clonic seizures.

History of the present illness

The patient developed intermittent bilateral frontal headaches in June 2008. She presented to the emergency room (ER) and underwent a computed tomographic (CT) scan of her head that revealed sinusitis. She was treated with amoxicillin/clavulanate for a presumed bacterial infection, but her intermittent headaches continued. Her headaches worsened throughout the month of July, during which she developed leg aches, wrist pains, stiffness in the small joints of her hands, and a faint photosensitive rash. She again sought medical attention but her laboratory studies, including an assay for antinuclear antibodies (ANAs) and Lyme disease serologies, were negative. The headaches and joint pains improved partially without treatment.

In late July, the patient presented to the ER on several occasions with abdominal symptoms. On each occasion, she was observed to have a peripheral leukocytosis that ranged from 14,000 to 30,000 white blood cells/mm^3 (normal value <11,500). She underwent imaging studies at each visit, including abdominopelvic CT scans and ultrasonography, which were all unrevealing. She was discharged on proton-pump inhibitors and stool softeners, but intermittent abdominal pain continued and her headaches and joint pains worsened over the next 4 weeks. She was admitted to a community hospital for diagnostic testing. During that evaluation, her erythrocyte sedimentation rate (ESR) was 120 mm/hour (normal value <20) and her serum C-reactive protein (CRP) concentration was 345 mg/dl (normal value <8).

CT scans of the chest and abdomen revealed small bilateral pleural effusions and a small pericardial effusion. Investigations of her headaches included a brain CT and CT angiogram, along with a magnetic resonance imaging (MRI) study, an electroencephalogram, and a lumbar puncture. All of these studies were normal. A bone scan showed mild but diffuse uptake of technetium in multiple joints consistent with an inflammatory arthropathy. The joint disease spared the axial skeleton and the hips.

The bone scan results triggered an additional rheumatologic evaluation. An ANA assay was positive at a titer of 1:40, as was an assay for antihistone antibodies (titer >2.0 units; normal titer <1.6). Drug-induced lupus was diagnosed. The human papillomavirus vaccine that the patient had received 6 months earlier was proposed as the inciting agent. The patient was treated with a 1-day pulse of methylprednisolone (1 gm), followed by prednisone 80 mg daily. Her symptoms improved on the high doses of prednisone, but arthralgias, myalgias, and headaches recurred during the glucocorticoid taper. A diagnosis of fibromyalgia was made, and the patient was treated with pregabalin and sertraline.

Shortly after starting pregabalin and sertraline and while taking prednisone 20 mg daily, the patient developed an extreme headache associated with double vision and vomiting. She experienced a generalized tonic–clonic seizure at home that was witnessed by her mother. Upon arrival of the ambulance, her systolic blood pressure was 220 mm Hg. She had a second seizure in the hospital ER. A lumbar puncture showed 1 white blood cell/mm^3 (normal value <5), a cerebrospinal fluid glucose concentration of 50 mg/dl, and a protein concentration of 40 mg/dl (normal value <45). A brain MRI scan showed patchy edema and multiple scattered T2 hyperintense lesions in the white and gray matter, focused predominantly in the occipital areas. Her course was complicated by hypertension refractory to multiple antihypertensive medications. She was treated with labetalol, amlodipine, and clonidine, as well as methylprednisolone and levetiracetam, and transferred to our hospital.

The patient's headaches were described as frontal and bilateral in location, and nonradiating and constant in character. They were associated with nausea but she de-

