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ORIGINAL ARTICLE

Posterior reversible encephalopathy syndrome (PRES) due to acute hypertension in children: 12 years single-center experience

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Abstract

The objective of the study is to evaluate the clinical and neuroradiological findings, the risk factors for recurrence and the prognosis in patients with posterior reversible encephalopathy syndrome developed secondary to acute hypertension in children. The study was conducted between 2008 and 2019 at Mersin University Faculty of Medicine. A total of 49 episodes were evaluated retrospectively in 38 patients with PRES secondary to acute hypertension. The demographic data, etiology, and clinical and neuroradiological findings were recorded. Twenty-one (55.3%) patients were female; the mean age was 11.8 years. The etiology of acute hypertension in 29 (76.3%) patients was end-stage renal disease (ESRD). The most common clinical findings were seizure (81.6%) and altered consciousness (79.6%). Status epilepticus developed in eight (16.3%) episodes. MRI lesions were atypical in 33 episodes (67.3%). In eight (21%) patients, PRES recurred. Irreversible brain damage was detected after PRES in three (7.8%) patients. C-reactive protein and erythrocyte sedimentation rate were elevated in 82.2% and 71.4% of the episodes, respectively. A statistically significant relationship was found between the recurrence, the duration of hospitalization at the PICU, SE and the occurrence of irreversible lesion ($p=0.013$, $p=0.015$, $p=0.001$ respectively). Also, there were statistically significant relationships between recurrence and ESRD; epilepsy and recurrences; SE and irreversible brain damage ($p=0.02$, $p=0.012$, $p=0.025$ respectively). Although PRES is usually known to have a good prognosis, the mortality and morbidity rates may increase in the long-term follow-up as in our study. In this study, the etiology, the presence of status epilepticus, PICU history, atypical MRI lesions and increased inflammatory markers were found to be important for the prognosis in PRES.

Keywords Acute hypertension · ESRD · Inflammation · Posterior reversible encephalopathy syndrome · Prognosis

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare disease characterized by sudden increase in blood pressure, seizures, headache, altered consciousness, visual impairment, and specific neuroradiological findings, which was first described by Hinchey et al. [1]. Fugate et al. defined the diagnostic criteria in patients with risk factors for PRES as (1) acute onset neurological symptoms, (2) focal vasogenic edema on neuroimaging, and (3) reversible clinical and/or neuroradiological findings [2]. The highest risk condition for PRES is acute hypertension due to renal diseases [3]. Other causes include collagen tissue diseases, immunosuppressive and chemotherapeutic drugs, eclampsia and blood transfusion. Typical neuroradiological findings of PRES are cortical and subcortical hyperintense lesions on T2W and FLAIR in the parietal–occipital lobes. In addition, involvement of the frontal and temporal lobe, cerebellum, basal ganglia, brain stem and corpus callosum may be observed [1–3]. Clinical and neuroradiological findings of the PRES do not differ based on the etiology. Vasogenic brain edema is considered to be the main pathophysiological mechanism of PRES. There are two basic theories about the formation of edema: (1) hyperperfusion due to autoregulatory insufficiency of cerebral vessels or (2) hypoperfusion as a result of vasoconstriction of cerebral arteries. Treatment in PRES is symptomatic which aims at the removal of the

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underlying cause. The treatment of PRES in cases with acute hypertension is the control of blood pressure and seizures, if any. Intravenous antihypertensive drugs such as sodium nitroprusside and hydralazine are used in the treatment of acute hypertension. Prognosis is usually good; rarely intracranial hemorrhage or irreversible brain damage may occur [2–5].

In this article, we analyzed the clinical and neuroradiological findings, the effect of inflammatory factors on prognosis, and the risk factors for recurrence and mortality in patients with PRES developed secondary to acute hypertension. To the best of our knowledge, this study contains the largest patient group with PRES due to acute hypertension in childhood with a long-term follow-up.

Patients and methods

The study was conducted with children diagnosed with PRES between January 2008 and December 2019 at Mersin University Faculty of Medicine, Departments of Pediatric Neurology and Pediatric Nephrology. The inclusion criteria of this study were: (1) patients aged under 18 years; (2) typical clinical (seizure, altered consciousness, headache, visual impairment) and MRI findings of PRES (regions of high signal intensity on T2WI and FLAIR images) during acute hypertensive attack. We used the definition of high blood pressure as that in the 95th percentile of height according to the criteria of the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Children and Adolescents [6]. The blood pressure of the patients was in normal limits previously. Patients with insufficient data and those who developed PRES secondary to collagen tissue diseases, immunosuppressive or chemotherapeutic drugs or blood transfusion were excluded. Clinical findings and MRIs of all episodes were reviewed by two authors (MK and AO).

