

Too Weak to Move

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From the Case Records of the Alpert Medical School of Brown University Residency in Emergency Medicine

DR. WENDY WONG: Today's case is a 31-year-old woman who presented with generalized weakness which had been worsening over 2 weeks. She was seen at an outside hospital 24 hours prior to her presentation and was diagnosed with a urinary tract infection (UTI). She was discharged home but her weakness worsened in severity. Just prior to arrival, she had been ambulating to the bathroom with a cane but became so weak that she slid to the ground. She denied loss of consciousness or any injuries.

The patient's medical history was significant for systemic lupus erythematosus (SLE), hypertension, deep vein thrombosis (DVT), and pulmonary embolus (PE) diagnosed 3 months ago. She takes prednisone daily, but has missed several doses of rivaroxaban and blood pressure medications due to nausea.

On review of systems, she reported a migraine headache associated with photophobia and blurry vision which improved minimally with Fioricet. She noted diffuse abdominal discomfort over the past few months associated with occasional nausea, vomiting, and anorexia. She reported normal bowel movements, denied dysuria, but reported decreased urinary output.

The patient's vital signs were: blood pressure 219/143 mm Hg, pulse 112 beats/min and regular, temperature 98.7°F, respirations 18 breaths/min, and oxygen saturation 98% on room air. The patient was somnolent but easily arousable. She was oriented to person, place and time and appeared much older than her stated age. She had symmetric mild weakness of the arms and legs. She was able to stand and ambulate with assistance. Reflexes were normal. Sensation was intact. Her oral mucosa was dry. Her cardiac exam revealed tachycardia without murmurs and her capillary refill was brisk. The patient's lung exam was clear to auscultation. Her abdomen was soft, obese, with normal bowel sounds but diffusely tender to palpation, without rebound or guarding. She had severe alopecia but the skin was otherwise unremarkable.

DR. ELIZABETH NESTOR: Her complaints were non-specific and her physical exam is non-focal. How did you direct your laboratory testing?

DR. NATHAN HUDEPOHL: Her vital signs were most significant for hypertension and tachycardia, which could be a response to infection as well as a cause of end-organ damage or ischemia. The use of immunosuppressants as well as her report of a UTI prompted us to look for an infectious etiology. We obtained a cbc, chem 7, troponin, and urinalysis which revealed acute renal failure and proteinuria >500 units. Her creatinine had increased to 1.99 from a baseline of 0.86. We also obtained an EKG which revealed sinus tachycardia without evidence of ischemia and a chest X-ray which revealed pulmonary edema. Computed Tomography Angiography (CTA) was negative for PE.

DR. MATTHEW SIKET: The patient had a hypertensive emergency with evidence of end-organ damage to her kidneys, brain and lungs. Do you think her signs and symptoms were due to poorly controlled hypertension and non-compliance with medications? Premature closure is the most common diagnostic error in clinical decision making, and this diagnosis did not encompass all of the patient's symptoms.¹ Was there a unifying diagnosis?

DR. HUDEPOHL: The patient's history of SLE and immunosuppression, in combination with her severe hypertension and myriad of signs and symptoms led us to consider a central nervous system cause of her weakness. Posterior Reversible Encephalopathy Syndrome (PRES), a clinico-radiologic diagnosis, is associated with autoimmune diseases and use of immunosuppressive medications.² We confirmed this diagnosis with CT brain and MRI brain imaging (see **Figures 1, 2**).

DR. DAVID PORTELLI: What exactly is PRES? How is PRES different from RPLS?

