

Resident and Fellow Section

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TEACHING CASE: HYPERTENSIVE HEADACHE

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Case Presentation.—A 48-year-old female with a past medical history significant for migraines, hypertension, posterior reversible encephalopathy syndrome (PRES) with related seizures, depression, chronic back and neck pain s/p cervical fusion, and lumbar laminectomy presented to the Emergency Department on outside hospital transfer with a breakthrough seizure and a several day history of poorly controlled headaches.

The patient was found to be quite sedated from intravenous benzodiazepines administered at the outside hospital upon initial neurological evaluation, thus the history at the time of presentation was limited. She was able to provide a 5-day history of an ill-defined headache that was not well-controlled with her outpatient medication regimen. She denied associated weakness, nausea, or vomiting. It was unclear how similar her current headache was to her typical migraine. She was able to deny associated head trauma. The patient could recall the occurrence of a generalized seizure the morning of presentation, but she was unable to state the events prior to and after the seizure. General and neurological review of systems was otherwise negative. Family history was noncontributory and her social history was pertinent for current disability due to her chronic pain and tobacco abuse. Her ambulatory medications included a baby aspirin, metoprolol, paroxetine, lamotrigine, quetiapine scheduled and sumatriptan, oxycodone, and alprazolam as needed.

The patient's history of PRES was investigated in more detail per electronic record. She presented

approximately 8 months prior with mental status changes and a generalized seizure. She has a history of absence seizures as a child and was managed on lamotrigine solely for bipolar disorder at this time. The patient admitted to a history of labile blood pressures (BPs) and had discontinued her β -blocker several weeks prior to presentation due to low systolic readings. She had not felt well for several weeks prior to her admission. In the evening of her admission, she developed a severe headache, took a dose of sumatriptan, vomited, then took another dose of sumatriptan prior to developing a generalized tonic clonic seizure. Her hospital course was notable for hypertension, normal electroencephalogram, lumbar puncture unrevealing for infection, and a magnetic resonance imaging (MRI) pertinent for T2 hyperintensity in the cortex and adjacent white matter posteriorly. Her presentation of hypertension, altered mental status, seizures, and headache in conjunction with her MRI findings raised suspicion for a diagnosis of PRES. The patient was discharged on improved antihypertensive control with continued lamotrigine for anti-epileptic management.

General examination in the Emergency Department at the time of current presentation was unremarkable with normal vitals (afebrile, BP 100/60-80 mmHg, heart rate 60 beats per minute, normal sinus rhythm, respiratory rate 8-11, Saturation of oxygen greater than 95% on room air). Neurological examination was pertinent for a somnolent female, arousable to drowsy with otherwise fluent speech, mild right-left confusion, intact cranial nerves (including visual fields), normal bulk and tone with a mild right upper extremity drift, normoreflexia, and normal sensation and coordination. Admission labs, including complete blood count, electrolyte, renal function, hepatic panel, and international nor-

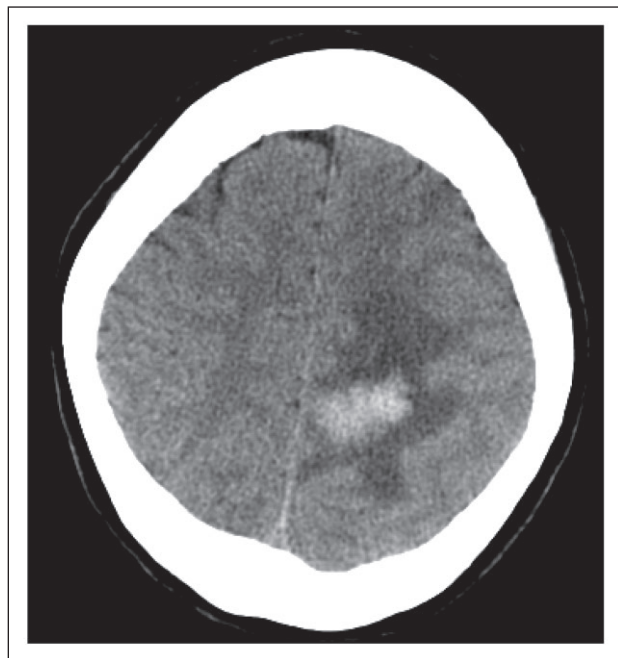


Fig 1.—Noncontrast head computed tomography.

malized ratio, were within normal limits. Lamotrigine level was subtherapeutic at 1.2. Urine toxicology screen was positive for marijuana. The patient underwent a noncontrast head computed tomography (CT), which was revealing for a (2 × 3cm) left parietal hemorrhage (Fig. 1).

