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Predictors of seizures in patients with posterior reversible encephalopathy syndrome

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ABSTRACT

Purpose: Although seizures are common in patients with posterior reversible encephalopathy syndrome (PRES), epilepsy is rare. Our objective was to identify predictors and impact of seizures in patients with PRES.
Methods: A retrospective review of the clinical and radiological parameters of all patients diagnosed with PRES from 2007 to 2014 was performed. Patients were divided into two groups based on the occurrence of PRES-related seizures at presentation or during their hospital course. Univariate and multivariate analyses were performed to determine factors associated with the occurrence of PRES-related seizures.
Results: Of 100 patients, 70% experienced at least one seizure from PRES. On univariate analysis, the factors associated with seizures were the following: high Charlson comorbidity index (4.16 ± 2.89 vs. 2.87 ± 2.20, $p = 0.03$), systemic malignancy (41.4% vs. 16.7%, $p = 0.02$), occipital lobe involvement (97.1% vs. 83.3%, $p = 0.02$), more lobes involved (4.6 ± 1.48 vs. 3.9 ± 1.32, $p = 0.03$) but less likely in patients with visual disturbances (15.7% vs. 46.7%, $p = 0.005$), and facial droop (12.9% vs. 16.7%, $p = 0.002$). On multivariate analysis, only occipital lobe involvement was significantly (odds ratio: 9.63, 95% CI: 1.45–64.10, $p = 0.02$) associated with the occurrence of PRES-related seizures. Despite the occurrence of seizures, they were less likely to require a nursing home placement upon hospital discharge (odds ratio: 0.17, 95% CI: 0.03–0.91, $p = 0.04$).
Conclusion: We conclude that seizures are common in patients with occipital lobe involvement from PRES.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a well-recognized acute neurotoxic syndrome characterized by a combination of clinical and neuroimaging findings. The spectrum of neurological features includes headache, impaired level of consciousness, seizures, visual disturbances, nausea/vomiting, and focal neurological deficits [1,2] in variable combinations. On neuroimaging, PRES is characterized by bilateral, cortical/subcortical vasogenic edema commonly involving the parietal and occipital regions, followed by the frontal, inferior-occipital, and cerebellar regions [3–5]. Commonly reported triggering factors include acute hypertension, preeclampsia or eclampsia, renal disease, sepsis, autoimmune diseases, and exposure to chemotherapeutic agents and immunosuppressants [6,7].

Seizures are a common manifestation and have been reported in 70–80% of PRES cases [6,7]; on occasion, status epilepticus may be the presenting symptom [8]. Despite these, epilepsy following PRES is rare [9]. Patients with seizures are frequently treated with antiseizure drugs (ASDs) for a short course. The pathophysiology of PRES is highly controversial. Various proposed hypotheses include vasoconstriction from hypertension with autoregulatory compensation, leading to ischemia and cerebral edema [10]; severe hypertension exceeding the autoregulatory limit, leading to hyperperfusion and cerebral edema [2,11]; and endothelial dysfunction [5,12]. Although initially thought to be reversible, recent literature has reported severe functional impairments in 44% of patients admitted to the intensive care unit [13], and the mortality is about 3–6% [6,14]. Besides, various clinical and experimental studies have reported neuronal damage from status epilepticus, although its extent following a single seizure or repeated brief seizures is controversial [15–18]. Thus, an improved understanding of the frequency and risk factors of seizures in patients with PRES would help us identify patients at risk of developing seizures and those who may benefit from continuous electroencephalographic (EEG) monitoring and prophylactic treatment in order to improve their functional outcome. The primary aim was to determine the frequency, risk factors, and discharge outcome of seizures in patients with PRES. The secondary aim was to determine the rates of recurrent seizures and epilepsy following PRES.

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2. Methods

2.1. Subjects

We retrospectively reviewed all electronic medical records using the International Classification of Diseases version 9 codes for encephalopathy and PRES in patients ≥18 years of age, admitted to our tertiary care medical center from 2007 to 2014. All consecutive records were screened for the inclusion of PRES. A diagnosis of PRES was based on the clinical and radiological features consistent with PRES [3–5]. Magnetic resonance imaging (MRI) studies were reviewed by two independent, certified, experienced staff neuroradiologists blinded to the clinical findings, and in case of disagreement, consensus was reached. Electroencephalographic (EEG) patterns were interpreted by an experienced epileptologist blinded to clinical information and outcomes.

2.2. Definitions

Diagnostic criteria of PRES were an acute neurotoxic syndrome with features of headache, impaired consciousness, seizures, visual abnormalities, nausea/vomiting, focal neurological deficits in variable combinations [1,2], and imaging findings consistent with PRES on MRI [5]. Visual disturbances included blurred vision, visual hallucinations, homonymous hemianopsia, visual neglect, and cortical blindness. Status epilepticus was defined as continuous seizures ≥5 min or two or more discrete seizures between which there was incomplete recovery of consciousness [19]. Posterior reversible encephalopathy syndrome-related epilepsy was defined as at least two unprovoked seizures occurring >24 h apart more than one month after the inciting episode with complete or near complete resolution of imaging abnormalities [20,21]. Additionally, patients with prior history of epilepsy were excluded. This time frame was selected since, although clinical recovery occurs in a few days in the majority of cases, it may occasionally take a month in certain cases [6,22,23]. A provoked seizure was defined as a seizure that occurred in the context of a precipitating cause that could lower the seizure threshold [20,21]. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg [24].