DR. WONG: PRES is a unique pattern of brain vasogenic edema associated with a number of medical conditions including hypertension, eclampsia/pre-eclampsia, autoimmune disease, use of cytotoxic/immunosuppressant drugs, chemotherapeutic agents, bone marrow or solid organ transplant, sepsis, collagen vascular disease, or renal failure.³ The disorder is a clinico-radiologic syndrome first described in a cohort of 15 patients with symptoms of altered mental status, headache, seizures, and loss of vision who also had "prominent white matter abnormalities" on CT consistent

Figure 1. CT Brain. Multiple areas of hypoattenuation bilaterally. The largest is centered at the right internal capsule and extends inferiorly to the right cerebral peduncle, midbrain and pons. An additional is found at the left periventricular white matter. Involvement at the left cerebellum concerning for underlying mass lesion.

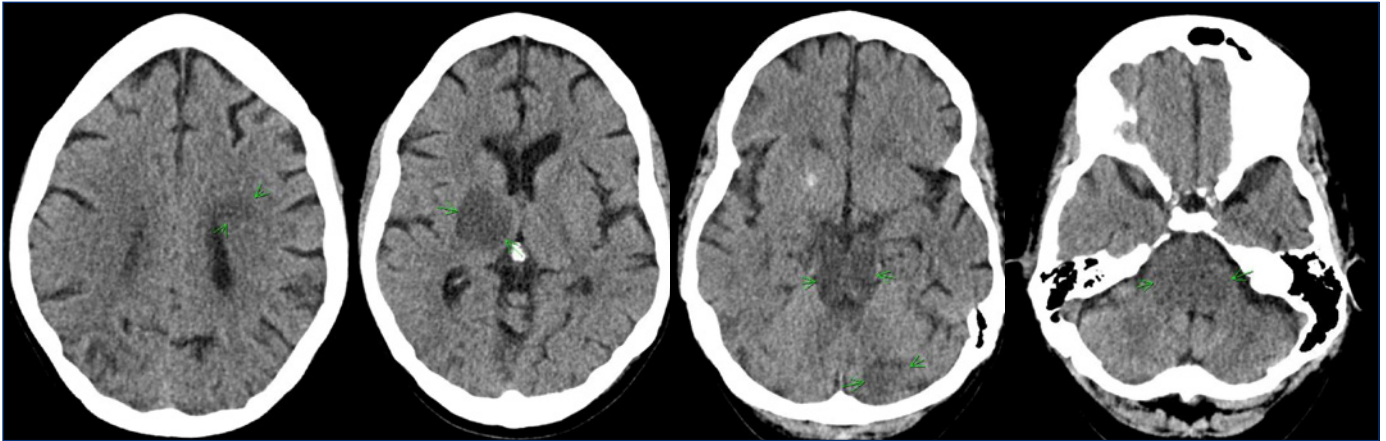
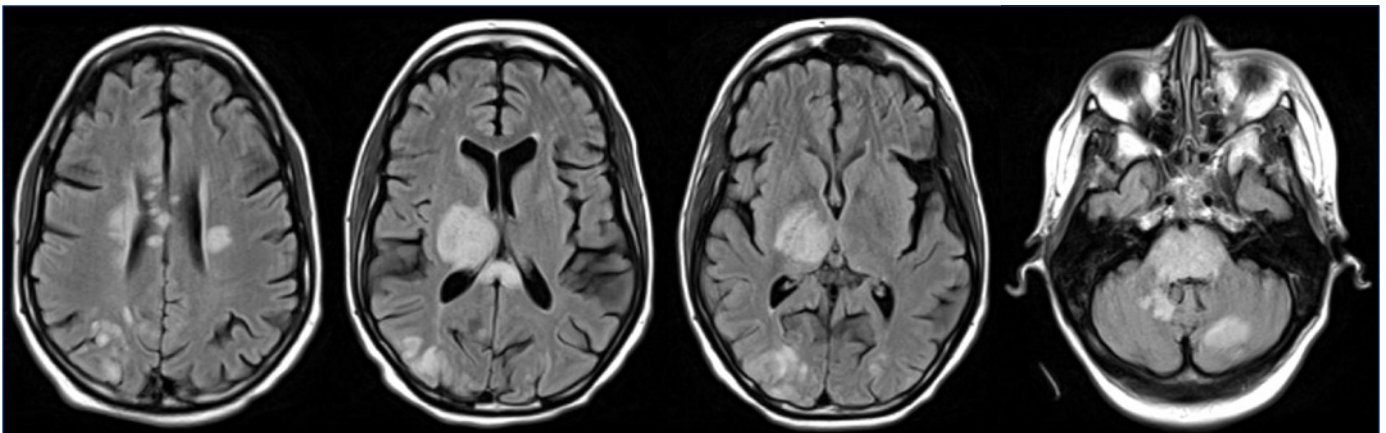


