Original Article

Prevalence and Risk Factors of Posterior Reversible Encephalopathy Syndrome in Isfahan, Iran

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Abstract

Background: Posterior reversible encephalopathy syndrome (PRES) is a rare clinical-radiological syndrome characterized by such symptoms as headaches, altered consciousness, blurred vision, seizure, and focal neurological deficits. We herein present well-documented PRES cases and discuss the risk factors and characteristic imaging patterns of this syndrome. **Materials and Methods:** We prospectively examined 31 patients with PRES in Alzahra Hospital, Isfahan, Iran, and compared the underlying diseases of PRES in terms of their clinical features and cranial magnetic resonance imaging (MRI) findings. **Results:** The most common underlying disease was hypertension (90.3%), followed by systemic lupus erythematosus (32.3%), preeclampsia (25.8%), chronic renal failure (22.6%), and rheumatoid arthritis (22.6%). Interestingly, we also reported heroin abuse as a possible risk factor for PRES (9.7%). The most frequent clinical signs were headaches (54.8%), seizure (54.8%), and blurred vision (35.5%). The most frequent lesions on cranial MRI were in the parieto-occipital area (87.1%), followed by the cerebellum (19.4%) and the frontal lobe (12.9%). Other abnormalities on MRI were less common. In addition, 16.1% of the study population had vasospasm on magnetic resonance arteriography (MRA). Clinical recovery was followed by radiological resolution in all the patients. **Conclusions:** The clinical presentation is nonspecific, most patients present with a combination of symptoms, particularly headaches and seizure. MRI is crucial for the diagnosis of PRES, and MRA is useful in that it can identify associated vasospasm. Timely diagnosis and treatment are required to avoid a devastating outcome.

Keywords: *Headache, posterior reversible encephalopathy syndrome, seizures, vasospasm*

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare clinical-radiological syndrome likely caused by the impaired neurovascular unit autoregulation of the cerebral blood flow which leads to endothelial dysfunction and vasogenic brain edema. PRES is characterized by such symptoms as headaches, altered consciousness, blurred vision, seizure, and focal neurological deficits.[1-3] The associated symptoms may completely disappear after treatment.[1,4-6] The risk factors for developing PRES in adults include hypertension, eclampsia, kidney disease, liver disease, autoimmune disease, infections, endocrine disease, organ transplantation, and cytotoxic medications.[3,7,8] The pathogenesis of PRES is based on transient changes in the posterior circulation of the brain. Neuroimaging is crucial for the diagnosis of PRES. Nonetheless, an understanding of this syndrome and its prevalence and prognosis in the general population is hampered by the small number of patients.[9,10] Various conditions may resemble PRES, and this syndrome can be confused with other diagnoses due to its lack of specific clinical symptoms and limited clinical and imaging data.

There is a rare epidemiologic study in Middle East area. In the present study, we present well-documented PRES cases and discuss the risk factors and characteristic imaging patterns of this syndrome. Interestingly, that opium can be a possible risk factor of PRES as well.

Materials and Methods

We prospectively analyzed the data of 31 patients who received a diagnosis of PRES in the rheumatology, neurology, oncology, nephrology, intensive care unit, gynecology, and organ transplantation units of Alzahra Hospital. The inclusion criteria

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were composed of symptoms and signs compatible with PRES (e.g., headaches, seizure, visual disturbances, and loss of consciousness) and imaging findings compatible with PRES. Patients' written consent was obtained for publication.

The study population's demographic data, clinical findings, concurrent medical illnesses, blood pressure, drugs, and brain magnetic resonance imaging (MRI) findings were recorded. Hypertension was defined as a systolic and/or diastolic blood pressure of higher than the 95% percentile for age.[11]

The MRI studies were performed on 1.5 Tesla MRI devices (Magnetom, Siemens, Germany). Fluid-attenuated inversion recovery (FLAIR) axial, T2-weighted axial and sagittal, and T1-weighted axial and sagittal sequences with or without contrast enhancement were acquired. In addition, diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps were obtained.

Brain MRI and magnetic resonance arteriography (MRA) were performed on all the patients within 3 days after the onset of their neurological symptoms. MRI findings were defined as hyperintensity in the subcortical white matter on T2 and FLAIR images and increases in ADC and normal DWI values in the bilateral occipital, parietal, frontal, and temporal lobes and sometimes in the cerebellum, basal ganglia, and brain stem in the posterior fossa and the cortical gray matter. Radiological complications were defined as cerebral ischemia and cerebral hemorrhage.[12]

Statistical analysis

The statistical analyses of the data were performed with the SPSS software, version 25.0. (SPSS, Chicago, Il, USA) The results are presented as means ± standard deviations.

