



New Developments in Hypertensive Encephalopathy

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Abstract

Purpose of Review This review summarizes the latest science on hypertensive encephalopathy and posterior reversible encephalopathy syndrome (PRES). We review the epidemiology and pathophysiology of these overlapping syndromes and discuss best practices for diagnosis and management.

Recent Findings Diagnosis of hypertensive encephalopathy largely relies on exclusion of other neurological emergencies. We review the extensive causes of PRES and its imaging characteristics. Management strategies have not changed substantially in the past decade, though newer calcium channel blockers simplify the approach to blood pressure reduction. While this alone may be sufficient for treatment of hypertensive encephalopathy in most cases, management of PRES also depends on modification of other precipitating factors.

Summary Hypertensive encephalopathy and PRES are overlapping disorders for which intensive blood pressure lowering is critical. Further research is indicated to both in diagnosis and additional management strategies for these critical conditions.

Keywords Hypertensive encephalopathy · Posterior reversible encephalopathy · PRES · Hypertensive emergency

Introduction

Clinical Case Scenario

A 48-year-old male presented to the emergency department (ED) after being found confused at home by his family members. The family members were worried that he had a syncopal event earlier in the day and had been disoriented since. On presentation, the patient was awake but unable to answer any questions. Pupils were 2 mm bilaterally and reactive. He appeared to be in no distress and was moving all extremities well. His initial blood pressure was 280/111 mmHg. Labs

were notable for troponin 0.56 ng/ml and creatinine 3.22 mg/dl. His electrocardiogram was normal. A chest radiograph showed mild pulmonary congestion, and a computed tomography (CT) scan of the head was unremarkable. The patient was started on nicardipine infusion for control of blood pressure and admitted to the intensive care unit (ICU) with a diagnosis of hypertensive encephalopathy.

Objectives

Uncontrolled hypertension remains a major health threat worldwide, and hypertensive encephalopathy reflects one of the most

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critical forms of uncontrolled hypertension. There exists a significant amount of uncertainty about its incidence, diagnosis, and relationship to posterior reversible encephalopathy syndrome (PRES). The primary aim of this review is to summarize the latest science and expert opinion on hypertensive encephalopathy and PRES. We review the pathophysiology, diagnosis, and management of these conditions in the ED and ICU settings and discuss considerations for further research.

Epidemiology

Hypertension, one of the most common disorders in the USA, is estimated to affect nearly 50% of the adult population under new guidelines [1••]. Although hypertension is prevalent in the American population, less than 2% of all hypertensive presentations can be classified as hypertensive emergencies [2, 3]. A recent study representing national data placed this estimate at only 2 per 1000 total visits and 6 per 1000 of hypertensive ED visits. Hypertensive encephalopathy itself accounts for approximately 15% of those presentations [4, 5]. Another recent study using administrative data sources indicated increasing diagnostic rates for hypertensive encephalopathy [6]. This rise, the authors argue, is likely due to changes in billing rather than a true change in epidemiology. There has been no rise in morbidity and mortality associated with hypertensive emergencies. While often due to hypertensive emergency, PRES is not always associated with severely elevated BP. This syndrome can also be the result of other disease processes and constitutes a small portion of hypertensive encephalopathy presentations [7•].

Hypertensive encephalopathy is a hypertensive emergency defined by acute neurological dysfunction associated with an acute and severe increase in blood pressure (typically > 220 mmHg systolic or > 120 mmHg diastolic blood pressure). Most patients have alterations in mental status. Some may present primarily with or have concomitant seizures, visual disturbance, or headache. Headache is the least specific symptom and alone cannot support the diagnosis of hypertensive encephalopathy. The presence of other significant life-threatening diagnoses that have overlapping symptoms creates a challenge in defining and diagnosing hypertensive encephalopathy in the ED. The subjective nature of mental status change or other neurological symptoms adds to this challenge. Furthermore, the specific diagnosis of PRES is challenging given its broad neurologic symptoms (discussed below), causes, and the lack of readily available confirmatory imaging in the ED.