Figure 2. MRI Brain. Scattered areas of T2/FLAIR signal hyper-intensity within the cerebrum, cerebellum, deep gray matter structures and pons, which are most suggestive of posterior reversible encephalopathy syndrome (PRES).



with posterior leukoencephalopathy.⁴ The symptoms and CT abnormalities resolved in all 15 patients after 2 weeks of anti-hypertensive medication and withdrawal or reduction of immunosuppressive treatment. Originally called Reversible Posterior Leukoencephalopathy Syndrome (RPLS), the disorder was re-named PRES because the reversible white matter abnormalities did not appear to be true leukoencephalopathy.⁵

DR. NOAH ROSENBERG: Clinical findings of PRES include seizures, which this patient did not have. How did you diagnose PRES?

DR. WONG: PRES is characterized by diminished mental status, headache, seizure, nausea/vomiting, and visual abnormalities. Decreased alertness, the most common feature, can range from drowsiness to stupor.^{2,6} Seizures may not be reported on initial presentation.⁵ Abnormalities in visual perception can range from blurry vision to visual neglect or hallucinations.⁴ On CT brain, the most characteristic

presentation is white matter edema in the posterior cerebral hemispheres that does not necessarily follow a vascular territory.^{4,7} Accumulation of large amounts of edema occurs in the subcortical white matter because the cortex is more resistant to edema as a result of being more tightly packed and organized.^{2,5} The posterior circulation is most affected because the vertebrobasilar circulation with its relative lack of sympathetic innervation, is more susceptible to sudden elevations in blood pressure.⁷⁻⁹

DR. JEFF FEDEN: Is it possible to have PRES with a normal CT brain? What is the best imaging modality to diagnose PRES? Is it always reversible?

DR. WONG: In a large multi-center retrospective study, 16% of patients had a normal CT of the brain.⁶ Brain MRI with FLAIR sequencing is the most sensitive imaging modality and T2 hyper-intense vasogenic edema is noted.⁵ PRES is neither always posterior nor reversible. While the parietal occipital pattern is the most characteristic, it is only

present solely in that location in 22% of cases.^{2,10,11} PRES has been seen to affect other regions of the brain: frontal lobe 77%, temporal lobe 64%, cerebellum 53%, basal ganglia 34%, brainstem 27%.² Spinal cord involvement in PRES (PRES-SCI) has also been noted in a recent case report of patients with neurologic signs referable to the spinal cord, MRI lesions that extend to the cervicomedullary junction, or grade IV hypertensive retinopathy.¹² Cerebellar involvement is most commonly associated with autoimmune disease.^{2,13,14} Although PRES is characterized by reversible symptoms and radiologic abnormalities, it occasionally may not be as benign or reversible as the name implies.^{15,16} In a retrospective study of 90-day outcomes, the case fatality rate was 16%, with 37% of patients experiencing significant functional impairments from secondary complications such as status epilepticus, intracranial hemorrhage, or ischemic infarct.^{6,16}

DR. OTIS WARREN: What is the pathophysiology of PRES?