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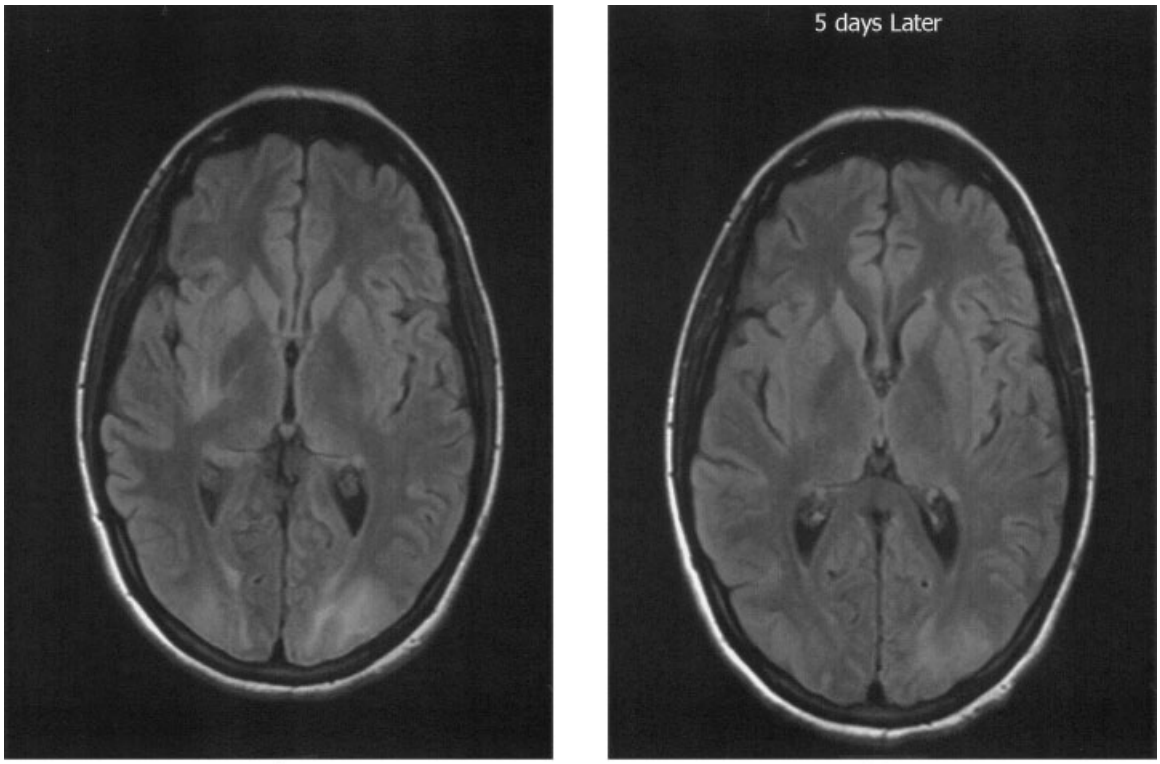

Figure 1. **A**, Brain magnetic resonance imaging scan revealing multiple nonenhancing white matter lesions confined predominantly to watershed areas on the posterior brain on the initial evaluation, and **B**, 5 days later.

nied visual changes, focal weakness, numbness, confusion, loss of consciousness, and hallucinations. The patient's blood pressure was 156/98 mm Hg upon arrival at our hospital. However, she quickly proved to require high doses of labetalol, captopril, and amlodipine to maintain a systolic blood pressure below 140 mm Hg. Despite adequate blood pressure control and pulse methylprednisolone (1,000 mg/day), the patient had persistent, albeit somewhat improved, headaches. The high-dose glucocorticoids, used empirically to treat presumptive lupus cerebritis or vasculitis, were discontinued after 2 days following a consultation by the rheumatology service.

The nephrology service was consulted to evaluate secondary causes of hypertension. A renal ultrasound, a 24-hour urine collection for protein and metanephrine, and serum concentrations of aldosterone, renin, and cortisol were all within the normal limits. A head CT and CT angiogram were negative. A brain MRI scan revealed multiple nonenhancing white matter lesions confined predominantly to watershed areas on the posterior brain (Figure 1). The MRI scan was interpreted as being consistent with the posterior reversible encephalopathy syndrome (PRES).

Past medical history

The patient had been healthy prior to the onset of her illness. She took an oral contraceptive (drospirenone and ethinyl estradiol) but had received no other medications before the onset of her current illness.

