

# Clinical Reasoning: A 54-Year-Old Woman With Progressive Headache and Neurologic Decline

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## Abstract

A 54-year-old woman presented with headache and vasculopathy. She was treated for reversible cerebral vasoconstriction syndrome but continued to have clinicoradiographic decline with headache, seizures, systemic symptoms, and progression of vasculopathy on imaging. We present the diagnosis of a rare genetic disease with its various neurologic complications and systemic manifestations. Our case also illustrates the importance of differences in the metabolism of various antiseizure medications, recognition of which may avoid precipitating the disease.

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## Section 1

A 54-year-old White woman with a medical history of migraine, anxiety, depression on duloxetine and buspirone, tobacco use, and prior polysubstance (cocaine and amphetamine) use presented to the hospital with a 3-month history of progressive headache. The headache was daily, 7–8/10 in severity, holocephalic, pounding, non-thunderclap, waxing and waning without triggers, with associated blurry vision, photophobia, phonophobia, nausea, and occasional vomiting. There were no alleviating factors including with position change. Outpatient magnesium oxide, buspirone, and butalbital-acetaminophen-caffeine were ineffective. She had a remote history of headache with similar characteristics. However, they were less severe. She had been sober from illicit drug use confirmed by urine toxicology screen. She continued to use marijuana and tobacco daily.

On arrival, she was afebrile with blood pressure at 174/73 mm Hg. Basic laboratory results including prothrombin time were normal. She received migraine cocktails including prochlorperazine, diphenhydramine, magnesium sulfate, and ketorolac and was discharged home. She represented 2 days later and was found to have a right frontal cortical subarachnoid hemorrhage (SAH) on CT head (Figure, A). The CT angiogram (CTA) of the head and neck showed diffuse multifocal abrupt high-grade narrowing (Figure, B). She was not on blood thinners. Her neurologic examination was unremarkable.

### Questions for Consideration:

1. What is your differential diagnosis?
2. What other testing would you like to order?

GO TO SECTION 2

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## Glossary

**ALA** = aminolevulinic acid; **ASM** = antiseizure medication; **CTA** = CT angiogram; **FLAIR** = fluid-attenuated inversion recovery; **PACNS** = primary angiitis of the central nervous system; **PRES** = posterior reversible encephalopathy syndrome; **RCVS** = reversible cerebral vasoconstriction syndrome; **SAH** = subarachnoid hemorrhage.

## Section 2

Common etiologies of secondary headaches with convexity SAH include arterial vasospasm, dissection, aneurysms, vascular malformations, and cerebral venous sinus thrombosis. The location of convexity SAH and angiographic abnormalities of multifocal segmental narrowing raise concern for CNS vasculitis, reversible cerebral vasoconstriction syndrome (RCVS), and moyamoya disease.

CNS vasculitis includes primary angiitis of the central nervous system (PACNS) and systemic vasculitic disorders, autoimmune diseases, or infection causing secondary CNS arteritis. PACNS requires prompt recognition and early treatment with immunosuppression.<sup>1</sup> RCVS is considered noninflammatory and self-limited compared with CNS vasculitis. It has been associated with pregnancy, vasoactive agents, vasoactive tumors, hypercalcemia, unruptured aneurysms, and head trauma. Arteriopathy of moyamoya disease is characterized by bilateral stenosis affecting the distal internal carotid arteries with the presence of prominent collateral vessels, commonly seen in young people with Asian ancestry.

