



Challenges of Diagnosing Pediatric Posterior Reversible Encephalopathy Syndrome in Resource Poor Settings: A Narrative Review

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a rare clinical syndrome that has been observed in different age groups, including pediatric patients. Identified triggers of PRES in both children and adults have included immunosuppressive and cytotoxic agents, organ transplantation, severe sepsis, blood transfusion, or evidence of human immunodeficiency virus-1 (HIV-1). Its clinical and radiological courses have been reported as mostly benign and reversible over days to weeks. Computed tomography (CT) scans are helpful in diagnosis, but magnetic resonance imaging (MRI) remains the gold standard. Unfortunately, because of the prohibitive costs of such medical equipment, diagnosis remains a challenge in developing countries. There is a dearth of information about pediatric PRES in resource-poor settings. This narrative aims to draw attention to the possible existence of PRES in children and to identify factors responsible for the difficulty in making the diagnosis. This review will hopefully increase awareness of PRES among pediatricians in order to make early diagnosis and institute appropriate management of this condition.

Keywords

children, encephalopathy, Nigeria, PRES, syndrome

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What is Already Known About This Topic

- Posterior reversible encephalopathy syndrome (PRES) is an uncommon but distinctive clinic-radiological entity associated and easily mimicked by a variety of medical conditions and co-morbidities with several identified triggers in both children and adults within the African context.
- The syndrome is often benign if recognized and managed timely with complete clinical reversal within days or weeks.
- Most of the cases of PRES observed in pediatric patients have been reported from developed countries with limited published works in pediatric PRES by researchers in resource-poor settings.

factors responsible for the difficulty in making the diagnosis.

- Even where MRI is available, without a high index of suspicion, the diagnosis may still be missed.

What are Your Research's Implications Toward Theory, Practice or Policy?

It is hoped that this narrative may lead to a higher index of suspicion of PRES among pediatricians in developing

What This Study Adds

- This narrative review has drawn attention to the existence of PRES in children while identifying

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countries and promote timely management of patients to improve the outcome.

Introduction

Posterior reversible encephalopathy syndrome (PRES) was first described in 1996 by Hinchey et al and known as Reversible posterior leukoencephalopathy syndrome (RPLS) following a finding of a reversible syndrome of headache, altered mental functioning, seizures, and loss of vision that was associated with posterior leukoencephalopathy on radiographic images.¹ It has since been recognized as PRES with improved and more readily available brain imaging,^{2,3} and the name “PRES” has now been universally adopted.² With further widespread use of MRI, this complex syndrome is better established, yet findings and appropriate diagnoses are still limited in children.⁴

Posterior reversible encephalopathy syndrome (PRES) is an uncommon but distinctive clinic-radiological entity that has been associated with a variety of medical conditions and co-morbidities. These include renal disease, connective tissue disorders, hematological diseases such as sickle cell anemia, cancer, and eclampsia.⁵ Published literature have documented that PRES occurs with acute hypertension in about 70% of patients, while in another 30%, the blood pressure is normal or only mildly raised.⁶ Identified triggers of PRES in both children and adults have included organ transplantation, the use of immunosuppressive and cytotoxic agents, blood transfusion, or evidence of human immunodeficiency virus-1 (HIV-1).⁷⁻⁹

Consideration must be given for PRES diagnosis in patients with predisposing conditions and observable rapidly progressive neurologic symptoms.⁶ With early recognition and appropriate treatment, this clinical syndrome resolves within a week and the changes seen in magnetic resonance imaging (MRI) also then resolve over days to weeks.^{1,2,6} The challenge then remains early recognition of symptoms with a high index of suspicion and making the appropriate diagnosis as required.

Most of the cases of PRES observed in pediatric patients have been reported from developed countries.^{2,4,10-21} This may be due to a range of factors that includes the lack of ready infrastructure such as MRI, to make eventual diagnosis. However, most of the risk factors of PRES in children such as severe sepsis, are very common in developing countries, including Nigeria.^{22,23} Despite this, there has been little interest and limited published works in pediatric PRES by researchers in resource-poor settings. This narrative review aims to draw attention to the possible existence of PRES in children in a developing country like Nigeria and to identify

factors responsible for the difficulty in making the diagnosis. This narrative will hopefully raise awareness among pediatricians regarding PRES and as such encourage having a high index of suspicion in order to initiate appropriate timely management.¹⁰

Methods

Literature search was conducted through PubMed and Google web search for articles on PRES. The following search terms were employed, “Posterior reversible encephalopathy syndrome Nigerian children,” “Posterior reversible encephalopathy syndrome Nigeria, or Africa,” and “Posterior reversible encephalopathy syndrome diagnosis.” Studies relevant to the objectives of the review were then selected and critically reviewed and reported in a narrative format.

