

Clinical and Neuroimaging Spectrum of Posterior Reversible Encephalopathy Syndrome in Pediatric Patients: A Review Article

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Received:
Feb 14, 2025

Accepted:
Mar 17, 2025

Published:
Mar 24, 2025

Abstract

Background and Objectives: Posterior Reversible Encephalopathy Syndrome (PRES) is an acute neurological syndrome distinguished by a variety of clinical features and characteristic neuroimaging findings associated with focal cerebral edema. Heterogeneous etiologies are encountered, with acute hypertension due to renal disorders being the principal risk factor.

Objectives: The primary aim of this study was to provide a comprehensive review of the available information regarding Posterior Reversible Encephalopathy Syndrome, including its clinical manifestations and risk factors in children.

Methods: An extensive search of the PubMed database was conducted for relevant articles published from January 2010 to December 2024. Correlated data from eligible articles were extracted and described.

Results: The principal neuroimaging finding of Posterior Reversible Encephalopathy Syndrome (PRES) is bilateral cerebral vasogenic edema, predominantly located in the occipital and posterior parietal white matter. Several mechanisms contribute to this condition, including dysfunction of cerebral autoregulation due to severe acute hypertension and breakdown of the blood-brain barrier resulting from endothelial injury. The combination of acute neurological manifestations, neuroimaging findings of vasogenic edema, and the presence of related provoking disorders raises suspicion for PRES. The mainstay of treatment is supportive care. In most patients, total resolution of abnormal clinical findings and imaging features occurs.

Conclusion: Although many clinical features of pediatric PRES are similar to those in adults, there are notable differences, particularly regarding neuroimaging findings. The spectrum of clinical and neuroimaging findings of PRES in children is not widely recognized. Early diagnosis of the syndrome, identification of related risk factors, and appropriate management are crucial and can be life-saving.

Keywords: Children, Neuroimaging, Posterior Reversible Encephalopathy Syndrome

Funding: None

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Cite this article as: Tavasoli A. Clinical and Neuroimaging Spectrum of Posterior Reversible Encephalopathy Syndrome in Pediatric Patients: A Review Article. *Iran Red Crescent Med J.* 2025.31.1-9.

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↑Question What are the clinical characteristics, risk factors, pathophysiology, neuroimaging findings, and treatment aspects of pediatric patients with PRES?

📌Findings Posterior Reversible Encephalopathy Syndrome (PRES) is an acute neurological syndrome characterized by a variety of clinical features and distinctive neuroradiological findings resulting from focal cerebral edema. Children with specific conditions, such as oncologic, rheumatologic, and renal disorders, are at an increased risk for developing PRES. The outcome largely depends on the presence of concomitant or pre-existing disorders. In most patients, a total resolution of abnormal findings occurs; however, neurological sequelae have been reported in some cases.

→Meaning PRES is a significant neurological condition that can complicate various underlying disorders, thereby increasing morbidity and mortality rates. Physicians, especially pediatricians, should be familiar with this syndrome because early diagnosis and appropriate treatment are crucial to prevent long-term neurological complications.

1. Introduction

The frequency of hypertension in the pediatric population has increased in recent years, ranging from 5.42% to 19.4% (1). Hypertension is among the most common complications in children and adolescents with chronic or acute renal disease (2, 3). In hemolytic uremic syndrome (HUS), neurological involvement is associated with high mortality rates, and hypertension is one of the primary factors contributing to neurological complications (4). Furthermore, hypertension has been linked to an increased incidence of long-term neurological problems in children with HUS (5). In patients with renal disorders, hypertension is also a significant trigger for Posterior Reversible Encephalopathy Syndrome (PRES) (6).

PRES is an acute neurological syndrome characterized by a variety of clinical features and distinctive neuroradiological findings resulting from focal cerebral edema (7). While heterogeneous etiologies are encountered, acute hypertension due to renal disorders remains the principal risk factor (6). Other related factors include collagen vascular disorders, autoimmune diseases, chemotherapy or immunosuppressive treatment, blood transfusions, sepsis, and preeclampsia/eclampsia (6, 8).

The main clinical findings of PRES include headache, altered level of consciousness, obscured vision, and seizures. The primary neuroradiological finding is bilateral cerebral vasogenic edema, predominantly in the occipital and posterior parietal white matter, which mainly results from disturbances in neural vascular autoregulation in the brain (9, 10). Several mechanisms are involved, particularly hypertensive encephalopathy; however, this mechanism is somewhat debated, as studies indicate that some patients may not present with hypertension (11). Another underlying mechanism is the breakdown of the blood-brain barrier due to endothelial injury (10).

