Neuroimaging Findings of Posterior Reversible Encephalopathy Syndrome (PRES) Following Hematopoietic Stem Cell Transplantation in Pediatric Recipients

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Abstract

Background: Hematopoietic stem cell transplantation (HSCT) is the intravenous infusion of hematopoietic progenitor cells derived from bone marrow, umbilical cord blood or peripheral blood to restore hematologic and immunologic functions of bone marrow. HSCT is the only curative treatment in many childhood disorders and is used worldwide. However, serious complications are still an important concern of management. Central nervous system (CNS) complications in pediatric HSCT recipients can be associated with high morbidity and mortality. Posterior reversible encephalopathy syndrome (PRES) is the most common of these neuroimaging abnormalities in patients having neurological symptoms following HSCT. The most common presentation is posterior encephalopathy in which the lesions are located at the posterior parts of cerebral hemispheres, namely parietooccipital lobes. However, it can also be found in non-posterior distribution and can be accompanied by various atypical imaging manifestations like restricted diffusion.

Methods: In this study, we aimed to describe the typical and also uncommon neuroimaging manifestations of PRES following HSCT in our pediatric patients. We evaluated the medical records of 300 pediatric HSCT recipients.

Results: We detected 14 cases of PRES, of which there were 3 cases of atypical neuroimaging manifestations, regarding both the sites of involvement and also the magnetic resonance imaging (MRI) manifestations.

Conclusion: Such different presentations should not dissuade the diagnosis of PRES in the appropriate clinical settings in order to manage these patients timely and accurately.

Introduction

Hematopoietic stem cell transplantation (HSCT) is the intravenous infusion of hematopoietic progenitor cells derived from bone marrow, umbilical cord blood or peripheral blood to restore hematologic and immunologic functions of bone marrow. In autologous transplantation, the donor is the patient himself/herself before the bone marrow ablation. On the other hand, in allogeneic transplantation the donor is usually human leukocyte antigen (HLA) compatible or sometimes may be a haploidentical (half matched, mismatched) donor. HSCT is the only curative treatment in many childhood disorders and is used worldwide. However, serious complications are still an important concern of management. Central nervous system (CNS) complications in pediatric HSCT recipients can be associated with high morbidity and mortality. Posterior reversible encephalopathy syndrome (PRES) is the most common of these neuroimaging abnormalities in patients having neurological symptoms following HSCT (1, 2). Magnetic resonance imaging (MRI) is the modality of choice and shows typical bilateral vasogenic edema which appears as high-signal intensity on T2-W and FLAIR images (3). The most common presentation is posterior encephalopathy in which the lesions are located at the posterior parts of cerebral hemispheres, namely parietooccipital lobes. However, it can also be found in non-posterior distribution and can be

accompanied by various atypical imaging manifestations like restricted diffusion. In this study we aimed to describe the typical and also uncommon neuroimaging manifestations of PRES following HSCT in our pediatric patients.

Methods

The study was conducted in our hospital's bone marrow transplantation department. The study was approved by the Institutional Review Board (Bakırköy Dr Sadi Konuk Training and Research Hospital Clinical and Research Hospital Clinical Research Ethics Committee) with the protocol number of 2019-/90. Medical records of 300 pediatric patients who underwent allogeneic HSCT according to the treatment protocols used by bone marrow transplant department of our hospital from January 2014 to November 2018 were retrospectively evaluated. There were 130 pediatric HSCT recipients who experienced neurological symptoms and so having neuroimaging examinations including MRI and/or computed tomography (CT). The 96 patients who had MRI were enrolled in the study. 3T MRI with a dedicated head coil (Siemens 3T MAGNETOM Skyra) was used and included coronal FLAIR (TE/TR = 125/10000 msec; TI = 2800 msec), axial T2 (TE/TR = 80/3000 msec), axial T1 (10/2000 msec), diffusion weighted imaging (DWI) (TE/TR = 120/3500 msec) with apparent diffusion coefficient (ADC) map and GRE (16/840 msec) sequences. In addition to the pathological signal intensities on conventional MRI sequences (T1W, T2W and FLAIR) any pathological findings on DWI, SWI and contrast enhanced T1W images were also recorded. Informed consent were taken from the parents of the study participants.

