

Cortical Blindness: Clinical and Radiologic Findings in Reversible Posterior Leukoencephalopathy Syndrome

Case Report and Review of the Literature

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Purpose: To alert ophthalmologists to the recognition of cortical visual loss as the presenting feature in patients with reversible posterior leukoencephalopathy syndrome (RPLES). Unique radiologic findings are paramount to the diagnosis.

Design: Interventional case report.

Methods: A patient was seen with perioperative bilateral cerebral visual loss that was misinterpreted initially as an irreversible ischemic event. Further detailed analysis of the radiologic findings and clinical history led to the correct diagnosis.

Main Outcome Measures: Visual acuity and magnetic resonance imaging (MRI) of the brain.

Results: Recognition of the correct diagnosis of RPLES led to the institution of antihypertensive therapy and recovery of normal vision.

Conclusions: The diagnosis of RPLES should be considered in all patients with acute cerebral visual loss, especially in the setting of recent surgery, blood transfusion, chemotherapy, immunosuppressant use, hypertension, eclampsia, or seizures. Prompt diagnosis requires close collaboration with a radiologist and an emergent MRI study, which ideally should include diffusion-weighted imaging with calculation of an apparent diffusion coefficient map. Differentiation from acute cerebral ischemia is important in order to avoid permanent visual loss by prompt and vigorous treatment of exacerbating factors such as intermittent hypertension. Prompt diagnosis will also help to avoid potentially dangerous invasive procedures such as thrombolytic therapy. *Ophthalmology* 2005;112:e7–e11 © 2005 by the American Academy of Ophthalmology.

Reversible posterior leukoencephalopathy syndrome (RPLES), also known as posterior reversible encephalopathy syndrome and reversible posterior cerebral edema syndrome, is a clinical entity that includes the acute or subacute onset of confusion, lethargy, and visual disturbances due to vasogenic edema of the posterior cerebral white matter. Reversible posterior leukoencephalopathy syndrome has been described in various clinical settings, including severe hypertension, chemotherapy, eclampsia, and seizures.^{1–12} Less commonly associated findings include a low hemato-

crit, blood transfusion, sickle cell complications, acute renal failure, and liver failure.^{13–21} Despite the variety of clinical settings, the etiologic insult is thought to be severe hypertension with dysregulation of the cerebral vasculature, although there is evidence of endothelial damage preceding the hypertensive episode.²² The reversible neurologic deficits associated with RPLES are felt to result from acute vasogenic edema, often with little, if any, permanent cellular damage.^{23,24} The diagnosis of RPLES is often made on the basis of the clinical setting and neuroradiologic findings consistent with vasogenic edema, as opposed to cytotoxic edema, in the parieto-occipital region. These characteristic parieto-occipital abnormalities are manifested by hypointensity on computed tomography (CT), and hyperintensity on T₂-weighted magnetic resonance imaging (MRI).

More recent advances in MRI technology highlight the features of vasogenic edema and allow for a more accurate radiologic diagnosis. Specifically, diffusion-weighted imaging (DWI) shows parieto-occipital signal changes caused by the entrapment of water in the edematous region.^{25–29} However, the DWI signal reflects both diffusion weighting and some underlying T₂ effects, such that a bright signal on DWI could reflect either true ischemic injury or simply T₂

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shine-through from vasogenic edema. Apparent diffusion coefficient (ADC) maps (made from the diffusion data) serve to remove the underlying T₂ signal contribution and highlight free unrestricted water. Therefore, the ADC maps allow distinction between vasogenic edema and cytotoxic edema due to brain infarction: ADC maps appear bright in vasogenic edema but dark in cytotoxic edema and acute stroke.^{25,30}

As early as 1984, Monteiro et al described a case of reversible cortical blindness related to hypertension.³¹ Their patient showed hypointensities on CT scan. In 1996, Hinchey et al coined the term *reversible posterior leukoencephalopathy syndrome*.^{1,32} Although several cases of RPLES have been reported in the neurology and neuro-radiology literature, exposure in the ophthalmologic literature has been rather limited.

We describe a patient who developed RPLES in the setting of intraoperative and postoperative hypertension and postoperative anemia. The cause of the patient's cerebral blindness was not immediately apparent. Radiologic studies were initially interpreted as consistent with cerebral ischemia. Reinterpretation, taking into consideration the findings on DWI and ADC, led to the diagnosis of RPLES. Because of this, strict blood pressure (BP) control was instituted, and the patient recovered fully within 3 days, consistent with the diagnosis of RPLES, as opposed to a cerebral ischemic episode.

