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Review Article

Posterior Reversible Encephalopathy Syndrome (PRES) Beyond Hypertension: Triggers, Pathophysiology, Management, and Outcomes

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ABSTRACT

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a neurovascular disorder characterized by vasogenic edema, most often affecting the parieto-occipital lobes. Although typically reversible, some patients develop lasting neurological sequelae such as cognitive or visual impairment and epilepsy. This review summarizes the current understanding of PRES beyond its classical association with hypertension, emphasizing emerging triggers, mechanisms, and updates in management.
Methods: A structured narrative review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) framework. Literature was systematically searched in PubMed, Web of Science, and Google Scholar for studies published between January 1996 and June 2025. Fifty-nine relevant publications, including original studies and reviews, were synthesized to integrate evidence on presentation, imaging, pathophysiology, genetics, and management.
Results: PRES can be triggered by a broad spectrum of hypertensive and non-hypertensive conditions, such as renal dysfunction, eclampsia, systemic lupus erythematosus, sepsis, and exposure to immunosuppressive agents (e.g., tacrolimus, cyclosporine, rituximab). The syndrome involves multifactorial mechanisms, including endothelial dysfunction, blood–brain barrier disruption, and dysregulated cerebral autoregulation. Emerging data indicate that genetic polymorphisms in endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), and aquaporin genes may influence individual susceptibility, although causality remains unconfirmed.
Conclusion: PRES is a multifactorial syndrome that extends beyond hypertension. Early recognition, prompt neuroimaging, and targeted management of underlying triggers are critical for improving outcomes. Future studies should focus on clarifying genetic associations, standardizing diagnostic criteria for atypical cases, and optimizing therapeutic strategies through personalized medicine approaches.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a reversible clinicoradiologic condition first described by Hinchey et al. in 1996 [1]. PRES occurs more commonly in females and has been reported in nearly all age groups. It is most frequent among middle-aged adults, with an average age of 44 years [2]. The syndrome is characterized by a range of acute and subacute neurological signs and symptoms accompanied by distinctive neuroimaging findings. Diagnosis is clinico-radiologic, with MRI crucial to confirm the presence and distribution of vasogenic edema [3]. On MRI, PRES typically appears as vasogenic edema involving the white matter of the cerebral hemispheres, predominantly in the posterior regions, including the parieto-occipital lobes bilaterally. Other regions may also be affected, including the temporal and frontal lobes, cerebellum, brainstem, and deep white matter [4, 5]. Symptoms usually develop over several hours to a few days and include headache, confusion, altered mental status, seizures, and visual disturbances [1]. Patients may also experience lethargy, stupor, or occasionally focal neurological deficits [1]. Less common manifestations include

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nystagmus and periodic alternating gaze deviation [6, 7]. PRES is frequently associated with hypertension, particularly in eclampsia, hypertensive encephalopathy, and post-transplant settings involving immunosuppressive agents [8]. The primary pathophysiological theory posits that a sudden increase in blood pressure exceeds the brain's autoregulatory capacity, leading to endothelial injury, fluid leakage, and vasogenic edema [9]. However, approximately 30% of patients with PRES are normotensive. This observation supports an alternative hypothesis of direct endothelial toxicity induced by factors such as inflammation, autoimmune disease, sepsis, renal failure, or certain medications [8]. Early recognition and management of PRES can significantly improve outcomes and reduce complications [10]. Clinico-radiologic features are potentially reversible, especially with timely intervention. Diagnosis, therefore, requires a high index of clinical and imaging suspicion to ensure early treatment and a favorable prognosis [11]. This review aims to provide a comprehensive understanding of PRES by exploring diverse etiological triggers beyond hypertension, analyzing proposed pathophysiological mechanisms, and examining the long-term outcomes and risks associated with persistent neurological deficits. It also considers whether the relative frequency of different triggers varies across regions due to differences in healthcare practice and access to care.

2. Methods

2.1. Methodology Overview

This study was conducted as a structured narrative review in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) framework to ensure transparency and methodological rigor. This approach was selected to synthesize and critically appraise the diverse literature on PRES, encompassing its clinical features, underlying pathophysiology, genetic associations, non-hypertensive triggers, and management strategies. Unlike systematic reviews, this narrative synthesis did not aim for quantitative pooling or bias scoring; instead, it focused on integrating evidence across clinical and mechanistic domains to provide a comprehensive conceptual understanding.