Pathophysiology

The human brain receives 15% of the cardiac output and consumes 20% of the total body oxygen consumption. It does so

while maintaining adequate cerebral perfusion pressure through an autoregulatory process that alters the precapillary arteriolar resistance in response to changing physiological conditions [8, 9]. Hypertensive encephalopathy, a term coined by Oppenheimer and Fishberg in 1928, occurs in the setting of acute rises in blood pressure that lead to arteriolar vasoconstriction in combination with a breakdown of the blood-brain barrier—resultant consequences include cerebral edema and petechial microhemorrhages [9, 10]. During hypertensive emergencies, the cerebral arteriolar endothelium responds initially with a release of NO and a forced hydrostatic dilation that in itself can lead to cerebral edema. However, when these mechanisms are saturated from persistent and sustained hypertension, the result is a state of increased resistance. This ongoing increased resistance contributes to endothelial damage and release of inflammatory cytokines that damage the blood-brain barrier, increasing its permeability, inhibiting fibrinolysis, and activating coagulation [9].

Posterior PRES, reversible posterior leukoencephalopathy syndrome (RPLS), and reversible posterior cerebral edema syndrome are synonyms for clinical and radiological spectrum of disease first described by Hinchey et al. as such in 1996 [11]. Although PRES was originally described in hypertensive patients, it has since been found in normotensive individuals and in association with numerous other clinical conditions such as renal disease, infections, immunosuppressive agents (cyclosporine, cytarabine), eclampsia, and rarely even antidepressants such as venlafaxine (Table 1) [11, 12••, 13]. Changes identified on neuroimaging are consistent with a perivascular edema [12••]. This focal edema likely results from a breakdown of the blood-brain barrier and frequently has petechial hemorrhages. It predominates in the posterior

Table 1 Conditions associated with posterior reversible encephalopathy syndrome

Medical conditions	Medications
Hypertensive encephalopathy	Immunosuppressant
Renal diseases (acute/chronic)	Cyclosporine, tacrolimus, cytarabine
Thrombotic thrombocytopenic purpura	Immunoglobulins
Hemolytic uremic syndrome	Chemotherapeutics
Eclampsia and preeclampsia	Sirolimus, cisplatin, gemcitabine
Sepsis/shock	Bevacizumab, tyrosine kinase inhibitors
Autoimmune: systemic lupus erythematosus, polyarteritis nodosa, granulomatosis with polyangiitis, scleroderma	Other: venlafaxine
Miscellaneous: hypomagnesemia, hypocalcemia, Guillain-Barre syndrome	

portions of the cerebral hemisphere and in particular the parieto-occipital regions [12••].

The pathophysiology of PRES remains controversial, but the leading theory posits a relationship with cerebral autoregulatory dysfunction [11, 13]. This results in hyperperfusion that contributes to the development of perivascular edema, which subsequently compresses the surrounding microvessels and contributes to a profound endarteritis [11, 13, 14]. The posterior regions of the brain that have less sympathetic innervation for autoregulation are thus most susceptible to this type of injury [11]. Alternatively, direct endothelial damage from fluctuations in blood pressures, release of cytokines, or circulating inflammatory markers contributes to the breakdown of the blood-brain barrier and increases the risk of infarction and petechial hemorrhages, with or without hypertension [11, 14]. The typically reversible vascular changes of PRES include vasoconstriction, focal vasospasm, and string of bean signs of the cerebral vasculature [13].

Diagnosis

Hypertensive Encephalopathy

The identification of hypertensive encephalopathy in the ED usually relies on the exclusion of alternative causes of altered mentation. Patients without a history of hypertension may develop hypertensive encephalopathy with blood pressure > 180/110 mmHg, but most patients with or without a history of hypertension have a blood pressure > 220/120 mmHg. Symptoms usually include change in mental status, though this may be subtle, and fluctuate. Concomitant symptoms may include headache, blurred vision, nausea, and seizures. Focal motor or sensory deficits are uncommon and, when present, more likely indicate acute stroke. As in the clinical case we presented above, findings of acute kidney injury, fragmented red blood cells, and elevation in cardiac biomarkers can accompany hypertensive encephalopathy. How commonly these multi-organ system findings overlap is not well described in the literature. Computed tomography of the brain is critical to evaluate for other causes as a hypertensive response in the setting of alternative etiologies is far more common than encephalopathy due to markedly elevated blood pressure alone [15]. These include traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke. Although petechial hemorrhage is possible in hypertensive encephalopathy and PRES, confluent intracerebral hemorrhage indicates an alternative diagnosis.