Evidence suggests that PRES is not always completely reversible, and its radiological findings are not limited to the parieto-occipital regions in some patients (6). Consequently, more presentations and radiological findings have been reported in recent years compared to the features initially described by Hinchey et al. in 1996 (12). The spectrum of clinical and neuroimaging findings of PRES in children is not widely recognized. Therefore, early diagnosis of the syndrome and its risk factors is crucial and can be life-saving (13).

2. Materials and Methods

The primary aim of this study was to provide a comprehensive review of the available information regarding Posterior Reversible Encephalopathy Syndrome (PRES), including its clinical manifestations and risk factors in children. An extensive search of the PubMed database was conducted for relevant articles published from January 2010 to December 2024 using the following query: ("Posterior Reversible Encephalopathy Syndrome" [Mesh] OR "Posterior Reversible Encephalopathy Syndrome" [tiab]) AND ("Child" [Mesh] OR Child*[tiab] OR Pediatric*[tiab] OR "Pediatrics" [Mesh]).

All study designs were included. Reference lists of appropriate articles were manually searched to gather additional data. Only articles with available full texts were included, while papers in non-English languages and non-human studies were excluded. Articles were screened based on their titles and abstracts, and irrelevant full texts were also excluded. The relevant data from eligible articles regarding the epidemiology, risk factors, pathophysiology, clinical presentations, neuroimaging findings, differential diagnosis, diagnostic evaluation, treatment, and outcomes of pediatric PRES were extracted and described.

3. Results

3.1. Epidemiology

PRES can occur in all age groups, from 4 to 90 years old; however, it is most common in young adults (14). In adults, there is a female predominance of the disease, excluding patients with eclampsia, which indicates gender specificity in some underlying disorders related to PRES (15-17). Conversely, some studies in pediatric patients have reported that PRES is more prevalent in boys (13).

Approximately 40% of all patients develop significant complications that lead to admission to the Pediatric Intensive Care Unit (PICU), including status epilepticus, increased intracranial pressure, intracerebral hemorrhage, or acute cerebral ischemia (14). The global incidence of PRES in the pediatric population is unknown, but it appears to be rare (18). Frequency rates of 3.5% and 5.6% have been reported following renal transplantation in different studies (19). Additionally, a rate of 0.4% has been reported among children admitted to critical care units, and 0.7% among children with malignancies (15).

Other studies have indicated an approximate incidence of 0.04% among general pediatric admissions for PRES-predisposing diseases (20). According to another study, 5.2% of complicated children who received hematopoietic stem cell transplants developed PRES (21). The most common underlying disorder provoking PRES in children is renal failure, followed by hematologic disorders and their treatments (21). Cancer chemotherapeutic drugs and total body irradiation may also trigger PRES in pediatric patients (21).

3.2. Pathophysiology

The exact pathological mechanisms of PRES have not been fully elucidated, leading to controversies surrounding the condition (13). Several mechanisms have been described, all of which result in vasogenic edema in the brain (8, 19). Four hypotheses have been proposed:

1. *Vasogenic Theory*: This theory posits that increased blood pressure is a key feature, and rapid increments in arterial blood pressure can overwhelm the cerebral autoregulatory system. Consequently, the failure of compensated vasoconstriction leads to arteriolar dilation, resulting in plasma leakage into brain tissue and concomitant brain edema. Disturbances in the blood-brain barrier and protein extravasation also occur (13). The posterior regions supplied by the posterior cerebral arteries, basilar artery, and

vertebral arteries are particularly at risk because the sympathetic innervation of the basilar artery is less than that of the anterior (carotid) circulation (22). The variation in innervation between the posterior and anterior circulation is less pronounced in the immature brain, which explains the greater variability in the distribution of neuroimaging lesions among pediatric patients (23). Notably, 30% of cases with PRES do not exhibit severe hypertension sufficient to overcome autoregulatory control (7). In the context of chronic hypertension, the range of autoregulation shifts rightward, allowing the autoregulatory system to function within a broader blood pressure (BP) range. Therefore, autoregulatory failure is more likely to result from acute increases in blood pressure compared to gradual changes (24). Studies indicate that the velocity of BP increase is a more significant risk factor for hypertensive encephalopathy and PRES than absolute BP values or even a history of previous hypertension (25).