2.2. Literature Search and Selection

A comprehensive literature search was conducted across PubMed, Web of Science (WOS), and Google Scholar for articles published between January 1996 (the first description of PRES) and June 2025. Searches were limited to the English language to ensure consistency in terminology and data interpretation across included sources. The search strategy incorporated Boolean operators (AND/OR) and utilized tiered search strings that combined primary and secondary keywords. A sample PubMed query was as follows: ("Posterior Reversible Encephalopathy Syndrome" OR "PRES" OR "Reversible Posterior Leukoencephalopathy Syndrome") AND ("pathophysiology" OR "vasogenic edema" OR "blood-brain barrier disruption") AND ("hypertension" OR "eclampsia" OR "sepsis" OR "autoimmune" OR "immunosuppressants" OR "systemic lupus erythematosus"). Searches were adapted to each database using compatible syntax. For Google Scholar, the first 200 results were screened and sorted by relevance to ensure the inclusion of gray literature and recent clinical observations, while minimizing search bias. After retrieving the results, all entries were exported into a reference manager (EndNote X9), and duplicate records were automatically removed. Titles and abstracts were screened to exclude clearly irrelevant, non-peer-reviewed, or non-English publications. The remaining full-text articles were reviewed in accordance with predefined inclusion and exclusion criteria. The inclusion criteria for this review encompassed original studies, reviews, case series, and reports that addressed any aspect of PRES etiology, pathophysiology, imaging, management, or outcomes, involving either adult or pediatric populations. Exclusion criteria included non-peer-reviewed materials such as conference abstracts without full text, editorials, or news items, as well as articles that were not directly relevant to PRES or were not available in English. This process yielded a balanced and comprehensive collection of sources representative of both foundational and contemporary evidence.

2.3. Rigor and Bias Minimization

To enhance objectivity and reproducibility, the review adhered to SANRA principles by implementing a transparent search strategy across multiple databases, applying predefined inclusion and exclusion criteria, and conducting a thematic rather than selective synthesis to avoid cherry-picking. High-quality evidence, including systematic reviews and large cohort studies, was prioritized, with case reports incorporated only to illustrate rare or atypical presentations.

3. Presentation, Risk Factors, and Epidemiology

An overview of clinical presentation, risk factors, epidemiology, evaluation, differentials, and complications is provided in **(Table 1)**.

4. Incidence

As illustrated in **(Figure 1)**, the incidence of PRES has been documented across multiple U.S. states with notable variation.

5. Non-Hypertensive Triggers of PRES

Initially, Posterior Reversible Encephalopathy Syndrome (PRES) was thought to occur in the context of severe hypertension, but now, growing evidence has proved the existence of multiple other triggers. The fact that 30% of PRES patients have no hypertension has supported this evidence [8]. These triggers include eclampsia or pre-eclampsia, immunosuppressive drugs, sepsis, autoimmune diseases, and rarely, renal failure [15, 16]. An elevation in the circulatory levels of toxins and cytokines, such as TNF-alpha, IL-1, and IL-6, is provoked by these triggers, causing damage to the blood-brain barrier (BBB) and allowing fluid leakage extravascularly [17]. More rarely, some rare triggers, such as hypercalcemia, hyperglycemia, and blood transfusion, have been reported. These triggers primarily cause PRES through osmotic shifts, leading to endothelial dysfunction [18, 19, 20].

5.1. Eclampsia/pre-eclampsia

A higher incidence of PRES in women with eclampsia or preeclampsia has been reported recently. In a recent meta-analysis of 29 studies, 51.4% of eclamptic women and 19.8% of pre-eclamptic women developed PRES [21]. Another study reported that PRES was detected in 22.5% of eclamptic women [22]. The mechanism of how eclampsia or preeclampsia occurs has not been confirmed yet. It is believed that endothelial dysfunction leads to vasogenic edema, which is well detected with MRI, predominantly in the parieto-occipital lobes. Cytokines and hypertension trigger this process, leading to the development of PRES [23, 24, 21].