Case Report

A 42-year-old woman with a history of hypertension, peripheral arterial occlusive disease, and failed aorto-bifemoral revascularization surgery 6 months earlier was admitted to the vascular surgery service with complaints of worsening claudication in both legs, including claudication at rest. Her medications included aspirin (81 mg daily) and tramadol (Ultram, Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ; 50 mg) for pain. She had an allergy to clopidogrel (Plavix, Sanofi-Synthelabo Inc., New York, NY), which caused extremity swelling and urticaria, and she had been diagnosed previously with heparin-induced platelet antibodies, a contraindication for the use of heparin products. She had a smoking history of 37 packs a year. However, she did not have thrombocytopenia and was negative for lupus anticoagulant factor and factor V Leiden. Her antithrombin III, protein S, and protein C levels were normal. Magnetic resonance arteriography showed clotting of her aorto-bifemoral graft, and a revision of the revascularization graft was performed without complications. Intraoperative records indicate that the highest BP recorded was 180/90, achieved at the midpoint and at the end of the surgery. Otherwise, BP intraoperatively was maintained at 120 to 150/60 to 80.

Postoperatively, the patient was admitted to the intensive care unit (ICU). She was treated with lepirudin and warfarin, and her partial thromboplastin time and prothrombin time were followed. Her BP medications were labetalol and furosemide as needed, and her electrolyte levels, including that of magnesium, were followed routinely and corrected when necessary. She was oriented to person and place, but her ICU chart noted disorientation to time throughout her ICU stay. Beginning on postoperative day 2, BPs measured by an arterial line were 140 to 183/65 to 86, with one instance of 196/82. She received a blood transfusion on postoperative day 3 to correct a hematocrit of 21 (from a preoperative level of 33). Throughout her ICU admission, regular neurologic exam-

inations, including determining Glasgow coma scores, were conducted, and the patient was neurologically intact except for mild to moderate confusion, especially related to time. Glasgow coma scores were normal or near normal; specifically, her Glasgow coma eye scores were either 3 or 4, implying normal visual function.* On postoperative day 7, the arterial line was removed, and the patient was transferred to the regular inpatient unit. Her BP that day was 151 to 186/75 to 85.

Upon transfer out of the ICU, the receiving nurse noted that the patient was unable to see out of either eye. She continued to be confused with respect to time, but was oriented to person and place. An emergent ophthalmology consultation was requested. Ophthalmic history was negative except for presbyopia. Bedside examination revealed a well-nourished woman with significant confusion and moderate lethargy. Visual acuity (VA) at near without correction was light perception bilaterally in all quadrants. Pupils were 6 mm in each eye and were reactive to light, with no relative afferent pupillary defect. Intraocular pressures were 18 and 19 mmHg. Random conjugate searching eye movements were present, but amplitude of movements was full in all directions. Portable slit-lamp and dilated fundus examinations were unremarkable. Disc borders were sharp, with a cup-to-disc ratio of 0.3. A diagnosis of cerebral visual loss was made.

An emergent head CT scan revealed diffuse hypodensity in the parieto-occipital area bilaterally, consistent with regional edema (Fig 1). Magnetic resonance imaging/magnetic resonance angiography studies of the head were obtained. Magnetic resonance angiography showed patent vasculature, and MRI showed diffuse hyperintensity of the parieto-occipital regions bilaterally on T₂-weighted images consistent with either ischemia or edema (Fig 1). A neurologic consultation was requested. The original MRI included DWI, which revealed hyperintensity of the same regions (Fig 1). However, at first only routine T₂ images and DWI were reviewed, without ADC maps, and the initial interpretation was of findings consistent with acute cerebral ischemia. Reinterpretation later in the day, taking into consideration the hyperintense signal on ADC maps, led to the finding of vasogenic edema and the correct diagnosis of RPLES. In view of this diagnosis, the neurologist recommended maintaining systolic BP under 140 to 150 mmHg. Blood pressure was maintained in the desired range, and the next day, VAs at near were 20/400 and 20/200. One day later, the patient was alert and oriented to person, place, and time. She was no longer confused, and VA at near was 20/25 bilaterally. The patient remained hospitalized for 2 more days until her prothrombin time ratio (international normalized ratio) was 2.1. Lepirudin was discontinued, and the patient was discharged. On follow-up in 1 month after surgery, VA was noted as normal and stable, and she had no neurologic complaints.