2. Neuropeptide Theory: The neuropeptide theory posits that the release of vasoconstrictors from disturbed endothelium leads to vasospasm, resulting in local ischemia, which subsequently causes blood-brain barrier dysfunction and vasogenic edema (8). Some authors also suggest that severe hypertension and an unbalanced autoregulatory response may exacerbate vasospasm (13).

3. Cytotoxic Theory: The cytotoxic theory emphasizes that endothelial disturbance is the primary defect, induced by various drugs and toxins, such as immunosuppressive or chemotherapeutic agents, ultimately leading to capillary extravasation and vasogenic edema (8, 26, 27). This has been reported in cases involving immunosuppressive drugs like FK-506 and cyclosporine A (13). This theory also accounts for the occurrence of PRES in patients with sepsis, where hypertension arises as a result of primary endothelial disturbance (6).

4. Immunogenic Theory: The immunogenic theory points to endothelial damage and dysfunction caused by T-cell stimulation, leading to cytokine secretion. This, in turn, results in endothelial activation and the release of vasoactive substances, ultimately causing vascular leakage and edema (8). For instance, unbalanced levels of vascular endothelial growth factor (VEGF), which regulates endothelial permeability, can lead to cerebral edema (21). This mechanism is implicated in the development of PRES in the context of autoimmune diseases or sepsis (28). The combination of these various mechanisms may coexist and contribute to the development of PRES in different patients (28).

In individuals with acute kidney injury, hypertension, along with concurrent endothelial injury in the brain, leads to PRES (9). Additionally, uremic encephalopathy in acute or chronic kidney disease is associated with oxidative damage, neurotransmitter dysfunction, hormonal imbalances, and metabolic disturbances (29, 30). In patients with hemolytic uremic syndrome or thrombotic thrombocytopenic purpura, endothelial cell disturbance plays a crucial role in the pathogenesis of PRES (16).

PRES has been commonly reported among patients receiving immunosuppressive agents after stem cell and bone marrow transplantation (8%) or solid organ transplantation

(0.4-6%) (6). This high incidence may be related to the elevated doses of immunosuppressive agents, which are responsible for the secretion of vasoconstrictors and subsequent hypertension (6). Furthermore, the range of cerebral autoregulatory function in children is narrower than in adults, making children more susceptible to cerebrovascular disturbances in the presence of hypertension. The minimum threshold for cerebral autoregulation is approximately 50-60 mm Hg in adults compared to 40 mm Hg in the pediatric population (21).

Studies have indicated that PRES can develop at a mean blood pressure of 140/85 mm Hg in children (31). Therefore, children are likely more prone to developing PRES (21). The reduction of blood pressure (BP) can inhibit the progression of cytotoxic edema and its complications, such as cerebral infarction (21). Other proposed causes of PRES include disturbances in circulatory volume, uremia, and electrolyte imbalances (24).

In general, the risk factors for the development of PRES are as follows: autoimmune disorders, acute or chronic renal disease, malignancy, inflammatory bowel disease, preeclampsia, hematopoietic stem cell or solid organ transplantation, sepsis, hypertension, and immunosuppressive or antineoplastic treatment (24) (Table 1). Studies indicate that among children with PRES under the age of 6, the likelihood of admission to the PICU and the occurrence of status epilepticus are greater compared to older patients (24).

Pediatric patients with hematologic malignancies and those who have undergone hematopoietic stem cell transplantation (HSCT) have a particularly elevated risk for developing PRES. The highest risk occurs during the induction phase of chemotherapy (32). Various chemotherapeutic agents have been implicated, including L-asparaginase, etoposide, and corticosteroids (33). Additionally, in pediatric patients with malignancies who develop PRES, electrolyte disturbances—especially hypokalemia, hypocalcemia, and hypomagnesemia—have been reported (34).