Ethical Approval and Informed Consent

Ethics approval was not required for this narrative review. This will have been obtained by the original authors of the various publications.

Current Status of knowledge

Pathophysiology of PRES

There are 3 main theories that explain the mechanisms involved in PRES and all 3 different mechanisms may be implicated, depending on the cause of PRES. The first is hypertension/hyperperfusion theory which postulates that elevation of systemic blood pressure beyond the upper limit of cerebral autoregulation causes arteriolar dilatation and cerebral hyperperfusion that leads to breakdown of blood-brain barrier and vasogenic brain edema.²⁴ The second theory is the auto regulation theory which suggests that hypertension seen in many patients with PRES, is due to an interruption of brain autoregulation. To maintain adequate perfusion, brain intracranial tension usually regulates a balance between dilatation and constriction of the vessels. When this is interrupted by any process such as severe hypertension, there is a breakdown of the autoregulatory mechanism with a resultant rise in mean arterial pressure (MAP). When this pressure rises way above the 95th centile (up to 160mmHg-200mmHg), it leads to some clinical manifestations seen in PRES.²⁵ In adults, the lowest limit of cerebral blood flow autoregulation is about 50mm Hg to 60mm Hg, but lower in children at 40mm Hg on the average.²⁶ In children, the cerebral blood flow autoregulation threshold is lower than in adults, therefore the mean blood pressure (MAP) at the onset of PRES symptoms is thus lower.²⁷ This second mechanism suggests that hypertension

activates the autoregulatory system, resulting in a vasoconstriction of brain vessels with hypoperfusion, ischemia, and cytotoxic edema. This theory does not explain why PRES can occur in the absence of hypertension and why sometimes the blood pressure readings in PRES do not reach the upper threshold of autoregulation²⁸ or why the extent of the edema is not directly related to the severity of the blood pressure rise.²⁵ In the third theory known as the endothelial theory,²⁵ patients with PRES have sometimes been observed to have normal blood pressure as seen in some cases of sepsis, eclampsia, transplantation, cancers, and autoimmune disease. The advocated pathway here involves inflammation with activation of the systemic inflammatory response syndrome (SIRS) which notably causes endothelial dysfunction. The endothelial dysfunction hypothesis postulates that these disease entities cause endothelial dysfunction leading to the activation of the immune system which results in the production of inflammatory mediators, that is, cytokines, which then alter the normal homeostasis of the blood brain barriers (BBB). What follows is fluid leakage and edema within the cerebrovascular endothelium. Chemotherapeutic and immunosuppressive drugs may also directly affect the cerebrovascular endothelium causing endothelial dysfunction with capillary leakage and vasogenic brain edema. PRES associated with chemotherapeutic drugs may also occur in normotensive patients.²⁵ However, when systemic blood pressure is high in such disease circumstances, vasoconstriction equally occurs and it could further exacerbate such inflammatory endothelial dysfunction. This would lead to hypoxia with subsequent vasogenic edema. This may explain why the control of hypertension assists in recovery in such patients with PRES.²⁹

It is important to note that the organs affected by the dysregulation in autoregulation whether by the hypertensive pathway, autoregulation pathway, or endothelial dysfunction/SIRS pathway, all eventually manifest with clinical features of PRES.

Common Presentation Patterns of PRES in Children

In the pediatric patient, PRES evolves over a few hours but can persist for several days and can be mistaken for a psychosis, drug intoxication, or psychogenic states.³⁰ The CNS is a major organ system affected in PRES. Hypertension is also a common presentation pattern in pediatric PRES and it is the most common identifiable trigger.²⁷ Patients with PRES notably present with systolic blood pressures that are above the 99th percentile + 5 mmHg for age, sex, and height.^{28,29}

The most common presenting CNS symptoms are seizures occurring in more than 90% of children in several reported series.^{27,31-33} The seizures can be convulsive (of

various types) or non-convulsive (staring, eye blinking, head turning), headache, visual disturbances which include blurred vision, homonymous hemianopia, cortical blindness, and visual neglect (lack of attention to parts of the visual field); and altered mental status (ranging from mild confusion, agitation to coma).⁴ Children in such case scenarios can be easily misdiagnosed as having meningitis or seizure disorders and in resource-poor settings the symptoms may not be investigated further due to limited access to appropriate investigative tools. Other symptoms may include nausea, vomiting, and brainstem deficits.³⁴⁻³⁶

The symptoms of PRES in children thus cut across various other systems beyond the CNS. Consequently, PRES may initially not be considered in thinking up differential diagnoses because of the non-specific nature of its clinical features in children.