Social and family history

The patient's family history was negative for rheumatologic and neurologic disorders. She lived with her parents and worked as a typist. She had smoked half a pack of cigarettes a day for 2 years. She drank alcohol socially and moderately, and denied illicit drug use. She was sexually active with one partner. She had no recent travel and was unaware of any recent tick or insect bites.

Review of systems

The patient reported persistent nausea and pain in her arms. She also denied chest pain, palpitations, orthopnea, paroxysmal nocturnal dyspnea, and lower extremity edema. She reported no dyspnea, cough, hemoptysis, or wheezing, and no hematochezia, melena, or changes in the color of her stools or urine.

Physical examination

On admission to the floor, her temperature was 97.8°F, her heart rate was 77 beats/minute, and her blood pressure was 156/98 mm Hg. Her respiratory rate was 14 and her oxygen saturation was 98% on room air. She was in mild discomfort from the headache. Her sclerae were anicteric and not injected. The mucous membranes were moist and the oropharynx had no ulcers on the tongue or buccal mucosa. She had a supple neck and no cervical lymphadenopathy. The cardiovascular examination was unremarkable, including intact pulses in both the upper and lower

extremities. Auscultation of the lungs revealed decreased breath sounds at the right base, but no pleural friction rub was present. Her abdomen was soft and nontender without rebound or guarding. Her lower extremities showed no edema. The musculoskeletal examination was remarkable for tenderness over the arms and thighs but no synovitis in any joint. There were no rashes. Her mini-mental status examination was 30/30. Cranial nerves II–XII were intact. Muscle strength was grade 5/5 in all muscle groups. The sensory modalities were intact to light touch, pinprick, and vibration. The deep tendon reflexes were 2+ and symmetric bilaterally, and the plantar responses were flexor. Clonus was absent.

Laboratory values

The patient had a white blood count of 16,000/mm^3 (76% neutrophils, 19% lymphocytes). The hematocrit was 33.6%, and the platelet count was 285,000/mm^3. The ESR and CRP level were 55 mm/hour and 41.4 mg/dl, respectively. The urinalysis showed 1+ red blood cells on dipstick, but microscopic examination of the urine showed neither red nor white blood cells. The liver function tests were within the normal limits. An ANA assay was positive at a titer of 1:40. Antibodies to the extractable nuclear antigens Ro, La, Sm, and RNP were not present, nor were antineutrophil cytoplasmic antibodies. The serum C3 concentration was 123 mg/dl (normal range 86–184), but the C4 complement level was 18 mg/dl (normal range 20–58). An assay for cryoglobulins was negative. Serum and urine toxicology screens were negative.

CASE SUMMARY

A healthy 22-year-old woman presented with malignant hypertension after experiencing multiple generalized tonic–clonic seizures. This presentation occurred after 2 months of progressive headaches, arthralgias, and abdominal pain. Her brain MR results were consistent with PRES.

DIFFERENTIAL DIAGNOSIS

A central question in this patient's evaluation is the etiology of her PRES. We first consider the diagnosis of PRES itself, and then weigh the likelihood of several potential causes.

PRES

PRES is associated with characteristic radiologic findings that consist of bilateral white matter changes associated with edema. The changes are usually distributed across the posterior cerebrum, and resolve within weeks (1). These MRI findings are often associated with a clinical syndrome of headaches, emesis, seizures, and altered mental status. Neurotoxicity from a variety of causes is thought to compromise the blood–brain barrier, leading to vasogenic edema (2).

The original descriptions of PRES were recorded in patients whose underlying disease processes were hypertensive encephalopathy, systemic lupus erythematosus (SLE), preeclampsia, and immunosuppressed states associated with solid organ or bone marrow transplantation (1). Radiologic features consistent with PRES have subsequently been identified in a number of other conditions (Table 1). PRES is known to occur in the setting of the systemic inflammatory response syndrome, high-dose chemotherapy, systemic sclerosis (when associated with renal crisis), a variety of other autoimmune diseases, acute intermittent porphyria, and an array of medications that includes intravenous immune globulin, erythropoietin, and ephedra (2–8).