Neurosurgery was initially consulted but deemed her spontaneous intraparenchymal hemorrhage non-surgical and more suitable for medical management.

The patient was admitted to the Neurology service for close monitoring of her vitals and neurological checks. Patient was administered labetalol as needed for BP greater than 160/90. CT angiography (CTA) was performed to rule out a potential aneurysm or vascular malformation and was unremarkable for an underlying vascular abnormality (Fig. 2). MRI of the brain with and without contrast was consistent with her known left parietal hemorrhage with stable size, surrounding edema, and mass effect but no underlying mass. Persistent signal abnormality was present in the right parietal lobe, consistent with the patient's history of PRES (Fig. 3).

Differential diagnosis for the potential etiology of the patient's hemorrhage included poorly controlled hypertension, reversible cerebral vasocon-

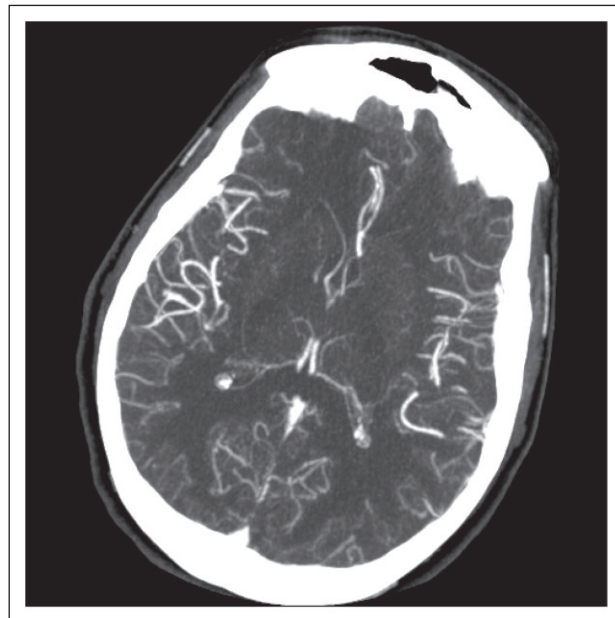


Fig 2.—Computed tomography angiogram.

striction syndrome (RCVS) secondary to selective serotonin reuptake inhibitor (SSRI) use, and central nervous system vasculitis. The following labs were obtained and found to be within normal limits, including C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, anti-nuclear antibody, myeloperoxidase antibody, proteinase3, c- and p-anti-neutrophil cytoplasmic antibody. Conventional angiogram was obtained and was revealing for small areas of distal arterial narrowing in the parietal and occipital lobes consistent with sequelae of PRES. No other arterial or venous abnormality was seen (Fig. 4).

The patient's mental status improved and she was able to provide additional history at this point and endorsed use of up to 8 tablets of 100 mg sumatriptan orally for several days prior to her admission. The possibility of transient vasospasm related to sumatriptan overuse leading to intraparenchymal hemorrhage was considered given her diagnostic work-up to date. Paroxetine and sumatriptan were discontinued and patient was transitioned from metoprolol to verapamil for dual BP control and migraine prevention. Gabapentin was initiated for neuropathic pain control with plan to consider narcotic wean as an outpatient and repeat CTA in 3 months.