According to one study, PRES was the most common

Table 1. Predisposing factors for PRES in pediatric population

Hypertension
Chronic kidney disease
Acute kidney injury
Bone marrow transplantation
Solid organ transplantation
Autoimmune diseases
Sepsis and multiple organ failure
Acute intermittent porphyria
Malignancy
Sickle cell anemia
Thrombotic-thrombocytopenic purpura
Blood transfusion
Acquired immunodeficiency syndrome
Surgery
Immunosuppressive medications
Cancer chemotherapy medications
Monoclonal antibodies
Immunomodulatory cytokines (Interferon, Interleukin)
Antibiotics (Linezolid, Ciprofloxacin)
Growth factors
Intravenous immunoglobulins
Other drugs (Intravenous contrast agents, Carbamazepine, Epi-nephrene)

neurological complication (60%) among childhood recipients of HSCT, highlighting the need to consider PRES in patients presenting with neurological issues (35). Calcineurin inhibitors prescribed to HSCT recipients may precipitate PRES; while the exact mechanism is unclear, it may be related to increased BP, a frequent side effect of these drugs. Another suggested mechanism, in the absence of hypertension, is direct endothelial toxicity (36).

3.3. Clinical Manifestations

PRES is characterized by various neurological manifestations that can present acutely or sub-acutely, typically within a few hours to several days (22). However, it usually has an acute onset that peaks within 12 to 48 hours (13). The clinical features are generally nonspecific (21). Patients may present with encephalopathy, headache, seizures, focal neurological signs, and visceral abnormalities.

Encephalopathy occurs in most patients and is the first manifestation in 28% of cases (13). Its severity can vary from mild cognitive deficits to stupor or coma and may be observed as ictal or postictal events during seizures (22). The incidence of altered consciousness in pediatric patients with PRES is lower than that in adults (21).

Headache has been reported in 50% of patients and is typically described as dull, persistent, and sometimes intractable (37). Seizures are observed in 81% of patients and are the most common findings in pediatric PRES patients. The seizures are predominantly generalized tonic-clonic (60-75%), although focal onset seizures and both convulsive and non-convulsive status epilepticus are also seen (37). Status epilepticus may develop in 13-15% of patients and can be the presenting sign, posing a potential life threat (6).

A significant risk factor for the occurrence of seizures is the involvement of the occipital lobes (13). Seizures may be preceded by visual disturbances indicative of occipital lobe origin (21). In pediatric PRES patients, seizures are more frequent and have an earlier onset compared to adult patients (21). In 64% of pediatric patients with PRES, electroencephalography (EEG) shows nonspecific changes associated with encephalopathy (38). When bilateral occipital sharp waves are observed on EEG, PRES may be suggested as the provoking factor for status epilepticus (28).

Focal neurological manifestations are reported in 5-15% of patients and are related to the location of the brain edema (6, 13). The deficits include hemiparesis in 8.5%, hemiplegia in 4.2%, and speech abnormalities in 4.2% of patients (22). Some studies have also reported myelopathy and involvement of the spinal cord (39). Visual abnormalities are common and can be severe, occurring in up to 39% of patients (13). These findings include visual field deficits, blurred vision, temporary visual loss, blindness, and visual hallucinations. Ophthalmologic examination is usually normal but may reveal papilledema in severe cases (39).

The incidence of visual disturbances in children is lower than in adults (38). According to studies, transient bilateral visual loss is the most common visual complaint, and a history of hypertension is present in all patients with visual disturbances (40). The frequency of ophthalmic manifestations appears to be higher in certain disorders associated with PRES, such as eclampsia (13). Visual involvement is

complete in the majority of cases. Hypertension occurs in 70-80% of patients, and its association with the aforementioned nonspecific neurological findings serves as a diagnostic hallmark (21, 38).

In children, a blood pressure (BP) that is 30% higher than the 95th percentile for age-appropriate BP is an alarming finding indicative of potential PRES onset (21). Studies indicate that 85% of pediatric PRES patients are hypertensive, underscoring the crucial role of elevated BP in the pathogenesis of the disease (41). Elevated BP in children is often associated with systemic disorders. The clinical presentation of PRES in younger children (under 6 years old) is typically more severe than in older children, and status epilepticus is more frequent in this age group (24, 42). Patients experiencing status epilepticus have a higher likelihood of developing later epilepsy (24). Rarely, involvement of the spinal cord may result in back pain, weakness in the lower limbs, and incontinence (21).

2.4. Diagnosis and Neuroimaging Features

The diagnosis of PRES is typically made by excluding other possible diagnoses (43). The combination of acute neurological manifestations, alterations in blood pressure, and neuroimaging findings of vasogenic edema, along with the presence of related provoking disorders, raises suspicion for PRES (6). The diagnosis is generally confirmed through brain magnetic resonance imaging (MRI) (13). Abnormalities in neuroimaging usually appear within 24 hours of the clinical onset (21).