The black blood MR vessel wall imaging protocol revealed concentric vessel wall enhancement of bilateral M2 segments (Figure, C). This protocol is used to detect pathologic

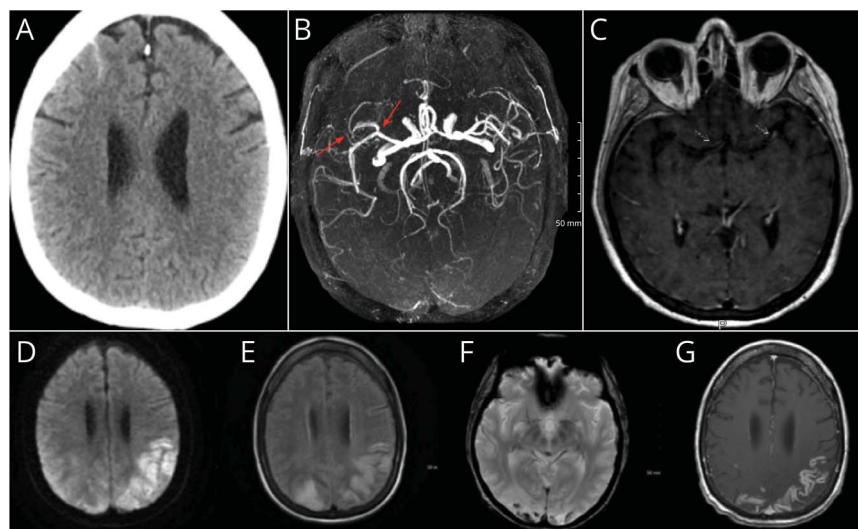
changes within the vessel walls beyond the luminal abnormalities. By contrast, lumenography-based imaging modalities such as digital subtraction angiography or CTA are useful to analyze luminal stenosis or occlusion.<sup>2</sup> Studies have shown that distinct wall thickening with a smooth, uniform, concentric enhancement pattern is observed in vasculitis due to increased permeability of endothelium from inflammation causing contrast leakage into the arterial wall, whereas vessel walls in RCVS are typically nonenhancing or mildly enhancing, if present.<sup>3</sup> However, the utility of the protocol remains ambiguous because there are cases of RCVS with more than minimal wall enhancement.

MRI brain showed right frontal SAH with corresponding punctate diffusion restriction and minimal adjacent fluid-attenuated inversion recovery (FLAIR) changes. Lumbar puncture was obtained to exclude vasculitis secondary to connective tissue, autoimmune, or infectious etiologies and PACNS. CSF analysis was negative for evidence of CNS inflammation. The serum vasculitic work-up was unremarkable (Table).

### Question for Consideration:

1. How would you proceed to treat the patient?

GO TO SECTION 3



CT head showed right frontal cortical SAH (A). CTA head and neck showed diffuse multifocal abrupt high-grade narrowing (red arrows) (B). The black blood MR vessel wall imaging protocol revealed concentric vessel wall enhancement of bilateral M2 segments (white arrows) (C). Repeat MRI brain without contrast on day 9 of second admission showed progressive T2 and FLAIR changes in bilateral cerebral hemispheres with a superimposed new acute infarct (D, E). Repeat MRI brain with and without contrast on day 15 showed stable diffusion restriction and FLAIR signal changes. There is mild petechial microhemorrhage (F) associated with occipital diffusion restriction. Gradient echo sequence showed gyriform enhancement correlating with areas of FLAIR changes (G). FLAIR = fluid-attenuated inversion recovery; SAH = subarachnoid hemorrhage.

### Section 3

RCVS was believed to be the working diagnosis due to high clinical suspicion with an RCVS2 score of 5, unremarkable CSF studies, and unremarkable vasculitis work-up. Although the MR vessel wall imaging showed enhancement, recent studies have shown that vascular wall enhancement can be found in up to 50% of patients with RCVS.<sup>4</sup> Patients with RCVS typically have normal CSF findings, whereas CSF studies in PACNS reveal inflammatory findings such as lymphomonocytic pleocytosis or protein elevation in more than 90% of patients.<sup>5</sup>

The patient was started on verapamil. Her home duloxetine and buspirone were discontinued because of concern for potentially increasing her risk of RCVS. Low dose divalproex acid 250 mg twice daily was started for seizure prophylaxis and mood stabilization. She was counseled on marijuana and tobacco cessation.