Discussion

Reversible posterior leukoencephalopathy syndrome is a clinical entity that may be unfamiliar to many ophthalmologists. However, the ophthalmologist is often the first consultant to evaluate patients with acute visual loss, and should therefore be familiar with this diagnosis. The clinical features that should alert the clinician to RPLES are the combination of confusion and lethargy, in conjunction with

*Spontaneous eye opening, 4 points; opening to speech, 3; opening to pain, 2; no opening, 1.

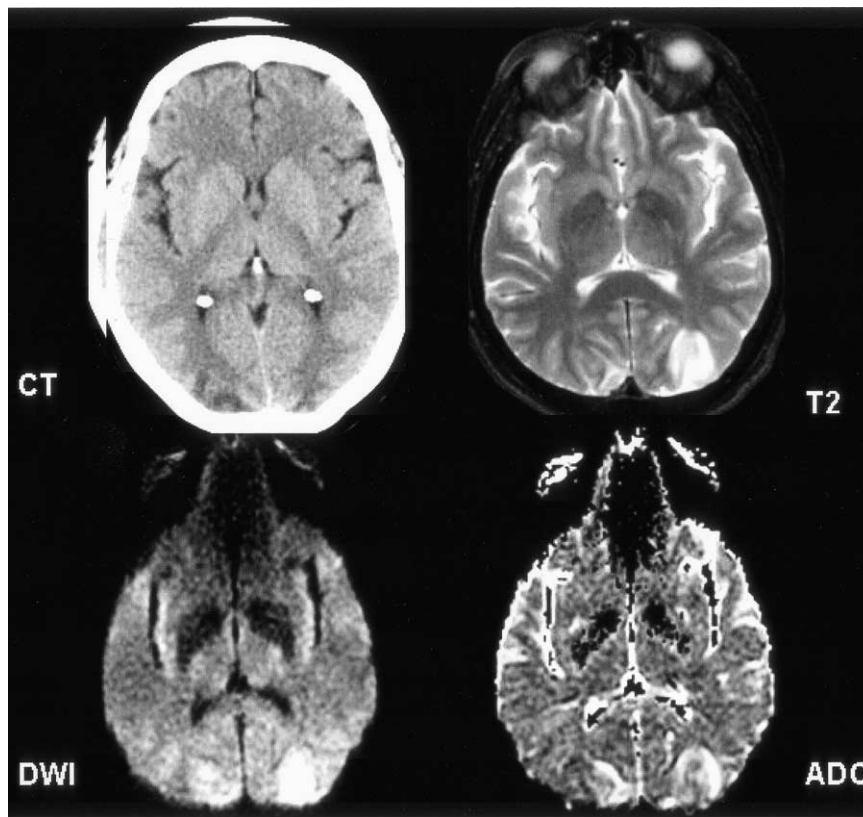


Figure 1. Computed tomography (CT) and magnetic resonance imaging (MRI) in reversible posterior leukoencephalopathy syndrome. CT, T₂, Bilateral occipital lesions with a white matter predominance seen on CT and T₂-weighted MRI. DWI, The diffusion-weighted image shows slight hyperintensity, left more than right. Although the DWI might at first suggest cytotoxic edema due to infarction, this is due to T₂ shine-through effects, confirmed by apparent diffusion coefficient (ADC) maps, which show a vasogenic pattern of edema (see text).

a rather acute episode of visual loss, usually in the setting of acute hypertension, seizures, or chemotherapy.¹ Transplant patients taking cyclosporine or FK-506 also seem to be at particular risk for this syndrome. A mini-mental neurologic examination can assist in determining the extent of confusion and can aid in making the diagnosis of RPLES. Early diagnosis of RPLES should lead to aggressive medical control of exacerbating factors, such as hypertension, and may prevent permanent neurologic damage. Ultimately, the diagnosis is made by MRI, including DWI.^{27,28} The diagnosis is subsequently confirmed clinically by a benign outcome, providing that the risk factors mentioned above are controlled. A case report employing proton magnetic resonance spectroscopy during and after the RPLES event revealed significant metabolic derangement that resolved completely after successful management.³³