Table 1. Potential causes of and conditions associated with posterior reversible encephalopathy syndrome (2)

Autoimmune diseases
Systemic lupus erythematosus
Systemic sclerosis
Wegner's granulomatosis
Polyarteritis nodosa
Guillain-Barré syndrome
Hypercalcemia
Hypomagnesemia
Hypertensive encephalopathy
Medications
Cisplatin
Cyclosporine
Cytarabine
Gemcitabine
Ephedra
Erythropoietin
Intravenous immune globulin
Tacrolimus
Porphyria (specifically, acute intermittent porphyria)
Post–bone marrow or –solid organ transplantation
Preeclampsia/eclampsia
Substances of abuse
Cocaine
Ephedra
Other
Systemic inflammatory response syndrome
Tumor lysis syndrome

Hypertensive encephalopathy

Severe hypertension can lead to radiographic findings that range from irreversible infarction and punctuate hemorrhages to reversible white matter changes characteristic of PRES (9–14). The underlying causes of hypertensive encephalopathy associated with PRES include chronic renal disease, essential hypertension, pheochromocytoma, primary aldosteronism, and a variety of other conditions treated with cyclophosphamide and glucocorticoids (12,14–16).

Our patient had no history of essential hypertension and her youth made that diagnosis less likely. She did not have chronic kidney disease, and an evaluation for causes of secondary hypertension was unrevealing. In terms of medications that might have caused hypertension, the only plausible candidate was prednisone. However, monotherapy with prednisone rarely causes severe hypertension in the absence of underlying essential hypertension or chronic renal disease.

SLE

The patient fits the classic demographic profile of SLE perfectly in both her age and sex, and meets the modified American College of Rheumatology criteria for the classification of SLE with her arthritis, serositis, seizures, and positive ANAs (17,18). Multiple case reports and one case series have shown a relationship between PRES and SLE (1,3,19,20). The common denominators for these two conditions are renal disease, hypertension secondary to fluid retention, and the use of cytotoxic treatments (3).

Because the most common central nervous system (CNS) manifestations of SLE include headache (24%), seizures (8.3%), and lupus cerebritis (3.7%), CNS lupus is easily confused with PRES (21). The underlying basis of lupus cerebritis and other CNS manifestations of the disease remain poorly understood. A well-established relationship exists between antiphospholipid antibodies (aPL) and the occurrence of stroke, but aPL do not explain the wide range of other CNS manifestations in SLE, nor do they illuminate cases of PRES in patients who are aPL negative (22).

Points against the diagnosis of SLE are the fact that her ANA was only weakly positive (1:40, speckled) and that other elements of her serologic profile did not suggest SLE. "ANA-negative" lupus patients often have antibodies to the Ro antigen (23), but our patient was Ro negative. Her headaches and abdominal pain had not improved and possibly had worsened while she was receiving prednisone.

Drug-induced lupus

The symptoms and signs of drug-induced lupus are generally milder than those of SLE and typically include arthralgias, rash, cytopenias, and serositis. Drug-induced lupus rarely includes CNS involvement or renal disease (24). To our knowledge, PRES has not been reported in association with drug-induced lupus. There are documented cases of cerebral ischemia in drug-induced lupus, but only in the setting of aPL (25). Drug-induced lupus has been reported to occur following vaccinations, particularly with the hepatitis B and rubella vaccines (26). In contrast, no cases of drug-induced lupus associated with the human papillomavirus vaccine have been reported.

The positive antihistone antibody at the outside hospital is consistent with drug-induced lupus. However, at the height of her clinical CNS symptoms, the patient had a negative assay for antihistone antibodies. The patient had not been receiving a medication classically associated with drug-induced lupus, e.g., hydralazine, procainamide, or minocycline (24). The short course of amoxicillin/clavulanate early in her clinical presentation was unlikely to have caused drug-induced lupus. Associations between oral contraceptives and drug-induced lupus consist of case reports only (24). In summary, drug-induced lupus did not appear to explain her presentation.