After discharge, she developed abdominal pain and constipation. She presented to the ED multiple times because of headache and abdominal pain and was eventually readmitted 6 days after her prior discharge. Blood work was significant for elevated lipase and liver enzymes. She developed progressive systemic and neurologic symptoms including generalized tonic-clonic seizures, encephalopathy, vision loss, paraparesis, dysphonia, dysarthria, hyponatremia, tachycardia, hypertension, and respiratory distress necessitating ICU care.

A repeat MRI brain revealed progressive T2 and FLAIR changes in the bilateral hemispheres with superimposed diffusion restriction reflecting progression of vasogenic edema and possible posterior reversible encephalopathy syndrome (PRES) (Figure, D–G). CTA showed progression of

multifocal stenosis. Transcranial Dopplers showed progression of vasospasm (Table).

Owing to clinoradiographic decline despite removal of precipitating factors for RCVS, the diagnosis of primary CNS vasculitis was reconsidered. A 5-day pulse dose steroid course was initiated. A brain biopsy was obtained before the initiation of steroids and later returned negative for vasculitis. The secondary work-up of RCVS ruled out medications or drugs, hypercalcemia, pheochromocytoma, or carcinoid tumor as the cause (Table). Urine porphyrins were sent as part of the RCVS work-up especially with unexplained progressive neurovisceral symptoms, ultimately returned positive for porphyria. An 11-day course of panhematin was initiated for acute hepatic porphyria. Her mental status and visual acuity improved rapidly. Her paraparesis improved over time but continued to have significant neuropathic pain. An EMG showed evidence of acute to subacute motor neuropathy (Table). Urine porphobilinogen (PBG) was elevated with normal urine delta-aminolevulinic acid (ALA). The diagnosis was later confirmed with genetic testing suggesting variegate porphyria.

In retrospect, the family reported that the patient had dark-colored urine for months with a long-standing history of abdominal pain and photosensitivity before her headaches. The photosensitivity was intense enough for her to avoid the sun due to skin blistering.

### Discussion

Porphyrias are a group of inherited disorders characterized by an enzyme deficiency in heme biosynthesis resulting in buildup of porphyrins causing systemic and neurologic symptoms. Most porphyrias are an autosomal dominant with

**Table** Investigation

	Result	Normal value
<b>Serum</b>		
Total calcium (mg/dL)	9.2	8.6–10.4
Prothrombin time (s)	10	9.7–12.6
ESR (mm/hr)	11	0–20
CRP (mg/dL)	0.3	0–0.5
ANA, ANCA, antiphospholipid, anti-SSA/SSB, anti-smith, anti-RNP & anti-dsDNA Abs	Negative	Negative
Hepatitis panel	Negative	Negative
Coccidioides Ab	Negative	Negative
Histoplasma Ab	Negative	Negative
CMV IgM and PCR	Negative	Negative
HIV-1, HIV-2 Abs	Negative	Negative
<b>CSF</b>		
Cell count (/μL)	2	0–5
Protein (mg/dL)	38	15–45
Glucose (mg/dL)	67	40–70
CSF, AFB & fungal culture	Negative	Negative
HSV-1, HSV-2, enterovirus, EBV, VZV, adenovirus, JCV & BKV-PCR	Negative	Negative
West Nile IgM and IgG	Negative	Negative
Lyme IgG	Negative	Negative
VDRL	Nonreactive	Nonreactive
Cryptococcus, Aspergillus, and Toxoplasma PCR	Negative	Negative
Paraneoplastic panel	Negative	Negative
<b>Urine</b>		
VMA (mg/24 h)	3.3	0–7.9
5-HIAA (mg/24 h)	2.4	2.0–9.0
Toxicology screen	Negative	Negative
Porphyrins	Positive	Negative
<b>TCDs</b>	Elevated mean velocities of both MCAs consistent with moderate vasospasm	
<b>Brain biopsy</b>	Rare intraluminal fibrin thrombin without evidence of inflammation within the lumen	
<b>EMG</b>	Widespread active denervation and chronic reinnervation not following a length dependent pattern. Sensory responses are relatively spared, consistent with a motor neuropathy	

incomplete penetrance, with a prevalence of approximately 0.5–10 per 100,000 people.<sup>6</sup> Acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria are the main subtypes causing neurologic diseases. Certain drugs, particularly medications with P450 metabolism, can precipitate porphyria attacks by stimulating heme production. In our case, the antiseizure medication (ASM) valproic acid may have aggravated an ongoing porphyria attack.