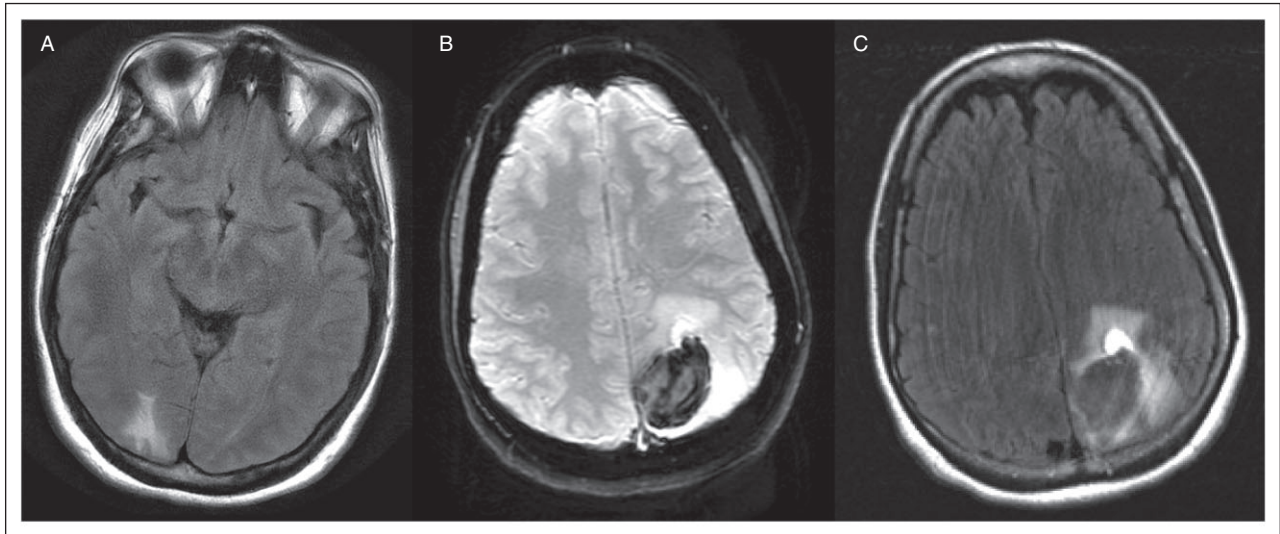


Fig 3.—Magnetic resonance imaging of the brain with and without contrast: (A) Axial fluid attenuated inversion recovery (FLAIR) sequence; (B) susceptibility-weighted imaging sequence; (C) T2-weighted sequence.

EXPERT COMMENTARY

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This report of purported recurrent PRES is a unique case that raises several important diagnostic and therapeutic issues. Since initially reported as a unique clinical and radiographic syndrome in 1996,¹ PRES has been increasingly recognized and its varied manifestations and causes have been appreciated.

The patient in this report presented with headaches, seizures, and parieto-occipital MRI find-

ings. The initial presentation included elevated BPs associated with recent cessation of BP medication as well as the use of sumatriptan. The subsequent presentation 8 months later that culminated in an intracerebral hemorrhage apparently did not include elevated BPs and it is unclear if sumatriptan was again used.

I agree with the authors that there are some important alternative diagnoses to consider. Some additional information would be helpful in this regard. Specifically, I would be interested in the MRI findings from the first presentation, ie, whether they were in fact bilateral, whether they were shown to be reversible, and if any type of angiography was per-

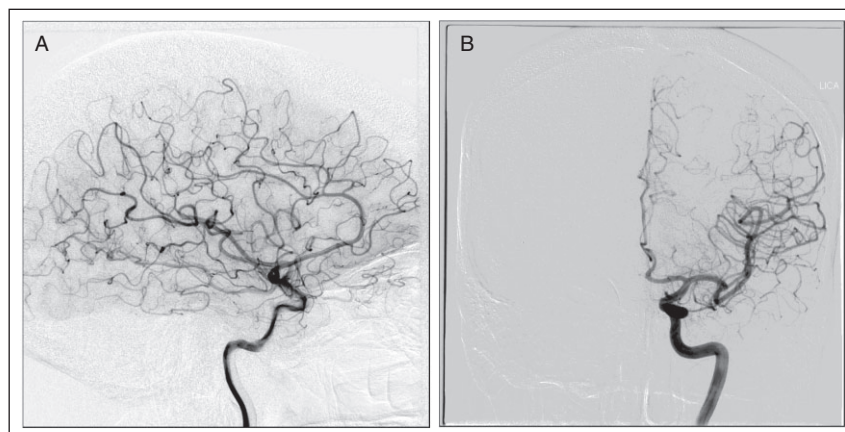


Fig 4.—Conventional angiogram: (A) Left carotid injection sagittal view; (B) left carotid injection coronal view.

formed. For the second admission, I am again interested in whether the imaging findings were shown to be reversible, if the initial BP was excessive (because a normal BP except when immunosuppressive drugs are used is unusual for PRES), if any visual symptoms were present, if the headaches had a thunderclap quality or any precipitating factors, and if sumatriptan was again used and in what quantities. Finally, I would like to see the posterior circulation injections on the angiogram.