Systemic sclerosis with scleroderma renal crisis

Scleroderma renal crisis is a severe complication of systemic sclerosis that usually occurs in the setting of patients with diffuse disease. It is defined by the presence of rapidly progressive renal insufficiency associated with oliguria or refractory arterial hypertension (and usually both). Scleroderma renal crisis is encountered most often during the first few years of disease and is sometimes the problem that brings the underlying diagnosis to medical attention. The administration of high-dose glucocorticoids has been implicated as a potential inciting factor for scleroderma renal crisis. The presence of endothelial activation in systemic sclerosis has been postulated to make these patients susceptible to PRES in the setting of relatively mild degrees of hypertension (2). Compelling arguments against systemic sclerosis as the cause of our patient's presentation are her lack of cutaneous stigmata of that condition and her low titer of ANAs.

POSTHOSPITAL COURSE

The patient's diagnosis of PRES was thought to be consistent with either malignant hypertension or SLE. She was discharged without a clear diagnosis on prednisone 20 mg/day and an antihypertensive regimen of labetalol, amlodipine, and captopril. She was scheduled for followup appointments with her primary care doctor as well as neurology, nephrology, and rheumatology consultants. A diagnostic test was received.

DIAGNOSTIC TEST

The diagnostic screening test was a urinary porphobilinogen (PBG) assay. The primary care physician had astutely suspected this diagnosis on the basis of the patient's constellation of symptoms and sent a urine sample for a PBG assay even before her admission to our hospital. The test result was not received until after the patient had been discharged. The urine PBG measurement was markedly elevated at 25 mg/dl (normal range 0–2.0), indicating that some form of porphyria was likely. The spot urine PBG elevation largely narrowed the possibilities to 1 of 3 conditions: hereditary coproporphyria, acute intermittent porphyria, and variegate porphyria (27) (Table 2). The elevated urine PBG reduced the likelihood of the rare diagnosis of 5-aminovelunic acid dehydratase (ALA) porphyria, even though the urinary ALA level was not known. Secondary testing of serum and urine samples was also performed to determine the precise porphyria diagnosis (Table 3).

Differentiation among hereditary coproporphyria, acute intermittent porphyria, and variegate porphyria depends on the porphyrin levels in serum, urine, and feces. In our patient, the urine uroporphyrins and coproporphyrins were all elevated. The PBG deaminase was 4.01 μU/gm (normal range 2.1–4.3) and the patient's serum porphyrin was negative. Porphyria stool studies were not performed. The negative erythrocyte PBG deaminase largely excluded acute intermittent porphyria, although there are rare subtypes of acute intermittent porphyria in which only the liver PBG deaminase levels are decreased. The fact that the serum porphyrin level was undetectable excluded variegate porphyria. Our patient's evaluation is most consistent with hereditary coproporphyria.

Table 2. Distinguishing acute intermittent porphyria, hereditary porphyria, and variegate porphyria using laboratory results (27)

Disease	Erythrocyte porphobilinogen deaminase levels	Urine porphyrin levels	Fecal porphyrin levels	Plasma porphyrin levels
Acute intermittent porphyria	Decreased by 50%	Increased and proportionally more uroporphyrin	Normal or slightly increased	Normal or slightly increased
Hereditary coproporphyria	Normal	Increased and proportionally more coproporphyrin	Increased and proportionally more coproporphyrin	Usually normal
Variegate porphyria	Normal	Increased and proportionally more coproporphyrin	Increased and proportionally more coproporphyrin and protoporphyrin	Increased

DISCUSSION

Porphyria is a group of disorders characterized by specific genetic defects that lead to partial deficiency in one of the heme biosynthetic enzymes (28) (Figure 2). The overproduction of toxic heme intermediates occurs in patients with acute porphyrias under certain clinical conditions, such as exposure to particular drugs, alcohol, calorie restriction, or infection (28,29). Porphyria was termed "the little imitator" by Waldenstrom (30) (Table 4). The aptness of that designation is illustrated by the fact that our patient carried the diagnosis of drug-induced lupus for several months before the diagnosis of porphyria was entertained.