A brain CT scan is often the early imaging performed in emergency settings and may reveal vasogenic edema as hypointense areas in the affected white matter regions bilaterally (6, 44). However, CT is not considered reliable for establishing a definitive diagnosis of PRES (21). The high specificity and sensitivity of MRI make it valuable for more precise characterization of abnormalities and for differentiating PRES from other clinically similar conditions (43).

In pediatric cases of PRES, the detection rate of lesions is 46% on initial brain CT compared to 98% on brain MRI (41). MRI findings indicative of vasogenic edema are typically distributed in the bilateral parietal-occipital regions, appearing as symmetric hyperintense areas on T2 and FLAIR images. However, the lesions may also spread asymmetrically (6). Subcortical white matter is predominantly affected due to its lower density, although cortical lesions have also been reported (6). On diffusion-weighted imaging (DWI), areas of vasogenic edema may show hyperintense signals that are not associated with corresponding reduced signals or restricted diffusion on the apparent diffusion coefficient (ADC) map. T1-weighted images commonly reveal hypointense foci at the same sites as the lesions, accompanied by normal DWI findings (44).

There are different patterns of cerebral involvement in PRES, including watershed pattern observed in one hemisphere, superior frontal groove pattern, and parietooccipital pattern. In some cases, brain edema may exhibit a central involvement pattern (affecting the brainstem) while sparing subcortical and cortical areas. This pattern impacts the periventricular regions, internal capsule, basal ganglia, brainstem, and cerebellum (28).

A few patients present with extensive longitudinal edema of the central cord without evidence of ischemia, demyelination, or infection (45). It has been reported that infratentorial manifestations are more frequent among PRES cases associated with significant hypertension (44). Atypical regions of cerebral lesions may occur in the cerebellum, basal ganglia, brainstem, corpus callosum, and other cerebral areas, with the inferior temporal and frontal lobes being particularly common atypical sites (13, 21) (Figure 1). Leptomeningeal enhancement on contrast-enhanced T1-weighted images and mild hyperintensity of the sulci on FLAIR images have been suggested as initial findings of PRES, often preceding the appearance of typical findings in the parieto-occipital regions.

In the majority of patients, complete recovery of imaging findings occurs over several weeks; however, lesions are not always reversible. Disorders that should be radiologically distinguished from PRES include those that present with similar confluent T2 hyperintensities in cerebral white matter, such as infarction, ischemia, infections, demyelinating disorders, metabolic disorders, vasculitis, and progressive multifocal leukoencephalopathy (46).

Acute ischemia can be differentiated from PRES in that ischemia results in cytotoxic edema, which appears as hyperintense areas on DWI images, accompanied by a related decrease in signal and diffusion restriction on ADC maps (47). However, in atypical cases of PRES, diffusion restriction observed on DWI or ADC may overlap with areas

of typical vasogenic edema. These atypical MRI findings can indicate cytotoxic edema due to acute ischemia, characterized by increased DWI but decreased ADC signals (47, 48).

In some patients, regions of diffusion restriction can lead to persistent cerebral injury and poor neurological prognosis (13). Occasionally, cerebral hemorrhage may complicate PRES (49), resulting in poor neurological outcomes (48). This complication occurs in 5-30% of adult patients (50). Neuroimaging findings may include gyral petechial hemorrhage, focal hematomas, or subarachnoid hemorrhage (13). The susceptibility-weighted imaging (SWI) technique has shown higher sensitivity than conventional imaging in identifying brain hemorrhages (50) (51).

Atypical MRI findings in PRES cases may include atypical locations of lesions, gadolinium enhancement of lesions, cerebral hemorrhage, and diffuse restriction of affected areas on DWI images (46-48). Gadolinium-enhanced features have been reported in 20% of patients and were not consistently related to clinical severity or prognosis in some studies (28). Atypical lesions have been described in 61-82% of pediatric patients compared to 10-58% of adult cases (48, 52). MRI findings of diffuse restriction have been demonstrated in 15-42% of children compared to 15-30% of adult patients with PRES (53). Additionally, involvement of the superior frontal groove is more common in pediatric PRES patients than in adults (52). The high frequency of atypical neuroimaging findings in pediatric