As the authors discuss, 2 other specific diagnoses producing headache and intracranial hemorrhage deserve consideration: cerebral vein thrombosis (CVT) and RCVS. Usually, these are easily distinguished from PRES by the clinical and radiographic findings.

Headache, perhaps the most common symptom of CVT, RCVS, and PRES, usually precedes and then is often dominated by the other, often more threatening, manifestations. The distinctive "thunderclap" headaches seen in RCVS are not seen in CVT and PRES. Rather, the headaches in these 2 conditions are less dramatic and specific. Although the headaches in PRES without hypertension have not been well-described, the headaches seen in hypertensive encephalopathy have been described and diagnostic criteria have been defined in the *The International Classification of Headache Disorders, 2nd edition* as follows:²

- A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
 1. Diffuse pain
 2. Pulsating quality
 3. Aggravated by physical activity
- B. Persistent BP elevation to >160/100 mm Hg with at least two of the following:
 1. Confusion
 2. Reduced level of consciousness
 3. Visual disturbances (other than those of typical migraine aura) including blindness
 4. Seizures
- C. Headache develops in close temporal relation to BP elevation
- D. Headache resolves within 3 months after effective treatment and control of hypertension

E. Other causes of the neurological symptoms have been excluded

A recent review discussed the clinical differences in PRES related to preeclampsia-eclampsia and PRES related to other conditions. Headache was much more common in the former, being present in only 18% of those without preeclampsia-eclampsia.³

Although both CVT and PRES can cause bihemispheric edema and hemorrhage as seen in this case, the radiographic changes in CVT usually do not have a parieto-occipital predominance as commonly, but not always seen in PRES.⁴ In transverse sinus thrombosis, more temporal lobe edema is usually seen and with superior sagittal sinus thrombosis, more anterior parasagittal edema involving the frontal and/or parietal lobes is typically seen. CTA, as done in this case, usually adequately opacifies the cerebral veins and would rule out this condition, but this can vary based on the timing of the bolus and the image acquisition.

RCVS typically causes convexal subarachnoid hemorrhage more often than parenchymal hemorrhage and also can cause infarctions, usually in borderzone areas rather than vasogenic edema as seen in PRES.⁴

The angiographic changes in RCVS are usually consistent of severe caliber changes that may preferentially affect the PCA branches but are usually somewhat diffuse. As seen in this case, the caliber changes that have been reported in PRES can also include caliber changes like those seen in RCVS but also include a more subtle "pruning" of the PCA/calcarine arteries and are more limited to the areas where brain edema and hemorrhage have occurred.⁵

PRES has been associated with many medications and conditions that can broadly be grouped into immunosuppressive/chemotherapeutic agents for transplant and cancer treatment that are thought to cause endothelial dysfunction and breakdown of the blood-brain barrier AND medications or conditions that induce hypertension including eclampsia and renal failure.⁴ Withdrawal from antihypertensive medication, as seen in this case, or withdrawal from alcohol, are common triggers for PRES. Exposure to SSRIs and triptans, as seen in this report, are potential triggers

for PRES, but cases proven to be caused by these medications are very rare.

One additional clinical point is that recurrent PRES, as reported in this case, has surprisingly been very rarely reported, and this is usually seen in patients posttransplantation, with autoimmune disease or with renal failure.^{4,6}

The treatment of PRES, as suggested by the authors, consists of the removal of any triggers, the lowering of elevated BP, and the treatment of seizures.⁴ The management of the headache accompanying PRES has not received much attention and is especially challenging when accompanied by intracerebral hemorrhage, because repeated doses of nonsteroidal anti-inflammatory drugs and sedating medications are usually avoided. Fortunately, these are usually self-limited, unless complicated by other issues including pre-existing migraine and medication overuse, as was present in this case.

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QUESTIONS FOR DISCUSSION

1. By what mechanism(s) do PRES, RCVS, and CVT produce headaches?
2. What is “hypertensive encephalopathy”? Is it a synonym of PRES?
3. Next time you suspect a patient of having PRES, what investigations would the most efficient work-up include?

This case presentation and discussion meets the Accreditation Council for Graduate Medical Education requirements for residency training in the following core competency areas: Patient Care, Medical Knowledge, Practice-Based Learning and Improvement, and Systems-Based Practice.