Notable co-morbidities in children linked to PRES thus include acute kidney injury/chronic kidney disease, autonomic disturbances such as Guillain-Barré syndrome, thrombotic thrombocytopenic purpura, systemic lupus erythematosus (SLE), use of illicit drugs like cocaine, acetaminophen-induced hepatorenal failure, exposure to immunosuppressive drugs such as cyclosporine, tacrolimus, or chemotherapeutic agents like tacrolimus, and interferon alfa.^{37,38,39-42}

Recurrent episodes of PRES in same individuals have been reported^{30,43} especially in patients undergoing dialysis.^{44,45} It is therefore imperative to closely monitor blood pressure in such patients and avoid further precipitants. Close differential diagnoses of PRES in children regarding clinical presentation include infectious encephalitis, autoimmune or paraneoplastic encephalitis, tumors, subcortical leukoariosis, CNS vasculitis, progressive multifocal leukoencephalopathy, osmotic demyelination syndrome, acute demyelinating encephalomyelitis, toxic leukoencephalopathy.²⁷ Infectious diseases such as meningitis, acute gastro-enteritis (AGE), malaria, pneumonia, sepsis, and septic shock have been identified as the commonest causes of admission into emergency wards in Nigeria,^{22,23} have also been implicated in the etiology of PRES.⁴⁶⁻⁵¹ These have sometimes also been misdiagnosed as PRES.⁴¹⁻⁴³ Other authors have also identified epileptic seizures, encephalopathy, visual deficits, hypertension, chemotherapy, and renal failure as best predictors of PRES in children.⁵² PRES may be associated with conditions which cause hypomagnesemia, hypercalcemia, and hypocholesterolemia.⁵³ PRES could also occur in an otherwise normal child with no underlying medical conditions. Therefore, maintaining a broad differential in patients with neurologic deficits will allow physicians to accurately diagnose and appropriately treat life-threatening conditions like PRES.⁵⁴

Investigating PRES in Children

Brain imaging such as CT scan and MRI, help to exclude the extensive differential diagnoses, and to confirm the diagnosis of PRES.²⁷ Cranial CT examinations serve as initial diagnostic test for patients presenting with acute mental status changes or seizures and often important in identifying possible alternative diagnosis. They may sometimes suffice and are particularly useful in settings where MRI may not be readily available. The findings on brain CT include hypoattenuating symmetric hemispheric edema in regions of the holo-hemispheric at watershed zones, the superior frontal sulcus and the parieto-occipital dominance.⁵³ Although brain CTs can be used to make a definitive diagnosis of PRES, they are not as sensitive as MRI.^{53,55} Patients with negative CT findings, but clinical symptoms highly suggestive of PRES should undergo an MRI of the brain when clinically stable while receiving aggressive hypertension control.⁵⁴ Brain MRI, particularly T2-weighted sequences such as fluid-attenuated inversion recovery (FLAIR) usually reveal vasogenic edema and is more sensitive than CT.²⁷ Similar to brain CT findings, 3 primary descriptive variations exist in about 70% of patients: a dominant parieto-occipital pattern, holo-hemispheric watershed pattern, and superior frontal sulcus pattern. The dominant parieto-occipital pattern describes the involvement of only the posterior brain. The holo-hemispheric watershed pattern describes the predominant involvement of the border zone between the anterior and middle cerebral artery territories in a linear pattern spanning the frontal, parietal, and occipital lobes. The superior frontal sulcus pattern manifests as more isolated involvement of the superior frontal sulcus without extension into the frontal pole.²⁷ In a classic neuroimaging as reported in some studies, edema is seen involving the white matter in the posterior portions of the cerebral hemispheres, and especially bilaterally in the parieto-occipital regions.¹¹ As more cases of PRES became documented and described, it became clear that such lesions may also involve different parts of the brain, such as frontal lobes, cerebellum, or brain stem, and sometimes there might be diffuse brain involvement.¹¹ Furthermore, on a fluoroscopy imaging using the digital subtraction angiography (DSA), it shows signs of vasospasm or arteritis, diffuse vasoconstriction, focal vasoconstriction vasodilatation, and string-of-beads appearance.⁵³