Results

Of a total of 31 patients, 23 (74.2%) were female and 8 (25.8%) were male. The mean age of the patients was 33 ± 12.27 years. The demographic and clinical data of the study population are summarized in Table 1. The most frequent underlying primary disease was hypertension (n = 28 [90.3%]), followed by systemic lupus erythematosus (n = 10 [32.3%]), preeclampsia (n = 8 [25.8%]), chronic renal failure (n = 7 [22.6%]), and rheumatoid arthritis (n = 7 [22.6%]).

The risk factors were not statistically significantly different between the male and female patients. The most frequent clinical signs were headaches in 17 (54.8%) patients, seizure in 17 (54.8%), and blurred vision in 11 (35.5%) [Table 2].

The most frequent lesions on cranial MRI were in the parieto-occipital area (n = 27 [87.1%]), followed by the cerebellum (n = 6 [19.4%]) and the frontal lobe (n = 4 [12.9%]). Other abnormalities on cranial MRI were less common. Five (16.1%) patients had vasospasm on MRA [Table 3 and Figure 1].

Clinical recovery was followed by radiological resolution in all the patients.

Table 1: Frequency of the risk factors in the patients with posterior reversible encephalopathy syndrome

Risk factor	Frequency (%)
Preeclampsia	8 (25.8)
Eclampsia	4 (12.9)
CRF	7 (22.6)
Kidney transplantation	3 (9.7)
ARF	1 (3.2)
SLE	10 (32.3)
RA	7 (22.6)
APS	2 (6.5)
MCTD	1 (3.2)
Hyponatremia	1 (3.2)
Multiple myeloma	1 (3.2)
CLL	1 (3.2)
Pancytopenia	1 (3.2)
Thrombocytopenia	1 (3.2)
TPP	4 (12.9)
Liver disorder	2 (6.5)
HEIIP	3 (9.7)
HTN	28 (90.3)
Adrenal cancer	1 (3.2)
Cushing's syndrome	1 (3.2)
Heroin addiction	3 (9.7)
Prednisone	1 (3.2)
Lidocaine	1 (3.2)
Corticosteroid pulse	4 (12.9)
CellCept	2 (6.5)
Hydroxychloroquine	2 (6.5)

CRF: Chronic renal failure, ARF: Acute renal failure, SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, APS: Antiphospholipid antibody syndrome, MCTD: Mixed connective tissue disease, CLL: Chronic lymphocytic leukemia, TPP: Thrombotic thrombocytopenic purpura, HELLP: Hemolysis, elevated liver enzyme, and low platelet count, HTN: Hypertension

Table 2: Frequency of the clinical features in the patients with posterior reversible encephalopathy syndrome

Symptom	Frequency (%)
Seizure	17 (54.8)
Headaches	17 (54.8)
Blurred vision	11 (35.5)
Vomiting	1 (3.2)
Ptosis	1 (3.2)
Muscle weakness	1 (3.2)

Discussion

Hinchey *et al*. was the first investigator to report PRES in the year 1996.[13] PRES is a clinical-radiological syndrome whose nonspecific clinical manifestations and

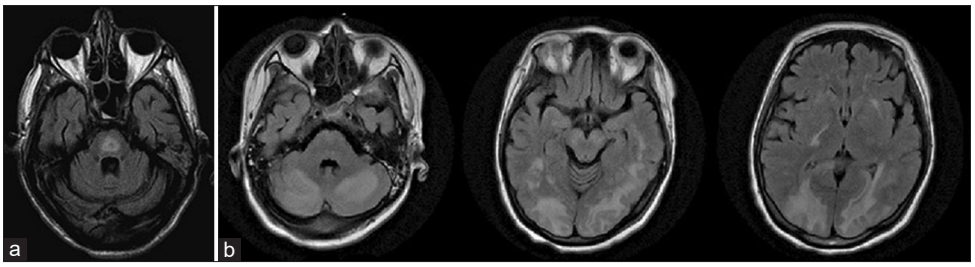

Figure 1: (a) Features of posterior reversible encephalopathy syndrome on axial fluid-attenuated inversion recovery images, showing edema in the central pons. (b) Features of posterior reversible encephalopathy syndrome on axial fluid-attenuated inversion recovery images, demonstrating edema extending into the parietal and temporal lobes, as well as within both cerebellar hemispheres

Table 3: Frequency of the magnetic resonance imaging abnormalities in the patients with posterior reversible encephalopathy syndrome

MRI	Frequency (%)
Parietal-occipital	27 (87.1)
Cerebellum	6 (19.4)
Frontal	4 (12.9)
Occipital	1 (3.2)
Temporal	1 (3.2)
Brain stem	3 (9.7)
Vasospasm	5 (16.1)
Hemorrhage	2 (6.5)

MRI: Magnetic resonance imaging

multiplicity of radiological patterns create diagnostic challenges.[14] It should, therefore, come as no surprise that the global incidence of PRES is unknown. The only epidemiological data in the existing literature come from retrospective studies on patients examined between 1988 and 2008.[13,15-19] PRES has been reported in patients aged between 4 and 90 years, with the majority of the cases occurring in young to middle-aged adults. There is a marked female predominance, which may reflect some of the possible causes of this syndrome. The mean age of the study population and female predominance in our study are concordant with the previous studies.