Confirmatory diagnostic testing is challenging in the ED. Head CT imaging that shows cerebral edema supports the diagnosis; however, CT is not sufficiently sensitive to rule out edema on its own. While magnetic resonance imaging (MRI) has greater sensitivity, its availability is limited in many

EDs and treatment will usually precede such imaging. Retinal findings can support the diagnosis of hypertensive encephalopathy. However, clinicians should be cautious to use findings of hypertensive retinopathy alone to support the diagnosis of hypertensive encephalopathy as the chronicity of retinal findings without papilledema can be difficult to determine. When present, papilledema does strongly support the diagnosis of hypertensive encephalopathy, provided pressure is adequately high and altered mentation is present. Advancements in retinal imaging in the ED setting may improve detection of papilledema [16]. Despite such considerations, a diagnosis of hypertensive encephalopathy is frequently established only retrospectively, once a patient's mental status improves with reduction of blood pressure. While this improvement can occur rapidly in the ED setting, it is often not established until later in a patient's hospitalization.

Posterior Reversible Encephalopathy Syndrome

There are currently no set guidelines or specific diagnostic criteria for PRES. Common symptoms include non-localized headaches, visual disturbances, and altered consciousness ranging from somnolence to agitation, confusion, and behavioral changes [12••, 17]. Seizures are a common presenting symptom, including status epilepticus [15, 18].

Neuroimaging with MRI is the modality of choice for diagnosis of PRES. Symmetrical white matter edema in the posterior cerebral hemispheres (usually posterior and occipital lobes) with eventual resolution of the findings is typically observed [17, 19]. The lesions can also frequently involve the cerebellar and brain stem and rarely may involve the spinal cord [20–22]. Typical MRI features of lesions display increased signal on T2 and fluid-attenuated inversion recovery (FLAIR) [15, 23]. Distinguishing PRES from an acute stroke can be challenging. Distribution of abnormalities beyond a single vascular territory, sparing of calcarine and paramedian occipital lobes, usually helps distinguish PRES from cerebrovascular infarction [12••, 17]. Moreover, diffusion weighted imaging (DWI) can help distinguish between PRES and bilateral posterior cerebral artery infarctions. In PRES, the edema is vasogenic and is represented by isointense or slightly hyperintense signals on DWI, whereas in an acute infarction, the edema is cytotoxic which manifests as marked hyperintensity on DWI [23, 24].

Although PRES affects the posterior hemispheres and is reversible in the overwhelming majority of patients, recent cases have shown more widespread findings than previously considered. Lesions involving the frontal lobes have been described and also isolated cases of irreversible PRES, sometimes progressing to a fulminant variant causing death [25, 26••, 27]. Despite the widespread involvement of lesions, currently, there is limited prognostic data to suggest specific anatomic distribution would affect outcomes [24].

Management

Blood Pressure Management

For patients with suspected hypertensive encephalopathy, the primary treatment aim is acute blood pressure reduction without over correction. No randomized clinical trials have been conducted to define end points of treatment or the efficacy of one anti-hypertensive related to another. Consensus opinion among experts and extrapolation from large animal studies has led to guidelines that recommend blood pressure reduction of approximately 20–25% as soon as possible once the diagnosis is suspected [3, 28]. Rapid correction beyond this threshold potentially exposes a patient to cerebral hypoperfusion [29]. The most commonly recommended medications include intravenous labetalol, nicardipine, and nitroprusside infusions for immediate and titratable control (Table 2). Although nitroprusside was a mainstay of treatment for hypertensive emergencies, newer agents such as nicardipine and clevidipine have supplanted its use in many centers. Nicardipine, for instance, is inexpensive, easier to titrate, and does not carry the concern for possible cyanide toxicity [4, 30, 31, 32].