In this study, age, sex, arterial blood pressure during PRES episode, etiology of acute hypertension, clinical findings such as seizure, altered consciousness, headache and visual impairment in the first and recurrent attacks were evaluated retrospectively. Additionally, MRI, diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps, and electroencephalogram (EEG) findings in the acute period were reviewed. Neuroimaging findings (MRI, DWI and ADC maps) in all episodes were obtained within the first 24 h of clinical onset. Axial T2W and FLAIR images were used to locate the lesions (occipital, parietal, temporal, frontal, cerebellum, basal ganglia, thalamus, mesencephalon, pons and corpus callosum) on MRI. MRI lesions were divided into two groups as typical and atypical. Typical lesions were defined as lesions only in the parieto-occipital region on T2W/FLAIR images without diffusion restriction. Atypical MRI findings were determined as the presence of additional lesions in the frontal or temporal lobes, cerebellum, and brainstem. Also, the presence of diffusion restriction and hemorrhage were considered as atypical findings.

To demonstrate the effect of inflammatory parameters on prognosis, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, duration of hospitalization in the pediatric intensive care unit (PICU) and pediatric nephrology inpatient clinic were evaluated during the PRES episode. CRP > 5 mg/dl and ESR > 20/h were considered as high and evaluated within the first 24 h of the PRES episode.

The prognosis of PRES, in the follow-up period, was evaluated according to morbidity and mortality rates. Epilepsy and recurrence of PRES was accepted as morbidity criteria of PRES. The risk factors of morbidity and mortality were analyzed statistically.

Statistics

SPSS 21.0 v package program was used for statistical evaluation of the data obtained from the study (SPSS Inc., Chicago, Illinois, USA). Categorical variables such as demographic data and etiologic characteristics of the patients were summarized in number (n) and percentage (%). Descriptive statistics about continuous variables are shown as mean ± standard deviation. The Chi square test was used to describe the relationship between neurological and radiological results, especially in the lesions in the acute phase or MRI findings. Statistical significance was taken as $p < 0.05$.

Results

Demographic and clinical findings

41 patients were diagnosed with PRES. Three patients with insufficient data were excluded. A total of 49 episodes were evaluated retrospectively in 38 patients with PRES linked to acute hypertension. The demographic data and etiology of the patients are shown in Table 1. Of 38 patients, 21 (55.3%) were female. The age at the time of PRES mean age was 11.8 years (ranging from 4.5 to 18 years). The underlying disorders leading to acute hypertension were reviewed; 29 patients (76.3%) had end-stage renal disease (ESRD) [lupus nephritis, nephrotic syndrome (NS), vesicoureteral reflux nephropathy, chronic pyelonephritis secondary to neurogenic bladder], 4 patients (10.5%) had NS without renal insufficiency (minimal change disease, mesangioproliferative glomerulonephritis), 3 patients (7.9%) were diagnosed with acute kidney injury (AKI) and 2 patients (5.3%) were diagnosed with acute post-streptococcal glomerulonephritis (APSGN) (Table 1).

Table 1 Demographic, clinical and MRI findings (patients: 38, episode: 49)

Age[a], (*n*)	49
Range	4.5–18 years
Mean	11.8 years
Sex, *n* (%)	38 (100%)
Male	17 (44.7%)
Female	21 (55.3%)
Underlying disease, *n* (%)	38 (100%)
ESRD	29 (76.3%)
NS	4 (10.5%)
AKI	3 (7.9%)
APSGN	2 (5.3%)
Clinical findings, *n* (%) (episode)	49 (100%)
Seizure	40 (81.6%)
Status epilepticus	8 (16.3%)
Altered consciousness	39 (79.6%)
Headache	36 (73.5%)
Visual impairment	22 (44.9%)

ESRD end-stage renal disease, *NS* nephrotic syndrome, *AKI* acute kidney injury, *APSGN* acute post-streptococcal glomerulonephritis

[a]The age at the time of PRES

Arterial blood pressures were within normal limits in all patients before the acute hypertension attack. In all 49 episodes, during acute hypertension, arterial blood pressure was between 110 and 160% according to the definition of NHBPEP. There was no relationship between the severity of blood pressure and clinical and radiological findings.