5.2. Immunosuppressive drugs

According to a study that included 3,278 cases, a link was identified between PRES and 73 drugs, with an overall mortality rate of 8.1% [25]. Among these, immunosuppressive agents, particularly

Table 1: Presentation, Risk Factors, and Evaluation of PRES

Symptoms	- Acute arterial hypertension (61–80%)
	- Epileptic seizures (70–74%)
	- Encephalopathy (28–92%)
	- Visual disturbance (20–67%)
	- Headache (26–53%)
	- Focal neurological signs (5–15%) [12]
Risk Factors	- Hypertension
	- Kidney disease
	- Pre-eclampsia
	- Liver disease
	- Exposure to chemotherapy agents (e.g., platinum drugs), immunosuppressive and cytotoxic medications [10]
Epidemiology	- More common in middle-aged females [10]
Evaluation	- CT scan
	- MRI
	- Blood work for electrolyte abnormalities (uremia, hypoalbuminemia, hypomagnesemia)
	- Lumbar puncture in immunocompromised patients
	- EEG [10]
Differential Diagnosis	- Intracranial, subdural, or subarachnoid hemorrhage
	- Cerebral venous sinus thrombosis
	- Hypoglycemia
	- Uremic encephalopathy
	- Encephalitis [13]
Complications	- Focal deficits from epilepsy, ischemic injury, or transforaminal cerebellar herniation [10]

the calcineurin inhibitors tacrolimus and cyclosporine, are the most frequently implicated, especially in patients receiving solid organ or hematopoietic stem cell transplantation, or in autoimmune and oncologic contexts [26, 27, 28]. PRES associated with systemic tacrolimus has been reported in transplant recipients and patients with autoimmune conditions. In contrast, topical formulations used for dermatologic indications, such as eczema, are not associated with this complication. Rituximab, used in systemic autoimmune diseases such as systemic lupus erythematosus and in certain malignancies, has also been linked to PRES, occasionally presenting with acute visual loss and seizures [27]. Patients with PRES related to immunosuppressive therapy generally show a favorable prognosis when detected early. However, delayed recognition can result in serious complications or death, underscoring the importance of prompt MRI evaluation in immunosuppressed patients presenting with neurological symptoms [29].

5.3. Autoimmune diseases

Multiple autoimmune diseases have a crucial association with PRES, as reported in a large cohort containing more than 3000 hospitalized PRES cases. These diseases include systemic lupus erythematosus, systemic sclerosis, systemic vasculitis, Sjögren syndrome, and vasculitis [30]. The development of PRES in patients

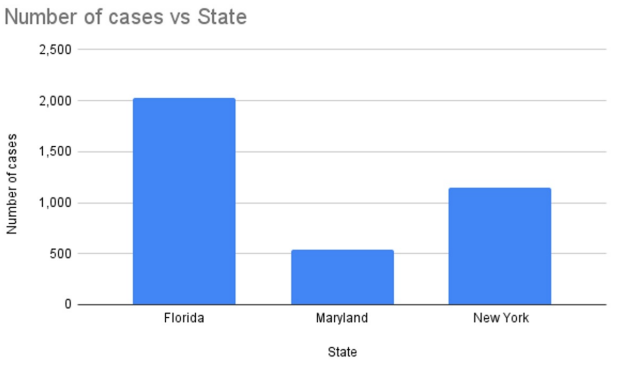

Figure 1: Number of Posterior Reversible Encephalopathy Syndrome (PRES) cases reported in Florida (2016–2019), Maryland (2016–2019), and New York (2016–2018), adapted from Otite et al. (2023) [14].

with autoimmune diseases is a multifactorial process, with endothelial dysfunction playing the central role. This process can also be exacerbated by hypertension and renal impairment [31]. Clinical manifestations of PRES in autoimmune patients do not differ from manifestations of other triggers, including visual loss and seizures. Additionally, MRI shows subcortical hyperintensities in the parietal and occipital lobes [32, 33].

5.4. Sepsis

Approximately 8.9% of patients with sepsis complicated by encephalopathy exhibited radiological features consistent with PRES in a published cohort study [34]. Moreover, a reported case of a patient with septic shock who developed PRES in the absence of hypertension underscores sepsis as a significant non-hypertensive trigger [35]. In one cohort study, gram-positive bacteria accounted for 84% of PRES cases associated with sepsis. This finding may reflect the microbiological profile of that specific population rather than a universal trend [36, 37]. The toxins produced by these organisms can induce a systemic inflammatory response, leading to endothelial injury and blood–brain barrier dysfunction, which contribute to the pathogenesis of PRES.