A 2008 Cochrane review of 15 randomized clinical trials concluded that there was insufficient evidence to determine which drug is most effective in the setting of hypertensive emergencies [33]. More recent studies still have not clearly defined a single agent of choice for hypertensive encephalopathy, although most support acute reduction of baseline blood pressure up to 25% using intravenous and titratable anti-hypertensive medications. The seventh report of the Joint National Committee (JNC) agreed with such treatment goals and did not recommend one medication over others [34]. Neither the eighth report from the JNC members nor the latest American College of Cardiology and American Heart Association guidelines did not tackle management strategies in hypertensive encephalopathy [1, 35].

For hypertensive encephalopathies, nicardipine has become a common initial choice given its rapid onset of action and ability to titrate without invasive monitoring. It is also dose-independent to body weight with relatively few major side effects or contraindications. Labetalol would also be an acceptable choice; it can be administered as an intravenous infusion or by repeated bolus and can be titrated to effect without invasive monitoring. Moreover, it is generally well tolerated. Bronchospasm and heart block at higher doses are possible but rarely reported. Nitroprusside has very rapid onset but typically requires invasive and constant blood pressure monitoring. This, in conjunction with its potential for cyanide toxicity, makes it less desirable and renders it second-line therapy after other available anti-hypertensives. Esmolol is a rapid onset beta adrenergic blockade but has a higher fluid burden with administration and is considered primarily an adjunct (rather than primary) therapy for blood pressure control with use generally restricted to perioperative patients or aortic dissection. Nitroglycerin is readily available but typically requires higher doses for blood pressure control and patients can develop tolerance with prolonged use. Finally, clevidipine is a rapid onset calcium channel blocker similar to nicardipine. Its potential pharmacological advantage is its shorter half-life compared to nicardipine [36].

Following the initial 25% reduction in blood pressure, patients require further gradual reduction over the next 24 h. There is no literature to support the exact timing of this blood pressure reduction and when it is safe to intensify treatment to reach normal blood pressure. While on a continuous anti-hypertensive infusion, a patient can initiate oral anti-hypertensive medications as soon as the individual clinical condition allows. Clinicians may then wean the intravenous infusion to produce a gradual reduction in blood pressure.

Table 2 Intravenous antihypertensive agents

	Class	Adverse effects	Dose	Onset	Half-life
Labetalol	Mixed alpha and beta adrenergic blockade	Nausea, vomiting, dizziness, bronchospasm, heart block	10–80 mg IV bolus every 10–15 min or 0.5–2.0 mg/min IV infusion	5–10 min	3–6 h
Nicardipine	Calcium channel blocker	Tachycardia, headache, flushing	2.5–15 mg/h IV, increase by 2.5 mg/h every 5–10 min	5–10 min	0.5–4 h
Nitroglycerin	Nitrate	Headache, vomiting, methemoglobinemia, tolerance	10–400 mcg/min IV infusion	2–5 min	3–5 min
Sodium nitroprusside	Nitrate	Headache, nausea, vomiting, thiocyanate, and cyanide toxicity	0.25–10 mcg/kg/min IV infusion	< 1 min	2–5 min
Clevidipine	Calcium channel blocker	Tachycardia, nausea, vomiting, headache	1–2 up to 16 mg/h IV infusion	2–4 min	5–15 min
Esmolol	Beta-blocker	Bronchospasm, heart block, nausea	250–500 mcg/kg/min IV bolus, then 50–100 mcg/kg/min IV infusion	1–2 min	5–10 min

Posterior Reversible Encephalopathy Syndrome

Treatment of PRES also involves early blood pressure reduction with concurrent intervention for contributing etiologies. There are currently no specific treatment regimens or societal guidelines advocated for PRES. When severely elevated blood pressure is causative of PRES, blood pressure treatment goals are identical to hypertensive encephalopathy. When patients have elevated blood pressure and a different cause for PRES, such as medication-induced, there is no specific literature suggesting a targeted lowering of blood pressure. Normalization of blood pressure to pre-morbid levels is a reasonable approach for these patients. Drugs causing PRES such as cytotoxic agents require reduction in dosages or complete discontinuation [37–39]. Complete discontinuation in the case of immunosuppressant medications may not be feasible.