The clinical findings of patients with PRES were reviewed. Seizures in 40 episodes (81.6%), altered consciousness in 39 episodes (79.6%), headache in 36 episodes (73.5%), and visual impairment in 22 episodes (44.9%) were present (Table 1). Seizures were controlled with a single antiepileptic drug (phenytoin, valproic acid or levetiracetam) in 32 of the 40 patients who had seizures during the acute episode. Since status epilepticus (SE) occurred in eight episodes (16.3%), a second antiepileptic drug was required in six patients and an additional midazolam infusion in two patients. In patients with SE, hospitalization rates at the PICU and secondary epilepsy due to PRES were higher. There was a statistically significant relationship between SE and hospitalization at the PICU and secondary epilepsy ($p = 0.015$, $p = 0.012$, respectively).

Twenty-eight (57.1%) of the patients were hospitalized in the PICU for an average of 4.3 days (1–47 days). The mean duration of stay at the pediatric nephrology inpatient clinic was 7.9 days (2–21 days).

Radiological and EEG results

Of the 49 episodes, 46 (93.8%) had lesion in the occipital lobe, 42 (85.7%) in the parietal lobe, 25 (52.1%) in the frontal lobe, 14 (28.6%) in the temporal lobe, 15 (30.6%) in the cerebellum, 4 (8.1%) in the basal ganglia, one (2%) in the thalamus, one (2%) in the brain stem and one in the corpus callosum (2%) (Table 2).

MRI lesions were typical in 16 (32.7%) episodes and atypical in 33 (67.3%) episodes (Fig. 1). In patients with atypical MRI findings, the presence of recurrence and irreversible lesions were higher than in patients with typical MRI findings with a statistically significant relationship ($p = 0.011$ and $p = 0.031$, respectively).

EEG was performed in 42 (85.7%) of the 49 attacks within the first 7 days. Thirty-two EEGs (76.2%) were abnormal. Focal slow waves in 23 episodes and focal spikes or sharp waves in 18 episodes were determined.

Table 2 Anatomical distribution of neuroradiological lesions in PRES

Anatomic location	Our study (*n*: 49) (%)	Yamamoto et al. [9] (*n*: 40) (%)	Gupta et al. [10] (*n*: 40) (%)	Li et al. [12] (*n*: 18) (%)	Liman et al. [13] (*n*: 96) (%)	Bartynski and Boardman [16] (*n*: 136) (%)	Habetz et al. [17] Pediatric (*n*: 19) (%)	Habetz et al. [17] Adult (*n*: 100) (%)
Occipital Lobe	93.8	90	37.5	93	85	98	89.5	93
Parietal Lobe	85.7	70	37.5	93	77	98	100	93
Frontal Lobe	52.1	25	56	64	57	68	84.2	89
Temporal lobe	28.6	33	–	–	48	40	63.2	39
Cerebellum	30.6	10	12.5	29	29	32	21.1	57
Basal ganglia	8.1	3	12.5	11	31	14	5.3	16
Thalamus	2	5	9.3	–	20	–	10.5	32
Brain stem	2	–	6.2	21	20	13	10.5	28
Corpus callosum	2	–	–	–	–	10	21.1	20