6. Pathophysiology of PRES

PRES is a neurologic condition characterized by vasogenic edema most often occurring in the parieto-occipital lobes. Endothelial injury, disruption of the blood-brain barrier (BBB), and loss of cerebral autoregulation are the major pathological factors that contribute to the occurrence of PRES. Depending on the cause, endothelial damage is the primary harm, occurring through several pathways. Acute blood pressure increases that exceed cerebral autoregulation cause physical damage at the endothelium level in early hypertensive PRES, which accounts for 60–80% of patients. Similar to this, endothelial integrity is compromised when immunosuppressants such as tacrolimus are present. This is due to the ability of these medications to block endothelial tight junctions by inhibiting the calcineurin-NFAT signaling pathway and reducing the production of occludin and claudin-5 [38, 39, 40]. Anti-angiogenic factors from the placenta, such as soluble endoglin and sFlt-1, are systemic VEGF antagonists in eclampsia [41]. After endothelial injury, the BBB can be disrupted in several ways. TNF-alpha, IL-1 beta, and IL-6 are a few inflammatory cytokines known to induce the production of matrix metalloproteinases that dissolve

tight junctions and facilitate edema. Hypoalbuminemia has also been implicated as a contributing factor in the development of PRES. Low serum albumin levels (<3 g/dL) have been reported in patients with PRES, which may decrease plasma oncotic pressure and exacerbate vasogenic edema following endothelial injury [8, 42]. Vasogenic edema is characterized by increased apparent diffusion coefficient (ADC) values on MRI, whereas restricted diffusion indicates cytotoxic injury [43]. Compared to the anterior regions, the posterior circulation has less sympathetic innervation, making it more vulnerable to damage [44, 26, 43]. Recent reports have investigated the de novo mechanism of intravascular permeability through vasopressin-induced V1a receptor recognition. Genetic polymorphisms in endothelial nitric oxide synthase (eNOS) (rs1799983) and endogenous vascular endothelial growth factor (VEGF) (rs699947) may also be associated with PRES. It was reported that systemic lupus erythematosus, an autoimmune-mediated PRES that is seen in approximately 10-15% of cases, may be associated with PRES due to complement activation and immune complex deposition [45, 46].

7. Genetic Predispositions Emerging Discoveries

As described previously, there has been a significant shift in the understanding of PRES over the years, and several hypotheses regarding possible genetic predispositions have been explored; however, none have yet been confirmed. Endothelial dysfunction plays a key role in the proposed pathogenesis of PRES. Polymorphisms in genes coding for endothelial nitric oxide synthase (eNOS) and methylenetetrahydrofolate reductase (MTHFR), which may impair vascular function, have been hypothesized to increase susceptibility to PRES, particularly in conditions such as preeclampsia that share overlapping mechanisms [47]. Similarly, potential associations between aquaporin-4 (AQP4) gene variants and reduced water permeability, leading to cerebral edema, have been described. Four non-synonymous single-nucleotide variants were identified, suggesting a theoretical role for AQP4 dysfunction in edema-related disorders [48]. However, a genomic study by Matiello et al. involving 23 PRES patients did not find supporting evidence [49]. Additionally, AQP4-IgG autoantibodies—typically seen in neuromyelitis optica spectrum disorder (NMOSD)—have not been detected in PRES without NMOSD, further supporting the argument against a direct causal link [50]. Rarely, PRES-like changes have been observed in recurrent NMOSD with AQP4 autoimmunity, which may reflect a distinct pathogenic process [51]. Emerging evidence has also suggested a possible role of the arginine vasopressin (AVP) pathway in PRES development, potentially through AVP-mediated cerebral vasoconstriction and endothelial stress. Genetic variants affecting the AVP axis, including genes that encode the hormone, its receptors, or modulators, may contribute to susceptibility; however, confirmatory studies are still required [46]. PRES has been reported in association with autoimmune diseases, particularly systemic lupus erythematosus (SLE) and neurolupus [52]. Elevated cytokines such as interleukin-6 (IL-6) and interleukin-10 (IL-10) have been observed in SLE patients who develop PRES [53]. IL-6 may also influence AVP release, providing a mechanistic link between inflammation, vascular regulation, and hormonal response [46, 54]. Furthermore, some reports suggest that immunosuppressive therapy, especially calcineurin inhibitors, may predispose to PRES, partly via AVP-mediated vasoconstrictive mechanisms [46, 55].

