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The Long-Term Clinical Experience on PRES of A Tertiary Pediatric Neurology Center in Türkiye

Türkiye'de Bir Üçüncü Basamak Pediatrik Nöroloji Merkezinin PRES ile İlgili Uzun Dönem Klinik Deneyimi

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Abstract

Objective: This study evaluates the clinical and radiological characteristics, treatment approaches, and outcomes of pediatric patients diagnosed with Posterior Reversible Encephalopathy Syndrome (PRES) in a pediatric intensive care unit and hematology service.

Materials and Methods: A retrospective analysis was conducted on 32 pediatric patients diagnosed with PRES between 2015 and 2023. Patients were followed up for at least two years. Demographic data, clinical features, and radiological findings were collected. EEGs were performed during the acute period and in follow-ups longer than three months. MRIs were evaluated by a multidisciplinary team. Vital signs were closely monitored, and blood pressure and intracranial pressure were managed.

Results: Of the 32 patients, 9 were female (28%) and 23 were male (72%), aged between 26-214 months. The majority had undergone bone marrow transplantation (BMT), with 81% developing PRES post-transplant. Seizures were the most common symptom, occurring in 94% of cases. Antiseizure medication (ASM) such as levetiracetam and clonazepam were used for seizure management. MRIs showed T2-weighted hyperintense lesions in all patients. The primary underlying conditions included acute lymphoblastic leukemia (ALL), chronic renal failure (CRF), and thalassemia major. Hypertension was present in all patients.

Conclusion: The study highlights the high incidence of PRES in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) and underscores the importance of early recognition and management of modifiable risk factors, particularly hypertension. Appropriate and timely intervention can significantly improve long-term outcomes for affected individuals. Further research is necessary to explore the pathophysiological mechanisms and optimize treatment strategies for PRES in pediatric populations.

Keywords: PRES, Hypertension, Chemotherapy, Bone Marrow Transplantation.

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Öz

Amaç: Bu çalışma, pediatrik yoğun bakım ünitesi ve hematoloji servisinde Posterior Reversibl Ensefalopati Sendromu (PRES) tanısı konulan pediatrik hastaların klinik ve radyolojik özelliklerini, tedavi yaklaşımlarını ve sonuçlarını değerlendirmektedir.

Gereç ve Yöntemler: 2015-2023 yılları arasında PRES tanısı konulan 32 pediatrik hasta üzerinde retrospektif bir analiz yapıldı. Hastalar en az iki yıl boyunca takip edildi. Demografik veriler, klinik özellikler ve radyolojik bulgular toplandı. Akut dönemde ve üç aydan uzun takiplerde EEG'ler yapıldı. MR'lar multidisipliner bir ekip tarafından değerlendirildi. Hayati bulgular yakından izlendi ve kan basıncı ile kafa içi basınç yönetildi.

Bulgular: 32 hastanın 9'u kız (%28) ve 23'ü erkek (%72) olup, yaşları 26-214 ay arasında değişmektedir. Çoğunluğu kemik iliği nakli (BMT) geçirmiş olup, %81'i nakil sonrası PRES geliştirmiştir. Nöbetler en yaygın semptom olup, vakaların %94'ünde görülmüştür. Nöbet yönetimi için levetirasetam ve klonazepam gibi antinöbet ilaçlar kullanılmıştır. Tüm hastaların MR görüntülemelerinde T2-ağırlıklı hiperintens lezyonlar saptanmıştır. Eşlik eden hastalıklar arasında akut lenfoblastik lösemi (ALL), kronik böbrek yetmezliği (CRF) ve talasemi major bulunmaktadır. Tüm hastalarda hipertansiyon mevcuttur.

Sonuç: Çalışma, allojenik hematopoietik kök hücre nakli (HSCT) geçiren pediatrik hastalarda PRES'in yüksek insidansını vurgulamakta ve özellikle hipertansiyon gibi değiştirilebilir risk faktörlerinin erken tanınması ve yönetiminin önemini ortaya koymaktadır. Uygun ve zamanında müdahale, etkilenen bireyler için uzun vadeli sonuçları önemli ölçüde iyileştirebilir. Pediatrik popülasyonlarda PRES'in patofizyolojik mekanizmalarını keşfetmek ve tedavi stratejilerini optimize etmek için daha fazla araştırma gereklidir.

Anahtar Kelimeler: PRES, Hipertansiyon, Kemoterapi, Kemik İliği Transplantasyonu.