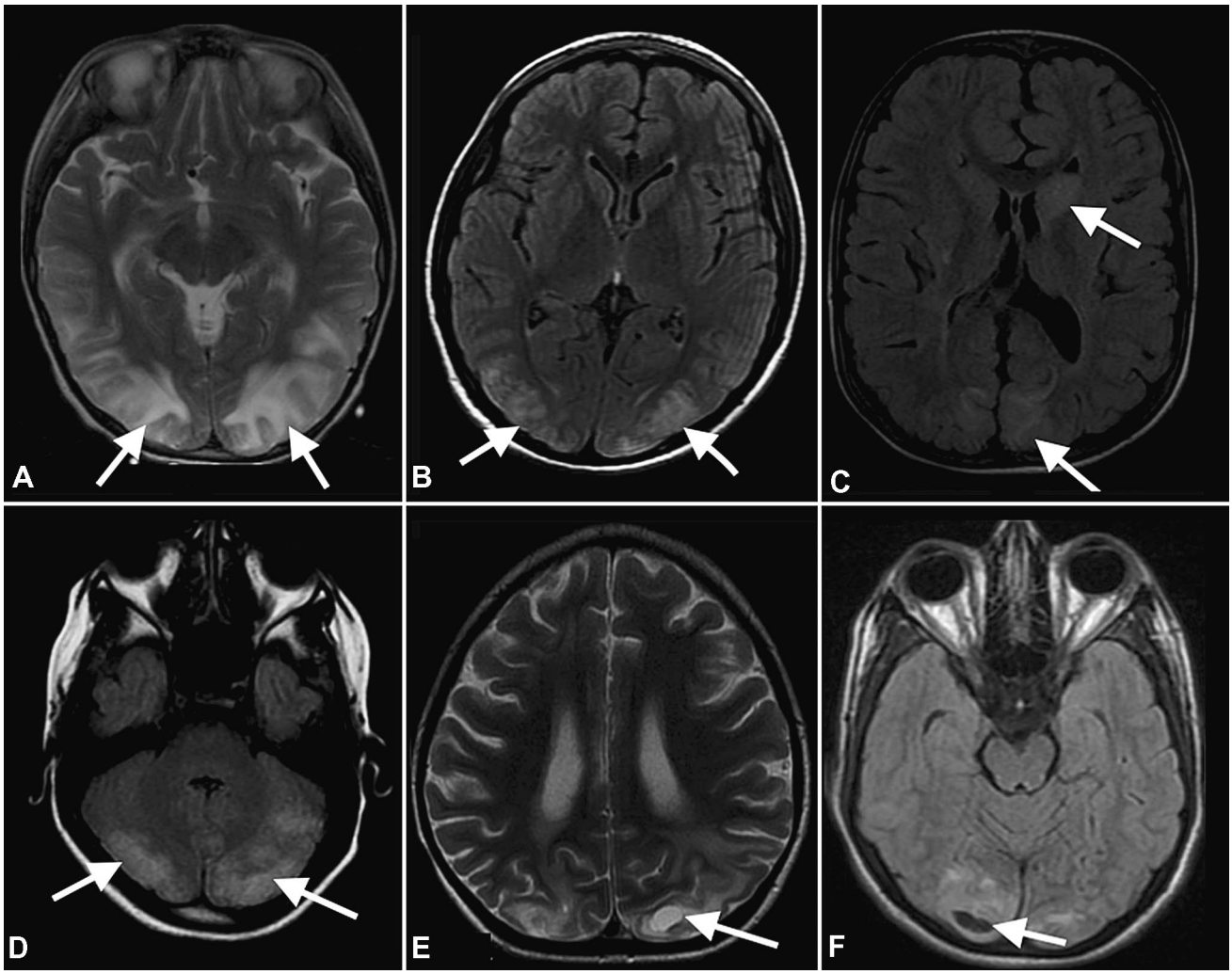

Fig. 1 Typical MRI findings in PRES. Bilateral symmetric parieto-occipital cortical–subcortical hyperintense signal changes on axial T2W (**a**) and FLAIR (**b**) images in two different patients. Atypical MRI findings in PRES. FLAIR images show high signal intensity on both parietal lobes in addition to the left caudate nucleus (**c**) and cerebellar hemispheres (**d**). Chronic sequelae MRI findings in PRES. Irreversible brain damage in the parieto-occipital region in the left side on axial T2W (**e**) and in the right side on FLAIR (**f**) images in two different patients with recurrent PRES

Recurrence in PRES and prognosis

In 8 (21%) of 38 patients, PRES episodes recurred during acute hypertension attacks. The etiology was ESRD in seven patients and NS without renal insufficiency in one patient. There was a statistically significant relationship between recurrence and ESRD ($p=0.02$). There were two episodes in five patients (13.2%), and three episodes in three patients (7.8%). The mean interval between the PRES attacks was 22.6 months (1–67 months).

Irreversible brain damage was detected in the parieto-occipital lobes after PRES episodes in three (7.8%) patients. Irreversible lesions developed after the second episode in one patient and after the third episode in two patients. In these patients, the hypertension could not be controlled within 72 h with medical treatment. There was a statistically significant relationship between the recurrence, the duration of hospitalization at the PICU, SE and the occurrence of irreversible lesion ($p=0.013$, $p=0.015$, $p=0.001$ respectively). Two of three patients who had irreversibl lesions died on follow-up.