DR. WONG: There are several competing theories, all of which involve disruption of the blood brain barrier resulting in the development of vasogenic edema. The most widely accepted theory is that severe increases in blood pressure cause a failure of cerebral auto-regulation, resulting in vasodilation, hyper-perfusion, extravasation and edema.^{2,4,14} Control of hypertension with anti-hypertensive medication often improves symptoms. However, PRES can develop in normotensive or mildly hypertensive patients and the severity of hypertension does not predict the development or severity of PRES.^{3,5,10,14} Furthermore, PRES patients often do not have a mean arterial pressure high enough to overcome cerebral auto-regulatory capacity.^{2,3,13}

Angiography of the posterior circulation in PRES reveals a “string of beads” appearance most consistent with vasospasm or arteritis, suggesting that vasoconstriction, vasospasm, and resultant hypo-perfusion leads to ischemia and vasogenic edema. MR perfusion imaging shows reduction in the relative cerebral blood volume indicating cerebral hypo-perfusion rather than hyper-perfusion.^{3,9}

Patients with PRES are often on cytotoxic medications, which may have a direct toxic effect on cerebral endothelium, resulting in vascular leakage.^{2,17} Symptoms may improve after discontinuing a potentially inciting agent.³ However, levels of cytotoxic agents in PRES patients do not correlate with the development or severity of PRES; PRES can occur even at therapeutic blood levels.^{2,4}

Interestingly, renal failure is a common manifestation of the conditions associated with PRES such as eclampsia, hypertension, sepsis, autoimmune disease and use of chemotherapeutic agents. Release of Vascular Endothelial Growth Factor (VEGF) from the kidney in response to damage can increase endothelial permeability with resultant cerebral vascular leakage, leading to edema.¹⁰

DR. ERIC GOLDLUST: Is PRES considered a neurologic emergency? How do we manage these patients?

DR. WONG: PRES does not reverse spontaneously and delay in the diagnosis and treatment can result in permanent neurological sequelae.^{7,14} With prompt treatment, complete reversal of PRES occurs within several days to weeks (range 2-15 days) with radiological improvements lagging behind clinical recovery.^{7,8} Management includes: 1. discontinuing the offending agent (ie. removal of cytotoxic/immunosuppressive drugs), 2. controlling blood pressure with anti-hypertensive medications, 3. Treating seizures/status with anti-epileptics.^{7,8,10}

DR. WILLIAM BINDER: Do you stop immunosuppressives when severe hypertension is thought to be due to poor control of the underlying autoimmune disorder?

DR. WONG: Patients with autoimmune disease pose a unique problem as it can be difficult to ascertain if PRES is caused by hypertension due to poor control of the underlying autoimmune disorder or if the use of immunosuppressive medications are to blame. Although there are case reports of symptom resolution while immunosuppressives are maintained, removal of cytotoxic drugs or substitution of another immunosuppressive agent is usually recommended if the inciting factor is unclear.⁸ If symptoms are improving with control of hypertension and etiology of PRES likely due to severe hypertension, it is reasonable to continue immunosuppressives. However, it is not recommended to reintroduce agents that were known to induce PRES in a patient as recurrence of PRES has been reported in this setting.⁸

DR. BECKER: What are your take-home points from this case?

DR. WONG: Consider PRES in the differential diagnosis of decreased mental status or headache in those with co-morbidities of hypertension, eclampsia/pre-eclampsia, autoimmune disease, use of cytotoxic/immunosuppressant drugs, chemotherapy, bone marrow or solid organ transplant, sepsis, collagen vascular disease, or renal failure. CT brain may be normal and diagnosis may require MRI brain if clinical suspicion is high. Once diagnosed, PRES is a neurologic emergency and should be treated promptly with control of blood pressure, removal of inciting drugs, and treatment of seizures. Although some case series support continuation of seizure prophylaxis for 1-3 months, there is no indication that PRES patients are at long-term risk for seizure recurrence or epilepsy. Anti-epileptics can be safely tapered as symptoms and neuroimaging abnormalities resolve, usually after 1-2 weeks.⁸

FINAL DIAGNOSIS: Posterior Reversible Encephalopathy Syndrome (PRES)

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