2.3. Data collection

Patients were dichotomized into two groups based on the occurrence of seizures either at presentation or during hospitalization. Comparison of their baseline demographics, medical comorbidities, neurological symptoms, predisposing conditions, vital signs, Glasgow Coma Score (GCS), length of hospitalization, laboratory values, and imaging was performed. In cases with more than one predisposing condition, the clinically dominant etiology was used for analysis. Comorbidities were quantified using the Charlson comorbidity index [25].

Imaging features evaluated included the distribution of vasogenic edema (parietal, occipital, frontal, temporal, cerebellar, thalamus, midbrain, pons, medulla, lentiform nucleus, caudate, putamen, corpus callosum), number of lobes involved, severity of vasogenic edema (grading scheme by McKinney et al.), cortical or subcortical involvement, typical and atypical features, presence of restricted diffusion, hemorrhage, contrast enhancement, and degree of resolution on follow-up imaging if available. Atypical features were defined as involvement of the frontal lobes, basal ganglia, brain stem, and deep cerebral white matter; contrast enhancement; hemorrhage; restricted diffusion; and minimal involvement of the parieto-occipital regions [26].

The EEG findings analyzed were the following: background activity (normal, focal, and generalized slowing), the presence of epileptiform discharges, electrographic seizures, and periodic lateralized epileptiform discharges. Mild slowing was referred to background frequencies in the alpha–theta range, moderate slowing for frequencies in the theta range, and severe slowing for frequencies in the delta range.

2.4. Outcome

Outcome was assessed using the modified Rankin Score (mRS), Glasgow Outcome Scale (GOS) at discharge, discharge disposition (home, rehabilitation facility, long-term nursing home), and in-hospital mortality. Information on neurological events, especially seizures and epilepsy, was evaluated if available upon follow-up.

2.5. Statistical analysis

For all statistical analyses, SPSS version 21 software was used, and a p value of <0.05 was considered significant. Univariate analysis was performed using Student's t-test for continuous variables and 'z' score for categorical variables to identify factors associated with clinical seizures. Multivariate logistic regression analysis of all significant variables ($p < 0.05$) on univariate analysis was performed to identify predictors associated with seizures in patients with PRES.

3. Results

3.1. Characteristics and comparison between groups with and without seizures

Based on the inclusion criteria, 100 patients with PRES were identified, of which 70% experienced at least one PRES-related seizure either upon presentation or during hospitalization. Details of the cohort are described in Table 1. On MRI studies, vasogenic edema was commonly observed in the occipital lobe (93%) and parietal lobe (93%) followed by the frontal lobe (89%), cerebellum (57%), temporal lobe (39%), and thalamus (32%). On univariate analysis (Tables 2 and 3), the factors associated with the occurrence of seizures following PRES were a high Charlson comorbidity index (4.16 ± 2.89 vs. 2.87 ± 2.2, $p = 0.03$); systemic malignancy (41.4% vs. 16.7%, $p = 0.02$); occipital lobe involvement (97.1% vs. 83.3%, $p = 0.02$); greater number of lobes involved (4.6 ± 1.48 vs. 3.9 ± 1.32, $p = 0.03$), with decreased probability in patients with visual disturbances (15.7% vs. 43.3, $p = 0.005$); and facial droop (15.7% vs. 46.7%, $p = 0.002$). On multivariate analysis (Table 4), only occipital lobe involvement was associated with the occurrence of seizures in patients with PRES (odds ratio: 9.63, 95% CI: 1.45–64.10, $p = 0.02$). Further occurrence of a seizure on initial presentation or hospitalization did not significantly increase the risk of subsequent seizures (21.2% vs. 21.4%, $p = 1.00$) upon follow-up (median: 14.5 months, IQR: 4.7 months to 30.3 months). Despite the lack of a significant difference in mortality or poor functional outcome at discharge (based on mRS and GOS) between both cohorts, patients with PRES-related seizures were less likely to be discharged to a nursing home (4.3% vs. 20%, $p = 0.01$).

Table 1
Demographics of 100 patients with PRES.

Clinical characteristics	Number of patients
Age (years, median, interquartile range)	50 (33–61)
Gender (males, %)	27
Precipitating cause	
Hypertension	49
Eclampsia	13
Renal failure	9
Malignancy	18
Chemotherapy	11
Seizures	70
Generalized tonic–clonic seizures	52
Status epilepticus	7
Focal seizures	11
Charlson comorbidity index (median ± SD)	4 (2–5)
Glasgow Coma Score (median ± SD)	15 (10–15)
Length of hospital stay (median ± SD)	9 (4–22)
Length of intensive care unit stay (median ± SD)	2 (0–5)
Mortality at hospital discharge	8