C-reactive protein was evaluated in 45 episodes and found to be positive in 37 (82.2%), while ESR was evaluated in 21 episodes and found positive in 15 (71.4%). A statistically significant relationship was found between CRP positivity, elevated ESR rate and the duration of hospitalization ($p=0.046$ and $p=0.019$, respectively). Moreover, there was a statistically significant relationship between CRP positivity and high ESR rate and irreversible brain damage ($p=0.02$ and $p=0.041$ respectively)

During follow-up, 9 (23.7%) of 38 patients had epilepsy. Epileptic seizures were controlled in seven patients with a single antiepileptic drug (levetiracetam or valproic acid) and in two patients with two antiepileptic drugs (levetiracetam + valproic acid). Recurrent PRES was detected in six of nine patients who had epilepsy. There was a statistically significant relationship between epilepsy and recurrences, SE, and irreversible brain damage ($p = 0.02$, $p = 0.012$, $p = 0.025$, respectively).

Nine (23.7%) of 38 patients died in the follow-up. The mean duration was 2.4 months (1–7 months) between PRES attack and mortality. None of the patients died due to PRES. The cause of death was ESRD-related complications (such as sepsis, hemorrhage, thrombosis, etc.) in all of patients. There was a statistically significant relationship in patients with ESRD and mortality ($p = 0.001$). Five patients died after the first episode, two patients died after the second episode and two patients died after the third episode. There was a statistically significant relationship between the recurrences and mortality ($p = 0.049$). The follow-up period of the remaining 29 patients ranged from 7 months to 12 years (mean = 34.5 ± 38 months).

Discussion

In this article, the demographic, clinical and neuroimaging characteristics of 49 episodes in 38 children with PRES due to acute hypertension were described. To the best of our knowledge, this study contains the largest patient group with PRES due to acute hypertension. Clinical and neuroradiological findings of PRES due to acute hypertension in childhood were found to be similar to those with PRES caused by other etiological causes [2–4]. It was also found that the clinical and neuroradiological findings do not seem to differ between the etiologies of hypertension. As a result of this study, it was confirmed that the most common risk factor for PRES was a sudden increase in blood pressure, and the incidence of recurrence and etiology (ESRD) were the most important risk factors for prognosis.

The most important risk factor for PRES has been reported as acute hypertension. Yamada et al. found no association between the duration or severity of hypertension in PRES patients and neurological symptoms and neuroimaging findings [7, 8]. In all of 49 episodes in our study, PRES developed during an acute hypertension. Similar to Yamada's study, we did not find any relationship between the severity of blood pressure and clinical/radiological findings [8].

Seizure is the most common clinical finding in all age groups with PRES. Although the second most common finding in children is altered consciousness, in youth and adults, relatively, headaches and visual impairment may be more common [2, 7–11]. Yamamoto et al. found seizures in 78%, altered consciousness in 63%, visual impairment in 28%, and headache in 25% of the 40 children [9]. Similar to the pediatric literature, we found seizures in 40 (81.6%), altered consciousness in 39 (79.6%), headache in 36 (73.5%) and visual impairment in 22 (44.9%) of the 49 episodes.

The most serious and potentially life-threatening complication during PRES episode is SE [2, 4, 12, 13]. The rate of SE varies between 3 and 25% due to differences in the definition of SE in the literature [2, 4, 12]. In our study, SE developed in eight episodes (16.3%). The high rate of SE in our study may be due to the new definition of SE. In patients with SE; hospitalization at the PICU and secondary epilepsy due to PRES were higher. There was a statistically significant relationship between SE and hospitalization at the PICU and secondary epilepsy ($p = 0.015$, $p = 0.012$ respectively). In our study, SE was found to adversely affect prognosis similar to previous studies [14, 15].

The neuroradiological findings are important in the diagnosis and differential diagnosis of PRES, and our neuroradiological findings were similar to those in the literature (Table 2) [9, 10, 12, 13, 16, 17]. It is controversial whether there is a relationship between etiology and anatomic location of the lesions in the literature [2, 9, 11, 18]. In our study, no correlation was found between the etiology and the anatomic location of the lesions. Atypical lesions were reported between 61 and 81.8% in the literature [7, 10, 19–21]. All of this studies showed no relationship between etiology and atypical lesions. In our study, the atypical lesion rate was 67.3% and we also found no relationship between atypical lesion and etiology. Kamiya-Matsuoka et al. showed irreversible lesion and more severe clinical findings in patients with atypical MRI findings [21]. We found a statistically significant relationship between PRES recurrence and irreversible lesion in patients with atypical MRI findings ($p = 0.011$ and $p = 0.031$, respectively). Our results suggest that patients with atypical lesions may indicate poor prognosis.