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Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical-radiological entity characterized by a constellation of neurological symptoms, including headache, altered mental status, visual disturbances, and seizures. First described in 1996, PRES is associated with vasogenic edema predominantly affecting the subcortical white matter of the posterior cerebral hemispheres, particularly in the parieto-occipital regions (1, 2). While the syndrome is typically reversible with appropriate management, delays in diagnosis or treatment may lead to irreversible neurological damage or even death.

PRES it is most reported in middle-aged adults, though pediatric cases are increasingly recognized, particularly in those undergoing chemotherapy or solid organ transplantation. From an epidemiological standpoint, PRES occurs across a wide demographic spectrum, though certain populations demonstrate a higher predisposition. Individuals with chronic kidney disease, autoimmune disorders, or those receiving immunosuppressive therapy are at elevated risk (3, 4).

The diagnosis of PRES is multifactorial, relying on clinical presentation combined with neuroimaging findings. Magnetic resonance imaging (MRI), particularly fluid-attenuated inversion recovery (FLAIR) sequences, remains the gold standard for detecting the characteristic parieto-occipital white matter hyperintensities indicative of vasogenic edema (5). Although initially thought to be exclusively reversible, permanent changes such as cytotoxic edema and infarction have been observed in some cases, highlighting the necessity of timely diagnosis and intervention (6, 7).

Supportive care, including seizure management and close monitoring of neurological status, forms the backbone of acute treatment. Most patients exhibit significant clinical and radiological improvement within days to weeks following appropriate therapy, but some may develop complications such as intracerebral hemorrhage or chronic epilepsy (8).

Given the diversity of clinical presentations and underlying triggers, the identification of PRES requires a high index of suspicion in at-risk populations. Further research into the pathophysiological mechanisms underlying PRES and the long-term outcomes of affected individuals is essential to improve diagnostic accuracy and therapeutic strategies, especially patients in childhood.

Materials and Methods

Informed consent was obtained from the files of individuals included in this study. The ethics committee approval was obtained from the Human Research Ethics Committee of Akdeniz University Clinical Studies TBAEK-544 25.07.2024 and the study was planned and conducted in accordance with the Declaration of Helsinki.

The study included 32 patients who were clinically and radiologically diagnosed with PRES between 2015 and 2023, hospitalized in our pediatric intensive care unit and pediatric hematology service, and followed up for at least two years.

At least 2 (Elektroensefelography)EEGs were performed, the first EEG in the acute period and control EEG in follow-up longer than 3 months. MR imaging was performed at the time of diagnosis.

Demographic characteristics, clinical findings, electrophysiologic findings, and radiologic features were evaluated.

Vital signs were closely monitored and blood pressure and increased intracranial pressure were carefully managed in all patients. At the same time, patient heads were kept at 30-45 degrees, normal partial oxygen pressure was maintained, hypercapnia was avoided, electrolyte imbalance was corrected, seizure control was ensured and blood pressure values were kept within normal limits.

MRIs of all patients were evaluated by a pediatric neurologist, radiologist and intensive care physicians. Electroencephalogram (EEG) tests were performed using a Nihon Kohden Neurofax EEG-1200K device.

Results

Demographic and clinical characteristics of our patients are shown in Table 1. Of the 32 patients, 9 (28%) were female and 23 (72%) were male. Their ages ranged between 26-214 months.

The number of patients who underwent BMT was 21 (66%), and the number of patients who developed PRES after BMT was 17 (81%). Four patients had developed PRES before BMT. The number of patients with PRES and seizures after BMT was 15 (71%). The most common neurologic symptom was seizure, and 30 (94%) patients were consulted due to seizure, while 2 (6%) patients were consulted due to encephalopathy. Six (19%) patients had used antiepileptic drugs for less than 6 months, and 5 (83%) of these patients had no seizure recurrence. Eighteen patients used ASM for more than 6 months, and 8 (44%) of these patients had no seizure recurrence. There were 11 patients (34%) with 2 or more seizures. These 11 patients had seizures outside the acute phase. One patient needed multiple ASMs. There were 14 (44%) patients with normal EEG, 10 (31%) patients with cerebral dysfunction, and 3 (9%) patients with epileptic activity. Epileptiform activity was observed in all three patients, and it was focal. The types of seizures did not vary according to the existing clinical diagnosis.

Two patients had a pre-existing diagnosis of epilepsy before developing PRES. During follow-up, neurological sequelae were identified in only two patients: one with hearing loss (associated with chronic renal failure) and the other with polyneuropathy (associated with acute lymphoblastic leukemia). These sequelae were likely attributable to their underlying medical conditions rather than PRES itself.