Radiological patterns in children are also similar to those in adults. However, atypical findings are commoner in children. These atypical findings are described as the involvement of gray matter, involvement of the frontal lobes, thalamus, brainstem, and cerebellum. The presence of diffusion restriction and contrast enhancement are also considered atypical findings.⁵⁶

In several published works, intracranial hemorrhage is a common complication seen in brain imaging in 8% to 28% in pediatric PRES^{12,56-58} and 10% to 25% in adult series.²⁷ The hemorrhages range from the commonest types of punctuate micro-hemorrhages and the less common sulcal subarachnoid hemorrhage and lobar haematoma.⁵⁹ However, the clinical significance of the micro hemorrhages is uncertain.²⁷

When imaged with non-invasive CT angiography or magnetic resonance angiography or by use of an invasive catheter to do cerebral angiogram, patients with PRES have also shown blood vessel irregularities consistent with vasoconstriction.²⁷ Although PRES is a clinical diagnosis that may be confirmed by radiological findings, it may also exist without abnormalities on brain imaging.⁵² In a documentation by Fugate and colleague²⁷ a patient with at least 1 acute neurological symptom, (seizures, encephalopathy/confusion, headache, or visual disturbances) and at least 1 risk factor (severe hypertension/blood pressure fluctuations, renal failure, immunosuppressant therapy or chemotherapy, eclampsia or autoimmune disorder) should be suspected to have PRES on clinical grounds irrespective of the MRI findings.²⁷

Beyond imaging, PRES diagnoses have also been made following a biopsy, usually at an autopsy. In a case report, the histology showed dilated perivascular spaces filled with proteinaceous exudates and macrophages. Other findings were fibrinoid necrosis and hemorrhage which were present in areas that had previously exhibited altered signal on MRI.⁶⁰

Treatment of PRES in Children

There are no specific treatments for PRES in children. The goal is to offer supportive treatment, while managing the underlying cause.²⁷ PRES is reversible when the precipitating cause is eliminated or treated thus averting permanent neurological damage, reducing morbidity, or eventual mortality if not properly managed.⁶¹ Patients with posterior reversible encephalopathy syndrome may need to be managed in the setting of intensive care units (ICU) since status epilepticus, coma, respiratory failure, or hypertensive crisis may develop and require prompt interventions.^{18,62} Treatment of hypertension is a mainstay management and seizures when present, can be controlled with antiepileptic drugs, though no specific published guidelines were seen as specific protocols for prescribing antiepileptics or antihypertensive drugs in PRES management.²⁷ If PRES is precipitated by a specific medication, the offending medication should be discontinued, be it temporarily.^{63,64} Other underlying disorders, such as sepsis and flare-ups of

autoimmune disorders, should be treated according to protocol guidelines.²⁷

Prognosis

The prognosis of posterior reversible encephalopathy syndrome is often benign when it is managed promptly and the expected pathway is complete clinical reversal within days or weeks.⁴ The mean time to clinical recovery has been reported as 4.8 days in pediatric case series⁶³ and 5.3 days in adult patients. In a study among children with PRES in Turkey, the mean time for clinical recovery was 3.8 days while total time spent on hospital admission was 36.4 ± 11.41 days (range = 27-56 days).¹⁸ The time of hospitalization varied depending on the underlying disease. The prognosis may be poor in the event of delayed diagnosis and improper management as these may result in permanent brain tissue damage or even death.²⁶

Challenges of Pediatric PRES Diagnosis in Nigeria and Other Resource-Poor Settings

Although the epidemiology of the diseases that predispose to PRES may not be entirely different to children from different parts of the world, the presence of infectious disease related aetiologies may predominate in low and middle income countries (LMIC) and PRES will need to be thought about when reviewing such children. Many children from High income countries may survive long enough if they have malignancies to then experience aetiologies like chemotherapy related PRES. However, due to shared clinical features, understandably, PRES is under reported in children as it presents a diagnostic challenge even in developed countries. Furthermore poor access (availability and cost even to the African pediatric child), to diagnostic imaging studies like MRI in LMIC remains a big challenge. Ogbole et al,⁶⁵ in their survey of West African countries reported that only 84 MRI units served a combined population of 372 551 411, with Nigeria accounting for more about 70% of the available units. Unfortunately, 77.6% of the available units were also of low-field strength.⁶⁵ With poor knowledge of this disease entity and low index of suspicion for PRES in resource-poor settings, the challenge of under-diagnosis and missed diagnoses is even more common. This diagnostic challenge affects clinical decision. Accurate diagnosis of PRES aids appropriate management decisions about ongoing empiric antimicrobial therapy and invasive diagnostic procedures such as lumbar puncture.⁵⁴ Stroke mimic not recognized as PRES leads to incorrect diagnostic pathway with potential for iatrogenic harm through improper administration of thrombolytic therapy.⁶⁶