The elevated heme intermediates associated with porphyria are toxic to multiple organ systems. Acute porphyrias can mimic multiple life-threatening conditions, including peritonitis, diabetic ketoacidosis, epilepsy, hypertensive crisis, and disorders in which autoimmunity is accompanied by systemic inflammation (31) (Table 3). The acute porphyrias are indistinguishable on clinical bases alone, but vary according to the specific deficient heme biosynthetic enzyme and abnormal levels of precursors found in blood, urine, and feces (28).

The finding of high urine coproporphyrins in the setting of a negative serum porphyrin is consistent with hereditary coproporphyria, one of several specific disorders that comprise the acute porphyrias. Hereditary coproporphyria is caused by an autosomal dominant enzymatic deficiency in coproporphyrinogen oxidase. This disorder is characterized by neurologic and other visceral manifestations within the spectrum of other acute porphyrias (see below). Hereditary coproporphyria is often associated with a photosensitive rash that is similar to that of porphyria cutanea tarda. Our patient's photosensitive rash was observed before her evaluation in our hospital.

Hereditary coproporphyria, acute intermittent porphyria, and variegate porphyria can all cause neuropsychiatric manifestations (30). Abdominal pain, a common presenting symptom in all of the acute porphyrias, is so severe that it is often mistaken for an acute abdomen (29). This is often accompanied by vomiting and/or constipation (30). Autonomic neuropathy associated with sympathetic activation can occur, leading to tachycardia and hypertension. These complications are believed to be secondary to the neurotoxicity induced by the byproducts of heme metabolism (30).

In retrospect, the patient presented with many of the classic clinical signs of an acute porphyria. Her presentation with headaches was nonspecific, but she then experienced repeated bouts of severe abdominal pain that raised concern for an acute abdomen. Her headaches and subsequent seizures were, in hindsight, neuropsychiatric manifestations of acute porphyria. The autonomic instability evidenced by our patient is also strongly consistent with that diagnosis. PRES has also been recognized in-

Table 3. The patient's laboratory evaluation for porphyria

	Urinary tests	Serum tests	Normal range
Random porphobilinogen, mg/liter	25*		0–2
Random 5-aminolevulinic acid, mg/liter	Not done		0–5.4
Uroporphyrins, μg/liter†	52*		0–20
Heptacarboxyl, μg/liter†	10*		0–2
Hexacarboxyl, μg/liter†	<1		0–1
Pentacarboxyl, μg/liter†	1		0–2
Coproporphyrin I, μg/liter†	25*		0–15
Coproporphyrin III, μg/liter†	128*		0–49
Porphobilinogen deaminase, μU/gm		4.01	2.10–4.30
Total serum porphyrins, μg/dl		<0.1	0–1

* Significant.
† The marker urine studies were conducted on a urine sample collected over a 24-hour period.