8. Management Strategies of PRES

The key element for efficient management is the early diagnosis, prompt recognition of signs and symptoms, and differentiation from other similar conditions, such as intracranial hemorrhage. Management strategies are tailored according to the underlying cause of PRES. That's why the first thing is to identify the trigger and to manage or reverse it. However, most of the cases require ICU care for aggressive management of their symptoms, e.g., seizures and status epilepticus. So, once PRES is suspected, transfer to the intensive care unit should be considered [56]. In general, the acute management of PRES is supportive, for example:

- Hemodynamically unstable: Adequate hydration and correction of any electrolyte disturbance.
- PRES with acute hypertension: As it is the most contributing factor according to the literature, blood pressure should be reduced gradually by approximately 20–25% within the first few hours to avoid cerebral, coronary, and renal hypoperfusion [56, 10]. First-line intravenous antihypertensive agents include nicardipine, labetalol, or clevidipine, selected according to comorbidities and local availability. Alternative agents such as hydralazine or sodium nitroprusside may be considered if preferred drugs are unavailable or contraindicated, though these are used less commonly in contemporary practice [56, 17, 10].
- Drug-induced PRES (e.g., immunosuppressive drugs): Immediate withdrawal of the offending immunosuppressive or cytotoxic agent is the first-line management strategy.
- Eclampsia or preeclampsia: Delivery remains the definitive treatment, but timing should be individualized based on gestational age, maternal condition, fetal well-being, and multidisciplinary assessment.
- Renal failure–induced PRES: Optimize renal function and manage contributing metabolic disturbances. Initiate dialysis only when standard indications are met, such as refractory uremia, fluid overload, or electrolyte imbalance unresponsive to medical therapy.
- Seizures in pregnant women: Magnesium sulfate remains the agent of choice for seizure control and prophylaxis of eclampsia [1].
- Seizures in non-pregnant patients: A stepwise approach is recommended, beginning with benzodiazepines (e.g., diazepam or lorazepam) as first-line therapy, followed by second-line antiepileptic drugs such as levetiracetam, fosphenytoin, or valproate if seizures persist. Agent selection should consider comorbidities, drug interactions, and reproductive status.
- Status epilepticus: Requires emergency management. Secure the airway, administer benzodiazepines, and then load with levetiracetam, valproate, or fosphenytoin. For refractory status epilepticus, anesthetic agents such as propofol, pentobarbital, or midazolam may be used under ICU monitoring [56, 17].

9. Malignant PRES and How to Manage

Malignant PRES, by definition, is characterized by the presence of coma with a Glasgow Coma Scale (GCS) score of <8, deterioration despite standard management for elevated intracranial pressure, and radiological evidence of edema [57]. This condition requires aggressive management that may include mechanical ventilation,

transfusion of blood products for reversal of coagulopathy, and corticosteroids for patients with autoimmune disorders. Furthermore, intracranial pressure should be monitored because it may cause obstructive hydrocephalus that requires an external ventricular drain [58].

10. Prognosis and Long-Term Outcomes

Regarding prognosis, although PRES was initially described as a benign and reversible condition, subsequent studies have shown that it can occasionally be associated with substantial morbidity and even mortality, depending on the underlying etiology and clinical context [8, 59, 39]. Many survivors may experience varying degrees of long-term neurological sequelae, including motor impairment, epilepsy, or cognitive dysfunction [59, 39]. Follow-up imaging frequently reveals residual structural lesions, and the overall outcome depends largely on the rapid identification and management of the precipitating cause [39]. Favorable outcomes are most often observed in cases related to pre-eclampsia or eclampsia, whereas poorer outcomes are linked to delayed recognition, severe encephalopathy, or extensive imaging abnormalities [59, 39]. Recurrent episodes of PRES have been reported in a small subset of patients, typically those with ongoing systemic or vascular risk factors such as autoimmune disease, renal impairment, or uncontrolled hypertension [39, 59] . Several clinical and radiological factors have been identified as predictors of poor outcomes in PRES, as reported in prior cohort and imaging-based studies. These include severe encephalopathy, hypertension-related or sepsis-associated PRES, delayed recognition or management of the underlying trigger, and the presence of comorbidities such as renal dysfunction or autoimmune disease. Laboratory abnormalities, such as elevated C-reactive protein, coagulopathy, and metabolic derangements, have also been associated with an unfavorable prognosis [8, 59, 45]. Radiologically, corpus callosum involvement, extensive cerebral edema, intracerebral or subarachnoid hemorrhage, and restricted diffusion on MRI have been described as adverse prognostic indicators. These findings are summarized narratively in the text rather than in tabular form, given the heterogeneity of reporting across studies [59, 45]. Despite recovery in many patients, structured long-term follow-up remains crucial. Regular neurological and neurocognitive assessments are recommended after discharge to detect delayed sequelae or recurrence. Patients with persistent deficits may benefit from individualized rehabilitation programs that incorporate physiotherapy, occupational therapy, and cognitive rehabilitation. However, no standardized follow-up or rehabilitation protocol currently exists, highlighting a key area for future research.