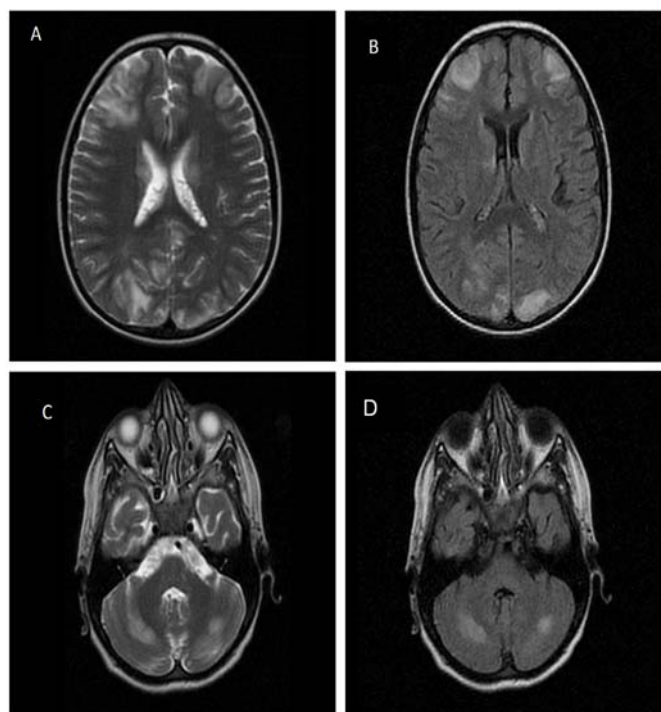


Figure 1. Atypical brain MRI findings of a 10 years old boy with chronic renal failure and hypertension who developed PRES. A-B: Coronal T2-FLAIR sequences shows Bilateral hyperintense lesions in cortical and subcortical white matter on the both occipital and frontal regions. C-D: Bilateral hyperintense lesions in cerebellar hemispheres in T2 and FLAIR images.

PRES complicates the diagnostic process (21).

Other imaging techniques have been utilized in challenging or uncertain cases. Magnetic resonance spectroscopy (MRS) indicates disturbances in neuroaxonal and synaptic function through a decreased N-acetyl aspartate (NAA) to creatine ratio and a decreased NAA to choline ratio (13). Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) reveal either hypoperfusion or hyperperfusion in the affected areas (13). Cerebrospinal fluid (CSF) examination aids in ruling out encephalitis or meningeal involvement in patients with hematologic malignancies (6). Increased CSF albumin levels and an elevated CSF/serum albumin ratio indicate blood-brain barrier disturbance, while albuminocytologic dissociation has been observed in some studies (6). A direct relationship between increased protein levels and the distribution and extent of brain edema has also been reported (28).

Hypomagnesemia during the initial days of the disease, as well as hypoalbuminemia, has been reported in patients with PRES (21). Elevated serum lactate dehydrogenase (LDH) levels may occur in patients with PRES due to malignancy, suggesting endothelial disturbance as a possible pathophysiological mechanism (28). This finding has been associated with more diffuse and larger MRI lesions (28). EEG may occasionally reveal spikes or slow activity, which can be helpful in assessing seizure activity or non-convulsive status epilepticus (19).

Neurological manifestations in patients with acute severe elevations in blood pressure are diagnosed as hypertensive encephalopathy, which is similar to PRES but lacks the characteristic neuroimaging features (24).

3.4. Differential Diagnosis

Despite being a rare disorder, PRES presents a wide range of clinical manifestations and various neuroimaging patterns, leading to diagnostic challenges. The clinical presentations are nonspecific, and MRI findings, combined with a thorough medical history, are essential for excluding other potential diagnoses. Some differential diagnoses for pediatric PRES include: encephalitis (infectious or autoimmune), cerebral venous thrombosis, malignancy, post-transplant lymphoproliferative disease, ictal or postictal state, acute disseminated encephalomyelitis (ADEM), progressive multifocal leukoencephalopathy (PML), ischemic stroke (posterior cerebral artery territory or watershed), cerebral vasculitis, osmotic demyelination syndrome, toxic leukoencephalopathy, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS) (21).

3.5. Treatment

To date, there are no clinical trials or standard therapeutic guidelines available for the management of PRES (13, 21, 24). Therefore, management is primarily supportive and involves the elimination of underlying risk factors, cessation of suspected drugs, prescription of anti-seizure medications for treating seizures, and management of hypertension (24). Therapy is individualized based on associated risk factors, clinical status, and tolerable drug therapy (21).