The typical features of PRES include seizure, headaches, visual abnormalities, consciousness impairment, and focal neurological deficits. The previous studies have reported incidence rates for headaches and nausea/vomiting of 26%–53% among patients diagnosed with PRES, with headaches and nausea/vomiting being associated with blurred vision in 7%–18%, seizure in up to 92%, and consciousness impairment in 13%.[13,16,18] In our study, the most frequent clinical features were headaches (57.8%), seizure (54.8%), and blurred vision (35.5%).

Hypertension has been reported in most of the previous studies.[13,16,18,19] These investigations have reported incidence rates for hypertension of 67%–80% among patients with PRES.[13,18] Nonetheless, although severe hypertension may frequently accompany toxic syndrome, significant hypertension may be absent.[18] The main cause of hypertension in our study population was acute or chronic kidney failure. Interestingly, in our study, hypertension was the most common risk factor for PRES in as much as it was observed in 90% of the patients. We detected hypertension in 22.6% of the cases with chronic renal failure and 3.2% of those with acute renal failure.

Exposure to drugs is the most common condition associated with PRES and has been reported to range from 11% to 61% of all cases with PRES.[16] Transplantation patients are also at risk for PRES as they are exposed to immunosuppressive therapy. In the current study, PRES was observed with prednisolone, high doses of methylprednisolone, CellCept, hydroxychloroquine, lidocaine, and heroin consumption. Toxic leukoencephalopathy was reported by some drugs of abuse such as heroin, environmental toxins, and chemotherapeutic drugs[20] that is in differential diagnosis of PRES, but we reported PRES due to heroin addiction in three patients regarding imaging and revolution of symptom. In a recent pandemic, the PRES has been reported to be associated with COVID-19 in some case reports.[21,22]

MRI is the key modality for the diagnosis of PRES. The topographic distribution of the radiological features of PRES has been reported in cohort studies.[13,15,16,18,23] In a study on 136 patients, the typical pattern consisted of bilateral and symmetric regions of edema in the posterior parietal and occipital lobes but other locations were common including the frontal lobes, inferior temporal lobes, cerebellar hemispheres, basal ganglia, brain stem and deep white matter including the splenium.[18] In our study, most of the patients presented with a dominant parietal-occipital pattern (87%). It is not completely known why PRES favors the posterior circulation, but this situation may arise from a relative lack of sympathetic innervation arterioles in the posterior circulation compared with the anterior circulation.[23,24]

Cerebral hemorrhage is an uncommon complication in PRES and ranges from 5% to 17% of patients.[16] It may be more common among patients with allogeneic bone marrow transplantation or those receiving an anticoagulant treatment; nonetheless, blood pressure levels may have no role in increasing the risk of bleeding.[25] In our study,

cerebral hemorrhage was reported in 2 (6.5%) patients with the risk factors of thrombotic thrombocytopenic purpura (TTP) and heroin addiction, respectively. This complication may have been caused by abnormal coagulation in TTP and vasoconstriction in heroin consumption.

Brain stem involvement is rare but may be correlated with severe hypertension.[15,26] In our study, 3 (9.7%) patients presented with edema in the brain stem, accompanied by severe hypertension. In this situation, the MRI differential diagnosis includes neoplasms, and pontine myelinolysis should be ruled out.

Although most patients with PRES have normal cerebral angiograms, MRA or angiograms may demonstrate cerebral vasospasm in patients suffering from hypertensive encephalopathy with eclampsia and intrathecal chemotherapy.[27,28] We found five patients with preeclampsia-eclampsia (16%), who presented with vasospasm. Hence, cerebral vasospasm may occur in patients with PRES in pregnancy. An inflammatory response may cause cerebral vasospasm, followed by vasogenic edema in preeclampsia.[27] Still, further studies are necessary to fully elucidate the pathophysiological features. The acute treatment of vasospasm with calcium antagonists[29] and magnesium sulfate[30] is essential in this situation, and outpatients are reported to respond well to nimodipine.

Conclusions

The current study presented a review of the clinical features, risk factors, and typical and atypical radiological findings of patients with PRES in our clinics. PRES classically seen in patients suffering from acute hypertension, perhaps, side effects of opium can cause PRES as well. Although the clinical presentation of PRES is nonspecific, most patients tend to have a combination of symptoms – not least headaches and seizure. MRI is a crucial modality for the diagnosis of PRES, and MRA is a useful tool in that it can identify associated vasospasm. Timely diagnosis and treatment are required to avert a devastating outcome. Further investigations are needed to identify the new risk factors of PRES and its atypical findings on MRI.

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Conflicts of interest

There are no conflicts of interest.

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