11. Clinical Practice Implications

Although PRES remains a heterogeneous syndrome, several practical points emerge from the current evidence synthesis. First, early clinical recognition and prompt MRI evaluation should be prioritized in any patient presenting with acute seizures, encephalopathy, or visual symptoms, particularly in the presence of hypertension, renal dysfunction, autoimmune disease, or exposure to immunosuppressive agents. Clinicians should maintain a low diagnostic threshold, as timely identification markedly improves outcomes [45, 14]. Second, management must be context-specific. In tertiary care centers, access to rapid MRI, neurocritical care units, and multidisciplinary teams (including neurology, nephrology, obstetrics, and intensive care) enables aggressive yet controlled management, including blood pressure titration, seizure prophylaxis, and etiologic treatment. In community or resource-limited hospitals, where MRI or intensive care may be delayed, clinical suspicion combined with CT and supportive measures (gradual BP reduction, removal of triggers, seizure control) remains the cornerstone, with transfer to higher-level care when feasible [12, 45]. Third, education and training are critical. PRES often presents across multiple specialties, such as neurology, internal medicine, nephrology, and obstetrics, and its reversibility depends on early detection. Incorporating PRES recognition algorithms, imaging interpretation workshops, and inter-disciplinary simulation exercises into postgraduate curricula and continuing medical education could bridge the existing awareness gap [36, 45, 29]. Finally, protocols should emphasize multidisciplinary coordination and structured follow-up imaging to detect residual lesions or recurrence, ensuring long-term neurological recovery.

12. Limitations

While this review provides an integrated synthesis of the literature on PRES, several limitations should be acknowledged. First, as a narrative review, the study is inherently subject to selection bias despite efforts to ensure comprehensive database coverage and predefined inclusion criteria. The absence of a formal quantitative synthesis or meta-analysis limits the ability to derive pooled effect estimates or assess publication bias. Second, the heterogeneity among included studies, which span different populations, clinical settings, diagnostic criteria, and imaging protocols, may influence the generalizability of the findings. Third, the reliance on English-language publications and exclusion of non-peer-reviewed material may have led to the omission of relevant evidence from other regions. Lastly, variations in reporting standards and retrospective data in many studies limit the causal interpretation and weaken the strength of conclusions. Future prospective and multicenter studies with standardized diagnostic and reporting frameworks are warranted to validate these observations and refine the understanding of PRES subtypes and outcomes.

13. Conclusion

Beyond its historical association with hypertension, PRES is now recognized as a multifactorial neurovascular condition with diverse etiologies and complex pathophysiology. Although hypertension remains a common precipitating factor, a considerable number of cases occur in normotensive patients, emphasizing the need to explore non-hypertensive mechanisms. PRES encompasses a broad clinical and radiologic spectrum, typically manifesting with vasogenic edema in the parieto-occipital regions, though atypical patterns are not uncommon. Diagnostic challenges persist, particularly in normotensive or atypical presentations, underscoring the importance of maintaining high clinical and imaging suspicion. While several mechanisms have been proposed, the pathogenesis of PRES remains incompletely understood, and emerging genetic hypotheses require further validation. The current evidence base, largely derived from observational, case-based, and heterogeneous studies, supports associations but does not establish definitive causation. Management continues to rely on prompt recognition, supportive care, and treatment of the underlying trigger. Although outcomes are often favorable, neurological morbidity and mortality may occur, especially in severe or delayed cases. Recurrent PRES has also been described in patients with persistent systemic risk factors. Given the heterogeneity and predominantly retrospective nature of existing evidence, future prospective and multicenter studies are needed to better characterize PRES subtypes, confirm genetic and molecular associations, and guide the development of targeted management strategies toward more individualized care.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Large Language Model

None.

Authors Contribution

MH and PS drafted the original manuscript, reviewed and edited the draft, and managed the project administration; AI and AH drafted the original manuscript and reviewed and edited the draft; SM drafted the original manuscript and contributed to visualization; GP, ES, AM, and RV drafted the original manuscript; HA contributed to visualization and table preparation; and SC reviewed and edited the draft and contributed to validation and supervision. All authors contributed to the manuscript's text and content, approved the final version, and agreed to be accountable for the work.

Data Availability

This study is a narrative review and does not involve the collection, analysis, or generation of new primary data. All data discussed in this article are derived from previously published studies that are publicly available through indexed scientific databases, including PubMed, Web of Science, and Google Scholar. No new datasets were created or analyzed for this review. Relevant references are fully cited within the manuscript. Data supporting the findings of the included studies can be accessed directly through their respective publications.

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