Results

14 cases of PRES were detected on MRI of these 96 patients. Among the 14 cases of PRES, the most common symptom was seizure which was present in 10 patients (71.4 %) with or without other nonspecific symptoms. On MRI, the typical parietooccipital vasogenic edema was present in 78.5 % of the PRES cases (11/14) (Fig. 1). The atypical neuroimaging manifestations were as follows; isolated involvement of bilateral frontal lobes in 1 case (Fig. 2), cerebellum in 1 case (Fig. 3) and the basal ganglia in 1 case (Fig. 4). MRI abnormalities were bilateral and almost symmetrical in all of the cases. Restricted diffusion associated with cytotoxic damage could be demonstrated in 1 out of 14 cases, who was presented with isolated cerebellar involvement (Fig. 3) Unfortunately, she died 3 weeks after the onset of PRES due to acute pulmonary growth versus host disease (GVHD). In addition, in 1 patient who presented with basal ganglia involvement, the lack of dark signal on ADC map despite increased signal intensity on DWI, was considered as ADC pseudonormalization seen in subacute stage of cytotoxic injury, rather than T2w shine through effect of vasogenic edema (Fig. 4). We think that due to the presence of volume loss and persistent signal changes on follow up imaging. In our patients with PRES, we did not detect hemorrhagic changes. Follow up imaging studies were present in 9 out of 14 patients with PRES. Regarding the other 5 patients, one died due to the fungal CNS infection. The remaining 4 patients died due to other complications associated with HSCT like GVHD. Among the followed 9 cases in one case

with PRES who presented with basal ganglia involvement, persistent signal changes were detected on MRI 3 months after the diagnosis.

Discussion

PRES is a clinical and radiologic diagnosis characterized by variable presentations with various combinations of acute neurological symptoms. In pediatric patients diagnosed with PRES, the most frequently reported primary presentation is seizure (4). The underlying pathophysiologic mechanism is debated. There are two main theories. In vasogenic theory, high blood pressure causes dysregulation of cerebrovascular autoregulation resulting in cerebral vasodilation and edema (2, 5). However, arterial hypertension is not present in all patients with PRES. In our study hypertension that required antihypertensive treatment was present in 5 cases of PRES. On the other hand, in the cytotoxic theory the cause is increased microvascular permeability as a result of direct toxic effect on endothelial cells (6–8). The absence of increased blood pressure in many of the patients supports the cytotoxic theory, as in our cases. Although there are various different causes of PRES in pediatric patients, it is mostly described as a complication following various types of transplantations and in many studies it is the most common neuroimaging abnormality following HSCT. Immunosuppressive medications, such as cyclosporine-A, tacrolimus, and steroids which are the most commonly used drugs for GVHD prophylaxis can induce PRES in HSCT recipients (9–12).

On MRI, typical findings of cerebral vasogenic edema as a result of extravasation of plasma proteins and cells into the extracellular space are demonstrated. In our patients, the typical parietooccipital vasogenic edema was present in 78.5 % of the PRES cases (11/14) (Fig. 1). In many studies predominantly parietooccipital involvement was reported variably as between 50–99% of their cases (4, 13). Cerebral cortical (grey matter) involvement is seen in many patients (14–16). In most of our cases cortical grey matter involvement in the form of corticocortical hyperintensity was present (Figs. 1 and 2) and cortical involvement was obvious in some cases (Fig. 1). Despite being termed as posterior, PRES can also be found in other distributions, mainly in watershed areas, which can be involved as a part or as in isolation (17). The uncommon localizations seen in our patients were as follows; isolated involvements of frontal lobes (Fig. 2), cerebellum (Fig. 3) and the basal ganglia (Fig. 4). The term central PRES is used to describe the isolated involvement of basal ganglia, thalami, brain stem and corpus callosum with lack of corticocortical involvement. The central variant of PRES was reported in 4% of cases in the study of McKinney et al. (18). In the study of Raman et al. (19) the basal ganglia were involved in 22%, the brainstem in 9% and the thalamus in 4% of the cases. However, all of these cases had lesions also in the bilateral parietooccipital subcortical white matter. In our study, a central PRES variant with isolated involvement of basal ganglia was observed in 1 patient (Fig. 4). In PRES, the lesions are usually symmetrical, as in our cases. However purely unilateral cases of PRES have also been demonstrated in the literature (17, 18). In PRES lesions, increased ADC values are characteristic and indicative for vasogenic edema. DWI may be normal or hyperintensity is observed often due to the T2-shine through effect of vasogenic edema. However, true restricted diffusion may also present as an atypical finding in PRES lesions (20). In the study of McKinney et al. (18) 17.3% of the 76 patients with PRES had restricted