Table 1.
Demographic and Clinical Characteristics of Our Cases

	n (%)
female	9 (28)
male	23 (72)
seizure	30 (94)
Case with BMT	21 (66)
PRES after BMT (Only cases with BMT)	17 (81)
Seizures in cases with PRES after BMT	15 (71)
≤6 months of ASM use	6 (19)
>6 months of ASM use	18 (56)
Number of seizures ≥2	11 (34)
ASM needs ≥2	1 (3)
EEG: no abnormalities	14 (44)
EEG: cerebral dysfunction	10 (31)
EEG: epileptic activity	3 (9)

In terms of antiepileptic drugs used, levetiracetam 21 (70%), clonazepam 6 (20%), oxcarbamazepine 3 (10%) and carbamazepine 1 (3%) were the most preferred antiepileptics. The main underlying diseases were ALL 6 (19%), AML 1 (3%), aplastic anemia 5 (16%) CRF (chronic renal failure) 8 (25%), CML 1 (3%), congenital neutropenia 1 (3%), chronic granulomatous disease 1 (3%), sickle cell anemia 2 (6%), severe combined immunodeficiency 1 (3%) and thalassemia major 6 (19%).

The highest blood pressure values measured after the development of PRES were above the 99th percentile for age in all patients (mean systolic blood pressure values: 145±19 mm Hg, mean diastolic blood pressure values: 94.1±9.9 mm Hg). Clinical presentation and etiology of the cases are shown in Table 2.

Table 2.
Clinical Presentation and Etiology of Cases

case	Age (mo*)	sex	underlying condition	clinical presentation	suspected etiology
1	78	m	aplastic anemia	seizure	chemotherapy hypertension
2	26	m	wilms tumor, CRF	seizure	hypertension
3	191	m	aplastic anemia, BMT	seizure	hypertension
4	146	m	relaps ALL	seizure	hypertension
5	144	m	ALL, BMT	seizure	hypertension
6	171	m	Thalassemia major, BMT	seizure	hypertension, GVHD
7	36	m	BMT, Renal tx	encephalopathy	hypertension
8	48	m	Aplastic anemia	seizure	hypertension
9	181	f	FSGS, RTx	seizure	hypertension
10	87	f	ALL	seizure	hypertension, chemotherapy
11	120	f	AML, BMT	seizure	hypertension, GVHD
12	120	f	congenital neutropenia	seizure	hypertension, chemotherapy
13	93	f	CRF-RTx	seizure	hypertension
14	131	f	ALL	seizure	hypertension
15	174	m	CML, BMT	seizure	hypertension, GVHD
16	211	m	Sickle cell anemia, BMT	seizure	hypertension
17	73	m	SCID, BMT	seizure	hypertension, GVHD, chemotherapy
18	70	f	Chronic granulomatous disease, BMT	seizure	hypertension, GVHD, chemotherapy
19	190	e	CRF	seizure	hypertension
20	154	m	ALL, BMT	encephalopathy	hypertension
21	134	f	ALL	seizure	hypertension
22	96	m	aplastic anemia, BMT	seizure	hypertension
23	57	m	Nefrotic syndrome	seizure	hypertension

24	106	f	thalassemia major, BMT	seizure	hypertension, GVHD
25	214	m	Sickle cell anemia, BMT	seizure	hypertension
26	142	m	aplastic anemia, BMT	seizure	hypertension
27	151	m	thalassemia major, BMT	seizure	hypertension
28	152	m	thalassemia major, BMT	seizure	hypertension, GVHD, chemotherapy
29	186	m	CRF-RTx	seizure	hypertension
30	145	m	CRF	seizure	hypertension
31	146	m	Thalassemia major, BMT	seizure	hypertension
32	95	m	Thalassemia major, BMT	seizure	hypertension

*mo: months, BMT: Bone marrow transplantation, ALL: acute lymphoblastic leukemia, CRF: chronic renal failure, RT: renal transplantation, GVHD: graft versus host disease

Imaging Findings

All patients (100%) exhibited hyperintense lesions in the parieto-occipital regions on T2-weighted and FLAIR sequences in magnetic resonance imaging (MRI). These findings were consistent with the characteristic radiological features of PRES. The distribution and intensity of the lesions reflected the typical pattern of vasogenic edema. Additionally, similar hyperintense lesions were observed in other regions, such as the frontal lobes, cerebellum, and brainstem, in some patients. These findings suggest that PRES is not limited to the parieto-occipital regions but may involve more widespread areas. The consistency of imaging findings supports the use of MRI as the gold standard for diagnosing PRES. Early identification of these radiological features can reinforce clinical suspicion, enabling timely initiation of treatment and potentially improving long-term neurological outcomes for patients.