The pathophysiology and even the nomenclature of RPLES (also known as posterior reversible encephalopathy syndrome) have been somewhat controversial. Earlier studies suggested that cerebral vasospasm, caused primarily by hypertension but exacerbated by other etiologic factors, leads to cerebral ischemia with underlying cytotoxic edema. As several authors have pointed out, the syndrome may not be completely reversible, is not always limited to the posterior regions, and may involve gray as well as white matter; hence the call for other names. However, the reversible

nature of the clinical and radiologic findings casts doubt on the role of cytotoxicity associated with this process. The alternative and currently favored hypothesis holds that RPLES is manifest as vasogenic rather than cytotoxic edema,^{28,34,35} although vasogenic and cytotoxic edema have been reported to coexist in some cases (Fig 2).³⁶ The posterior circulation may be predisposed to RPLES because perivascular sympathetic activity is reduced in the posterior relative to the anterior cerebral region, leading to loss of protective vasoconstriction and, therefore, breakthrough vasodilation in the face of hemodynamic challenge.³⁵ This, in turn, leads to an increase in local hydrostatic pressure, resulting in extravasation of fluid into the surrounding brain tissue. Therefore, vasogenic edema develops preferentially in the posterior cerebral territories and appears hyperintense on T₂, diffusion, and ADC maps.^{37,38}

Interestingly, in vasogenic edema associated with pre-eclampsia/eclampsia,³⁶ elevated levels of lactic dehydrogenase and abnormal erythrocyte morphology preceded the development of radiologic and neurologic abnormalities.²² Schwartz et al speculated that endothelial cell damage may participate in the dysregulation of the cerebral vasculature, leading to vasogenic edema.

Performance of MRI with diffusion-weighted images is central to the evaluation of patients with suspected RPLES and has helped advance our understanding of the pathophys-



Figure 2. Acute occipital infarction. **Left**, T₂-weighted images show hyperintensity along the right calcarine cortex. **Top right**, Diffusion-weighted images show the typical marked hyperintensity (lightbulb sign) characteristic of acute infarction. **Bottom right**, Hypointensity on apparent diffusion coefficient maps confirms that this is restricted diffusion related to cytotoxic edema.

iology. Diffusion-weighted imaging creates images based on the molecular movement of water, and has been used to document the abrupt slowdown of water movement in cytotoxic edema due to acute ischemic stroke. Ischemic stroke has a pattern opposite the accentuated water motion seen with vasogenic edema, the dominant pattern seen with RPLES. However, DWI has signal contributions from both underlying T₂ weighting as well as diffusion weighting. Therefore, hyperintensity on DWI can result from true diffusion restriction or strong T₂ effects—so-called T₂ shine-through. Fortunately, a simple postprocessing step—namely, the construction of an ADC map—can remove the T₂ contribution and allow the reader to see pure diffusion characteristics. As noted earlier, ADC maps allow distinction between vasogenic edema and cytotoxic edema due to brain infarction: ADC maps appear bright in vasogenic edema, but dark in cytotoxic edema and acute stroke.³⁰ In this case, as in others of RPLES, the ADC maps confirm a predominantly vasogenic (and therefore reversible) pattern of edema.

In the evaluation of cerebral blindness, diffusion-weighted MRI is invaluable in differentiating RPLES from an ischemic stroke. The important features of cranial imaging studies in the context of RPLES include diffuse posterior white-matter abnormalities manifested as hypointensity on CT, hyperintensity on T₂-weighted MRI, and hyperintensity on both DWI and ADC maps.

The diagnosis of RPLES should be considered in all patients with acute cerebral visual loss. This diagnosis is especially relevant in patients with some degree of lethargy and confusion, often in the setting of recent surgery, blood transfusion, chemotherapy, immunosuppressant use, intermittent hypertension, or seizures. Prompt diag-

nosis requires close collaboration with a radiologist and an emergent MRI study, which ideally should include diffusion-weighted images and ADC maps. Differentiation from acute cerebral ischemia is important to avoid permanent visual loss by prompt and vigorous treatment of exacerbating factors such as intermittent hypertension. Prompt diagnosis will also help to avoid potentially dangerous invasive procedures such as thrombolytic therapy.

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