Development of epilepsy has been reported in 10–15% of patients after PRES in all ages [2, 22]. In the study of Khan et al., epilepsy was reported in 19% of pediatric patients with PRES [23]. In our study, 9 of 38 (23.7%) patients with PRES had epilepsy, similar to the Khan et al. study. The high rate of epilepsy in our study may be due to the relatively long-term (12 years) follow-up period. Our results indicate that there was a statistically significant relationship between epilepsy and PRES recurrences, SE, and irreversible brain damage ($p = 0.02$, $p = 0.012$, $p = 0.025$, respectively). Similar to our study, Heo et al. suggested that SE and irreversible brain damage may predict the development of epilepsy [22].

The rate of recurrence in PRES has been reported in 3.8–12.5% in the literature [12, 15, 24–26]. Onder et al. reported that acute hypertension due to ESRD is the most important cause both in first and recurrent attacks [7].

Donmez et al. also reported that the most important cause of recurrence is acute hypertension due to chronic renal diseases [26]. We found recurrence in 8 (21%) of 38 patients. In seven of eight patients, the etiologic factor was ESRD. A statistically significant relationship was found between PRES recurrence and ESRD ($p=0.02$). This high recurrence rate may be attributed to the relatively long-term (12 years) follow-up period and the etiology of patients. It is not clearly defined whether there is a relationship between the recurrences and prognosis [4, 12, 26]. In our study, a statistically significant relationship was found between the recurrence rate, irreversible brain damage and epilepsy ($p=0.007$ and $p=0.02$ respectively). Thus, we may speculate that there may be a relationship between recurrence, etiology (ESRD) and poor prognosis in patients with PRES.

The main goal of treatment is to control the blood pressure in cases with acute hypertension. Irreversible brain damage has been linked to the unachievable control of blood pressure [2–4]. In our cases, complete improvement of the clinical findings was achieved by controlling the hypertension in 46 of the 49 episodes (93.9%). Similar to the literature, irreversible brain damage occurred in the occipital region because of hypertension. In patients with irreversible brain damage, both development of epilepsy and mortality were found to be high. Thus, irreversible brain damage may be a sign of poor prognosis [2–4].

Some studies have suggested that inflammation has a negative effect on morbidity and mortality in PRES [27–29]. Siebert et al. reported that sepsis and CRP elevation during the first episode of PRES had a statistically significant role in mortality [26]. Infections may cause new lesions in patients with recurrent PRES [24, 28]. We found a statistically significant relationship between CRP positivity and high ESR and the length of hospitalization ($p=0.046$ and $p=0.019$, respectively). Also, there was a statistically significant relationship between CRP positivity and high ESR rate and irreversible brain damage ($p=0.02$ and $p=0.041$ respectively).

The mortality rate of patients with PRES has been reported as 4.8–28 [2, 27, 29, 30]. In the study of Yamamoto et al., 11 (28%) out of 40 patients died, but none due to primary PRES [9]. In our study, 9 of 38 patients (23.7%) died and, similar to Yamamoto et al's study, none due to primary PRES. The mean duration was 2.4 months (1–7 months) between PRES attack and mortality. The cause of death was ESRD-related complications (such as sepsis, hemorrhage, thrombosis) in all the patients. According to our results, a statistically significant relationship was found between mortality and ESRD ($p=0.001$) and between mortality and recurrences ($p=0.049$).

In conclusion, although the prognosis of PRES is considered generally as good, the mortality and morbidity rates may increase in long-term follow-up as in our study. In patients with a history of recurrence and atypical MRI findings of PRES, more aggressive blood pressure monitoring is needed. PRES may completely recover with early diagnosis and treatment of acute hypertension. The etiology (ESRD) of PRES, presence of SE, having increased CRP, ESR and atypical MRI lesions during PRES episode were found to be important in the prognosis of PRES. In the presence of such factors, morbidity and mortality can be predicted to be higher. Therefore, we think that such patients should be monitored more closely.

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Compliance with ethical standards

Conflict of interest The authors declared that they have no competing interests.

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