Discussion

Our study confirms the high prevalence of PRES in pediatric patients undergoing allogeneic HSCT and highlights the significant clinical burden of seizures in this population. Early recognition and management of PRES, with a focus on controlling modifiable risk factors such as hypertension, early recognition and management are essential to improving patient long-term outcomes.

The data show that 94% of patients experienced seizures, with 34% experiencing recurrent episodes. This high prevalence of seizures is consistent with the well-established clinical presentation of PRES, where seizures are one of the most common manifestations. The high incidence of PRES observed in this cohort, particularly among patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), aligns with previous studies that highlight HSCT as a significant risk factor for the development of PRES (9, 10). In this study, 81% of the patients who underwent allogeneic HSCT developed PRES. This finding supports existing evidence suggesting that HSCT patients, especially those receiving high doses of immunosuppressive agents such as cyclosporine or tacrolimus, are at elevated risk due to endothelial damage and impaired cerebral autoregulation (11). These results underscore the importance of close neurological monitoring in this patient population, particularly during the immediate post-transplant period.

When compared to other studies, the demographic characteristics of this cohort, particularly the male predominance (72%), may reflect a higher male representation in the overall HSCT population or gender-related differences in susceptibility to PRES. Previous literature has reported mixed findings on gender distribution in PRES, with some studies suggesting a slight female predominance due to the association with

pregnancy-related conditions like pre-eclampsia. However, in the context of HSCT, gender-related immunological or pharmacological factors might contribute to the increased prevalence in males in pediatric ages observed here.

All patients demonstrated characteristic MRI findings of hyperintense lesions in the parieto-occipital regions on T2-weighted and FLAIR sequences, which is consistent with the classic radiological features of PRES (12). This uniformity in imaging findings reinforces the utility of MRI as a diagnostic tool in suspected cases of PRES, especially in post-HSCT patients presenting with seizures and altered mental status. The involvement of the parieto-occipital regions in all patients within this cohort may suggest a predilection of these regions for vasogenic edema in PRES, though other studies have also identified additional regions, such as the frontal lobes, cerebellum, and brainstem, in some cases (3). Future research could explore the correlation between specific radiological patterns and clinical outcomes to improve prognostication.

The findings from this study carry significant clinical implications, particularly for high-risk patient populations. A proactive approach is essential for integrating these insights into clinical practice. Early identification and close monitoring of risk factors, such as hypertension and immunosuppressive therapy in post-HSCT patients, are critical for preventing the development of PRES. Tight blood pressure control and careful adjustment of immunosuppressive drug dosages can serve as effective strategies to mitigate risk. Furthermore, implementing more aggressive antiepileptic treatment protocols in patients prone to seizures may help prevent recurrence and related complications. These measures have the potential to reduce both acute morbidity and long-term neurological sequelae, ultimately improving patient outcomes.

The high incidence of recurrent seizures despite anticonvulsant therapy underscores the need for vigilant neurological monitoring and potentially more intensive seizure management in patients at risk of PRES. Additionally, the elevated incidence of PRES following HSCT highlights the importance of early recognition of modifiable risk factors, such as uncontrolled hypertension or high-dose immunosuppressive therapy, which could facilitate timely interventions to reduce risk. Preventive strategies, including strict blood pressure management and judicious use of immunosuppression, should be prioritized in high-risk patients (13, 14).

One limitation of this study is the relatively small sample size, which may limit the generalizability of the findings. Furthermore, the retrospective nature of the data collection may introduce bias in the reporting of clinical features or treatment outcomes. Future studies with more significant, prospective cohorts are necessary to validate these findings and to explore additional factors, such as long-term outcomes, the role of specific immunosuppression agents, and the impact of different seizure management strategies.

Further research is needed to better understand the pathophysiology of PRES in the context of HSCT, particularly for the role of immunosuppression agents, endothelial dysfunction, and cerebral auto-regulation. Additionally, studies should explore whether early intervention strategies, such as preemptive anti-hypertensive therapy or alternative immunosuppression regimens, could reduce the incidence of PRES in high-risk populations.

During the follow-up of our patients, sequelae were observed in only two cases (one with hearing loss—CRF, and the other with polyneuropathy—ALL), which were thought to be related to their underlying conditions. Long-term follow-up studies are also required to assess the potential for permanent neurological sequelae in patients who experience PRES after HSCT.

Ethics Committee Approval: The study was approved by the Human Research Ethics Committee of Akdeniz University Clinical Studies (decision number: TBAEK-544, date: 25.07.2024).

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