diffusion and in the study of Covarrubias et al. (21) 27% of 22 patients with PRES showed restricted diffusion. This is important because higher values of ADC is associated with reversibility in contrast to the decreased ADC values which indicates cytotoxic injury and poor prognosis (22). In our study, restricted diffusion could be demonstrated in 1 of 14 PRES cases involving the cerebellum. Unfortunately, since the patient died from acute pulmonary GVHD 3 weeks after the onset of PRES, there was no follow up MRI to show if the abnormal signals were persistent (Fig. 3). However, in the patient presented with basal ganglia involvement, despite the absence of dark signal on ADC map, we thought that increased signal on DWI was not due to T2-shine through and we considered it as a true restricted diffusion accompanied by ADC pseudonormalization, a normal phase in the subacute stage of cytotoxic injury. The reason we think that was the volume loss and persistent signal changes on follow up images (Fig. 4). The other reported atypical neuroimaging finding associated with PRES is hemorrhage and contrast enhancement, which were not present in our cases.

Conclusion

PRES usually presents with typical clinical and imaging findings. However, there may be atypical MRI manifestations, which should not dissuade the diagnosis of PRES in the appropriate clinical settings. Because timely diagnosis is crucial for early management of these patients.

Main points;

- Variable neuroimaging presentations should not dissuade the diagnosis of PRES in the appropriate clinical settings following allogeneic HSCT in pediatric recipients.
- In PRES, since ADC values are associated with prognosis, normal ADC values should also be considered in terms of being ADC pseudonormalization rather than typical T2 shine-through effect.

Declarations

Ethics approval: Ethical approval has been taken from Bakırkoy Dr Sadi Konuk Training and Research Hospital Clinical and Research Hospital Clinical Research Ethics Committee. All methods were performed in accordance with the relevant guidelines and regulations.

Informed Consent for publication: informed consent has been taken the parents of the patients.

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Tables

Table : Distribution of the neuroimaging abnormalities

	n	%
Leucoencephalopathy	5	
PRES	13	
PRES + Fungal CNS Enfeksiyonu	1	
SDH	3	

Figures

Figure 1

An 11 year old boy presenting with seizure and visual disturbances 3 months after undergoing allogeneic HSCT for acute myeloid leukemia, a) Axial and b) coronal FLAIR images demonstrate bilateral symmetrical parietal (a) and occipital (b) corticosubcortical hyperintensity (black arrows). Note the prominent involvement of cortical gray matter (1a, white arrow). c) DWI and d) ADC map show high signal (arrows), representing T2 shine through effect not true restricted diffusion. e) Follow-up coronal FLAIR image demonstrates complete resolution of the vasogenic edema in the occipital lobes after 3 months.

Figure 2

An 17 year old girl presenting with altered level of consciousness 6 months after undergoing allogeneic HSCT for thalassemia major, a) axial T2W image shows bilateral frontal corticosubcortical hyperintensity (arrows). b) DWI and c) ADC map show high signal (arrows), representing T2 shine through effect not true restricted diffusion. d) axial T2W image demonstrates complete resolution of the vasogenic edema after 3 months.

Figure 3

An 7 year old girl presenting with seizure and headache 37 days after undergoing allogeneic HSCT for hemophagocytic lymphohistiocytosis, a) axial T2W image shows abnormal cerebellar hyperintensity (arrows) b) DWI and c) ADC images show diffusion restriction (arrows). She was died 3 weeks after the onset of PRES due to acute pulmonary GVHD.

Figure 4

An 17 year old girl presenting with altered level of consciousness, 6 months after undergoing allogeneic HSCT for Thalassemia major, a) Coronal FLAIR image shows hyperintensity at bilateral basal ganglia (arrows) b) DWI shows increased signal intensity in the basal ganglia with c) ADC map showing normal signal intensity, which has been considered to be ADC pseudonormalization. d) Follow-up coronal FLAIR image after 6 months demonstrates persistent hyperintensity associated with volume loss suggesting a cytotoxic injury.