When compared to the high income countries also, poverty and poor clinical settings in LMIC contributes to the diagnostic challenges and may contribute to limited research interest in pediatric PRES with consequent underreporting of PRES⁶⁷⁻⁶⁹ Most of the reports of pediatric PRES have been from developed countries^{2,4,10-21} and a few from Africa. Nandi and colleagues⁷⁰ in South Africa were able to diagnose PRES in 4 children with novel aetiological associations: hypoxia following accidental strangulation, near-drowning episode, a child with thalassaemia receiving routine blood transfusions, and a fourth child who had PRES while recovering from toxic epidermal necrolysis syndrome (TENS). These all presented in such a way that the diagnosis of PRES would have been missed easily. In another report where the diagnosis and outcome of PRES in pediatric renal patients at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa was reviewed by Strong et al,⁷¹ the 5 reported patients were all hypertensive at the time of diagnosis and presented with seizures. This highlights the need to investigate children with similar clinical presentation in the midst of many possible differential diagnoses. In India, Zaki et al⁷² reported a case of a child with arteritis who presented Takayasu with PRES with loss of consciousness. He had been started on anti-tuberculosis therapy for abdominal tuberculosis. PRES was diagnosed by magnetic resonance imaging and the child was promptly started on anti-hypertensive medications following which the child regained his consciousness within 48 hours of admission. Prompt treatment of hypertension thus led to rapid reversal of neurological symptoms. This further highlights the need to think outside the box when managing a child with neurological symptoms. In Turkey, 5 children reviewed and diagnosed with PRES by Emeksiz et al¹⁸ showed that 2 had acute lymphocytic leukemia, 1 had Henoch-Schönlein purpura, another had systemic lupus erythematosus and acute poststreptococcal glomerulonephritis was diagnosed in the fifth child. The only 2 case reports on PRES in Nigeria were in adults (two separate reports of women with eclampsia),^{73,74} a worrisome finding since early recognition of PRES and optimal therapy are important to limit morbidity and mortality in children.⁷⁵ Renal diseases as a precipitating factor for pediatric PRES, as seen in other reports and infectious diseases in children are still a major challenge in resource poor countries such as Nigeria and thus provide a background for PRES etiology. It is thus difficult to critically analyse the contribution of PRES to the under-five deaths and other unacceptably high morbidity statistics in Nigeria and align to the United Nations' Sustainable Development Goals.⁷⁶ The dearth of case reports and publications of children with PRES in Nigeria, may be because no one is looking for it, hence the need for this

narrative review. Furthermore, since PRES diagnosis relies significantly on magnetic resonance imaging (MRI),⁷⁷ and the utility of more available CT are not highlighted; and because the availability and utilization of MRI units across sub-Saharan Africa countries still remain poor due to enormous acquisition costs, lack of infrastructure and the expertise required for maintaining and running the systems.⁶⁶ The diagnosis of PRES may continue to be elusive, until more awareness is created. In addition, the high cost of these imaging studies to the patient paying out-of-pocket, may be prohibitive in developing countries where socioeconomic factors contribute significantly to child neglect⁷⁸ and add to the limitations to pediatric PRES diagnosis with associated data loss about pediatric PRES.

Conclusion

Pediatric PRES is a well-recognized neuro-radiological syndrome which is underreported in Nigeria and other resource-poor countries. With a high index of suspicion, pediatric PRES can be identified on clinical grounds, however a clinical diagnosis of PRES should always prompt a request for a brain CT and an MR imaging of the brain where available. It is our hope that this article will stimulate scholarly dialog and research among pediatricians about PRES despite socioeconomic challenges that hamper confirmation of its diagnosis by MRI. Increased data base of information about PRES may lead to increased efforts to subsidize MRI for children and open pathways for future research.

Author Contributions

All contributors are seasoned and published consultant pediatricians with between 15 and 60 published articles on pediatric medicine and emergency medicine (see Google scholar or research gate). They have all worked with children with these neurological symptoms for years including the children that were admitted severally to the emergency ward where the first author currently works and has experience.

Declaration of Conflicting Interests

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