Further management of PRES depends on associated conditions contributing to this syndrome as described in Table 1. Treatment of seizures which commonly accompany PRES includes benzodiazepines followed by phenytoin or levetiracetam. In cases of PRES leading to status epilepticus, anesthetic agents like propofol or midazolam infusion should be used along with anti-epileptic drugs. However, in cases of PRES associated with eclampsia, magnesium is considered the drug of choice. Eclampsia causing PRES may also necessitate emergent cesarean section delivery.

Given the pathophysiology of PRES and the associated vasogenic edema, the role of corticosteroids has been widely debated. Corticosteroids have been both implicated as causative of PRES and used for treatment in a number of case reports [40, 41]. There exist conflicting schools of thought pertaining to steroid induced hypertension as an etiological factor versus anti-inflammatory effects of corticosteroids which may contribute to reduction of vasogenic edema and resolution of PRES. A recent retrospective analysis by Parikh et al. showed a possible association of corticosteroid therapy and the development of PRES [40]. The mean duration corticosteroid use was 6 days before the onset of PRES. The study showed no benefit with continued corticosteroid therapy and no association of corticosteroid dose with the extent of edema. At this time, current literature does not support the use of corticosteroids in the treatment of PRES.

Future Directions

There remain many unanswered questions regarding the evaluation and management of patients with suspected hypertensive encephalopathy. In the absence of an accessible and simple gold standard for diagnosis, diagnostic

uncertainty persists. It is probable that higher reimbursement tied to diagnostic codes for hypertensive encephalopathy leads to overdiagnosis of the disease in administrative data sources [42]. Future clarification of diagnostic criteria that include structured assessment of mental status change, imaging for PRES, digital retinal artery scans, and consideration of systemic vasculopathy could add substantially to our understanding of hypertensive encephalopathy. There may additionally be a role for non-invasive cerebral blood flow monitoring with either transcranial Doppler monitoring or evolving perfusion devices as both a diagnostic tool and measure to guide therapy [43]. In the management of PRES, there remains uncertainty as to whether corticosteroids and routine anti-epileptics may play a role in management. Research in these areas remains challenging due to the low incidence of true hypertensive encephalopathy and the critical nature of the diagnosis.

Conclusions

The patient in the case presentation had rapid improvement in encephalopathy with early blood pressure reduction. He manifested concomitant vascular pathology resultant of a hypertensive emergency. His nicardipine infusion was weaned as oral agents were added, and he required a short stay in the ICU without further complication.

Hypertensive encephalopathy and PRES are uncommon but critical diagnoses. Hypertensive encephalopathy is often considered in patients with markedly elevated blood pressure, but it is typically a diagnosis of exclusion that becomes fully recognized when symptoms improve with anti-hypertensive therapy. Imaging with MRI can confirm the presence of cerebral edema, particularly in patients with PRES, whether due to severely elevated blood pressure or other albeit less common etiologies such as those shown in Table 1. Blood pressure management targets up to a 25% reduction as soon as possible with subsequent more gradual reduction. The preferred agent in our experience is nicardipine. Further research is indicated both in improving the diagnosis of these critical diagnoses and defining treatment goals.

Compliance with Ethical Standards

Conflict of Interest Dr. Levy reports grants and funds in part by the National Heart, Lung and Blood Institute, grants from Novartis, Trevena, Cardiorentis, and BMS, and personal fees from Novartis, Trevena, and Cardiorentis, outside the submitted work. The other authors declare no conflicts of interest relevant to this manuscript.

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- Of importance,
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