Photosensitivity, dark urine, abdominal pain, and transaminitis are typical findings of porphyria. Hypertension and tachycardia are common because of activation of the sympathetic nervous system causing catecholamine release.<sup>7</sup> The classic triad of neurologic manifestations includes motor-predominant peripheral neuropathy, neuropsychiatric disturbance, and abdominal pain. Typical neuropathy is an acute or subacute motor axonal neuropathy affecting mainly proximal muscles, generally worse



in the arms than the legs.<sup>8</sup> Autonomic nerve dysfunction contributes to constipation and poorly localized abdominal pain.<sup>6</sup> Seizures may be secondary to neurotoxicity or hyponatremia. Excess PBG and ALA induced SIADH through neurotoxicogenic mechanisms might contribute to seizures in porphyria.<sup>7</sup>

PRES is by far the most common MRI abnormality in porphyria. Other MRI findings in reported literature include central pontine myelinosis, gyriform enhancement, and reversible splenial lesion syndrome.<sup>9</sup> RCVS is rarely associated with porphyria, especially with the absence of typical thunderclap headache.<sup>10</sup> A decreased production of the vascular dilator nitric oxide is believed to result in vasoconstriction.<sup>11</sup>

Diagnosing RCVS can be challenging because RCVS and CNS vasculitis frequently have overlapping features. Features such as thunderclap headache, vasoconstrictive triggers, female sex, and convexity subarachnoid hemorrhage were predictors of RCVS, which were incorporated into the RCVS2 score. Our patient's presentation was also confounded by abnormal enhancement on vessel wall imaging. A rare RCVS-PACNS overlap syndrome was hypothesized because intense, prolonged vasoconstriction may cause inflammation.<sup>12</sup> As previously discussed, the utility of MR vessel wall imaging protocol remains ambiguous. Studies have shown that watershed infarcts and vasogenic edema are distinctive features for RCVS, whereas patients with PACNS have more diffuse distal artery involvement causing disseminated small infarcts and small vessel white matter changes.<sup>13</sup>

Previous studies showed comorbid RCVS and PRES at a rate of 15%–30%, signifying notable overlap between PRES and RCVS.<sup>14</sup> PRES-like reversible cerebral edema can be seen in up to 38% of patients with RCVS.<sup>15</sup> Nearly half of patients with PRES can have the angiographic sausage on a string pattern typically seen in RCVS.<sup>14</sup>

Removal of precipitating vasoactive substances, blood pressure control, rest, and empiric therapy with calcium channel blockers, such as nimodipine and verapamil, are associated with an excellent clinical outcome in RCVS. Medications such as sympathomimetics and serotonergic agents can cause hypertension and worsening of vasoconstriction.

This case illustrates neurologic manifestations of porphyria such as motor neuropathy, RCVS, and seizures. Precipitants of porphyria including ASMs such as valproic acid, phenytoin, barbiturates, carbamazepine, and topiramate should be avoided. Rather, P450-sparing ASMs should be selected. Other neurologic medications with reported porphyrogenicity include benzodiazepines, estrogen, progesterone, certain anesthetics, and neuromuscular blocking agents. This case report also adds to a handful of cases worldwide associating porphyria with RCVS.

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## Appendix Authors

Name	Location	Contribution
Yao Cheng, MD	Neurology, Corewell Health	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Joseph Zachariah, DO	Neurology, Corewell Health	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

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