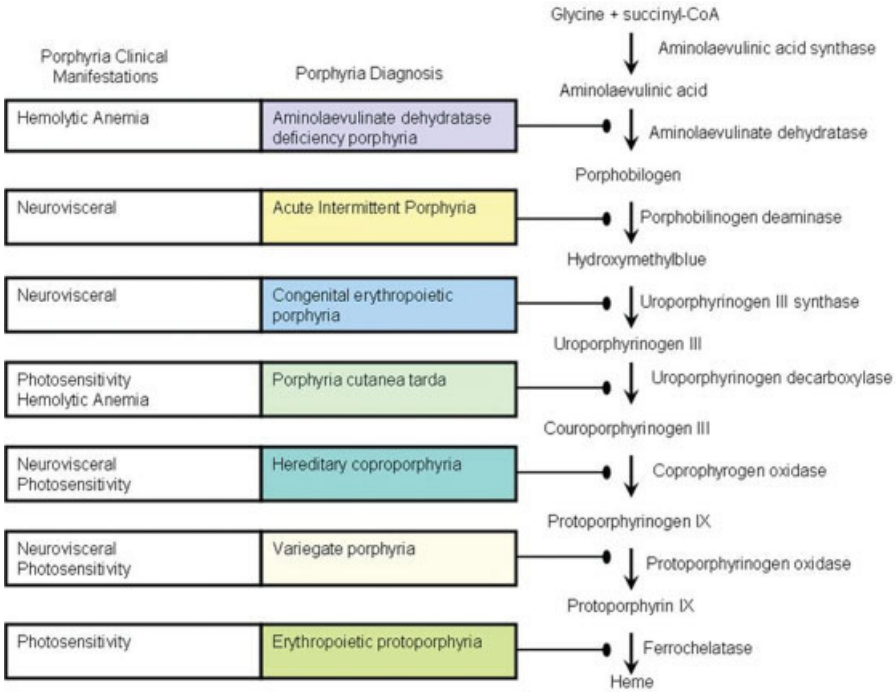

Figure 2. Porphyria clinical manifestations and diagnoses.

creasingly as a clinical manifestation within the spectrum of acute porphyria, but to our knowledge, has previously been reported only in acute intermittent porphyria (4,6–8).

Many medications (e.g., glucocorticoids, barbiturates, oral contraceptives, angiotensin-converting enzyme inhibitors, and calcium-channel blockers) can exacerbate the disease by inducing cytochrome P450, leading to an increased demand for heme synthesis (31). Clinicians should note that the patient developed all of her more severe (and classic) symptoms and signs of porphyria while she was receiving prednisone. Tobacco and alcohol use can also trigger porphyria exacerbations.

Significant overlap exists between the symptomatic manifestations of SLE and acute porphyrias. The similarities between these two conditions often cause delayed or missed diagnoses (32–34). The neurologic and psychiatric symptoms of these two conditions are virtually indistinguishable in some cases (30). As in this case, the rarer disease, acute porphyria, is generally the one overlooked. Both disorders tend to affect young women. Factors such as medications, intercurrent infections, and hormonal changes can precipitate either disease. The cardinal manifestations of acute porphyria, e.g., body aches, neuropathies, central nervous system and psychiatric manifestations, and abdominal pain, are also potential presenting features of SLE. Anemia, renal failure, and hypertension are common in both disorders.

PRES should be regarded as part of the spectrum of neuropsychiatric symptoms common to both SLE and acute porphyrias. Hypertension often accompanies acute porphyrias and is sufficient by itself to explain the development of PRES in some patients. An alternative potential explanation is that the neurotoxic effects of heme byproducts also cause PRES. An increasingly popular pathophysiologic explanation is that a combination of endothelial dysfunction, hypoperfusion, and vasoconstriction in the setting of neurotoxicity leads to compromise of the blood–brain barrier and resultant brain edema. The posterior areas of the brain are more sensitive to changes in perfusion and therefore are predominantly affected. By either mechanism, both acute porphyrias and SLE must be considered in the differential diagnosis of patients who present with PRES.

Table 4. Differential diagnosis of the "little imitator" (30)

Diseases mimicked by acute porphyrias
Addisonian crisis
Diabetic/alcoholic ketoacidosis
Drepanocyte crisis
Epilepsy
Gastroenteritis
Guillain-Barré syndrome
Hemolytic crisis
Hypertensive crisis
Hypocalcemic crisis
Lead poisoning
Myopathies
Psychotic attack
Systemic lupus erythematosus

FINAL DIAGNOSIS

Hereditary coproporphyria.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Dahlgren, Khosroshahi, Stone.
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