Complete correction of offending causes, such as renal

failure, hypertension, or immunosuppressive medications, can reduce the risk of permanent complications from PRES, including brain hemorrhage or ischemia, and improve overall outcomes (13, 21). The primary goal of management is to treat hypertension and maintain BP within a normal range (39, 37). Untreated systemic hypertension can lead to cerebral edema. Vigorous BP monitoring and management can decrease related complications in patients with hypertension-associated PRES (13). However, some studies have reported that aggressive BP control did not stop or regress clinical or neuroimaging findings (6). Reduction of BP in children is generally better tolerated compared to adults, except in cases of brain vasculitis and chronic hypertension (21).

Typically, non-rapid lowering of BP is preferred to avoid the development of cerebral ischemia (13). Accordingly, a gradual reduction of mean BP by 20-25% during the initial 2 hours is recommended (22). Following the initial management, a reduction of 30% of the calculated BP is planned within the first 6 hours, another 30% over the subsequent 24-36 hours, and the final third within the following 24-96 hours or later (54). It is crucial to prevent fluctuations in BP, which necessitates continuous use of antihypertensive agents and regular BP monitoring (6). Management of acute hypertension may include oral medications, intermittent parenteral agents, and continuous infusions (24). One of the most frequently used and well-tolerated antihypertensive drugs in children is nitroprusside (21). Other safe agents for children include labetalol, hydralazine, diazoxide, nifedipine, and enalapril (21).

Immediate treatment of seizures is essential, and continuous EEG monitoring is warranted to detect subclinical seizures. Generally, no specific drug is recommended for seizure control (6); however, benzodiazepines and sodium valproate are preferred over cytochrome P450 inducers such as carbamazepine, phenytoin, and phenobarbital (55). Antiseizure therapy is also suggested for the prophylaxis of secondary seizures in patients with PRES (56). The optimal duration of antiseizure treatment is unclear, but long-term treatment is usually not warranted (21, 28). Antiseizure medications can be discontinued when symptoms and imaging findings have improved (6).

Based on a study, a median treatment period of three months is recommended (57). Other authors suggest a duration of 3-12 months for seizure treatment or prophylaxis in cases of PRES; however, in patients with status epilepticus or recurrent seizures, longer durations may be necessary (55). Generally, the interval of treatment depends on underlying triggering factors, the likelihood of continued exposure, and the patient's previous history of seizures (26). It is important to note that in children with renal failure and PRES, the dosage of medications should be adjusted according to renal function (21). Any electrolyte imbalances should be corrected, and serum levels of sodium, magnesium, and calcium should be monitored closely (41). Approximately 35-40% of individuals with PRES may require respiratory support and mechanical ventilation for several days due to refractory seizures or decreased levels of consciousness (21).

Monitoring of intracranial pressure and vigorous supportive management are essential in the treatment of malignant PRES. Malignant PRES is characterized by clinical features (Glasgow Coma Scale score lower than 8 and medical deterioration despite standard management for increased intracranial pressure) and neuroimaging criteria (mass effect due to edema or brain hemorrhage, obliteration of basal cisterns, and cerebral herniation) (28). Recent studies suggest that the pathophysiology of PRES may be related to the stimulation of the arginine vasopressin (AVP) system, either through increased AVP secretion or enhanced receptor density (15). Therefore, inhibiting AVP hypersecretion or suppressing AVP receptors could represent a promising treatment strategy for PRES (21).

3.6. Prognosis

The outcome of Posterior Reversible Encephalopathy Syndrome is primarily determined by concomitant or preexisting disorders (6). In most patients, total resolution of abnormal clinical and neuroimaging findings occurs (24). However, recurrence of PRES is possible (24). Recovery in the majority of patients typically occurs within a week; however, some patients may take longer to recover. It has been reported that 10-20% of adult patients develop neurologic residue.

Permanent complications, particularly epilepsy, may arise in patients with persistent MRI abnormalities (18). Although the long-term frequency of epilepsy remains low (21). Neurologic sequelae have also been described in 10-20% of children with PRES, which likely contributes to prolonged hospital stays and extended PICU admissions (24). According to the results of a meta-analysis, poor prognosis is associated with cerebral hemorrhage and cytotoxic edema observed on neuroimaging.

Another study on adult patients indicated that underlying diabetes mellitus and involvement of the corpus callosum on brain MRI are strong risk factors for poor prognosis in PRES (58). Other factors contributing to poor outcomes in adult patients include hypertension, severe encephalopathy, prolonged time to control the underlying cause, the presence of multiple comorbidities, decreased CSF glucose levels, elevated C-reactive protein (CRP), and coagulopathy (28). Conversely, the presence of seizures or CSF markers has not been reported as prognostic factors among children with PRES (6).

The severity of MRI lesions, including apparent diffusion coefficient (ADC) maps, has been correlated with prognosis in some studies and may be a significant factor in assessing long-term outcomes (59). Mortality in patients with PRES is influenced by underlying disorders and comorbidities, appearing to be higher in patients with malignancies and those undergoing HSCT (24). Causes of serious neurologic damage and death include intracerebral hemorrhage, elevated intracranial pressure, brainstem compression, or hydrocephalus due to posterior fossa edema (15). Overall, total mortality rates in patients with PRES range from 3.2% to 19%, according to various studies (24, 60, 61). Some pediatric patients have exhibited abnormal MRI findings, including leukoencephalopathic lesions, hyperintense changes, and chronic hemorrhagic lesions (31, 62). Brain

MRI findings of cytotoxic edema appear to be a poor prognostic factor (63).

Currently, there are no evidence-based recommendations regarding the optimal timing for obtaining follow-up imaging; this appears to be determined by general clinical considerations (24). According to a previous study, complete or nearly complete resolution of MRI lesions occurred in 85% of patients within 29 days (21). In 5-10% of patients, a transient recurrence may occur 1-2 weeks later, particularly in those with uncontrolled hypertension (64). Overall, the recurrence risk of PRES is estimated to be between 3.8% and 12.5%, although it seems to be higher in pediatric patients (65).

The most common causative factor for both the initial episode and recurrence of PRES in children is repeated hypertension in the context of chronic kidney disease (6, 21, 65). Delayed diagnosis, misdiagnosis, inappropriate management, and failure to adequately address causative factors may lead to worse outcomes in patients with PRES (66). Prognostic determinants in adult patients with PRES include complications from subarachnoid hemorrhage and elevated CRP levels (67). In contrast, prognostic factors in childhood PRES encompass underlying chronic renal disease, duration of stay in the PICU, occurrence of status epilepticus, presence of atypical MRI findings, and elevated inflammatory markers (21). Despite the reversibility of MRI findings, some children may develop permanent brain lesions and brain atrophy. Sclerosis of the hippocampus may also occur, potentially leading to temporal lobe epilepsy several years later (68).

In pediatric patients with PRES, abnormal MRI features in the later stages of the disease have been associated with the occurrence of neurologic sequelae (61). Based on studies involving adults, the distribution and signal intensity of MRI lesions are not correlated with clinical severity, disease complications, or blood pressure levels (21). Notably, it has been suggested that increased signal intensity in DWI is correlated with poorer outcomes in the adult population (69). Additionally, elevated serum levels of CRP and lactate dehydrogenase have been reported as predictors of outcomes in some patients (21, 67, 70). Subtle neurologic complications, such as learning disorders and developmental delays, are particularly significant in children (19).

4. Conclusion

Posterior Reversible Encephalopathy Syndrome (PRES) is a significant neurologic condition that can complicate various underlying disorders and increase mortality rates. Pediatric patients with specific diseases, such as oncologic, rheumatologic, and renal disorders, are at an elevated risk of developing PRES. Children with renal diseases face a particularly high risk due to increased susceptibility to hypertension, electrolyte imbalances, and volume disturbances. Additional risk factors include the underlying pathology of renal disease, toxicity from prescribed medications, and other treatment-related complications.

It is crucial to consider the diagnosis of PRES in pediatric patients presenting with acute headache, new-onset seizures, visual disturbances, or altered levels of consciousness.

ness, especially in the presence of hypertension or other related risk factors. Prompt diagnosis and treatment are essential to prevent long-term neurological sequelae.

Ethical Statement

Not applicable.

Authors' Contributions

Azita Tavasoli: Study design, data acquisition, interpretation and discussion of results, and manuscript writing.

Acknowledgement

This study was supported by Iran University of Medical Sciences. The author would like to thank the Ali Asghar Clinical Research Development Center and Ms. Negar Gholampour for her kind cooperation.

Conflict of Interests

The authors declare that they have no competing interests.

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