Posterior reversible encephalopathy syndrome in patients with hematologic tumor confers worse outcome

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Background: **This study aimed to evaluate the clinical features of posterior reversible encephalopathy syndrome (PRES) in children.**

Methods: **The medical records of 31 patients from five medical centers who were diagnosed with PRES from 2001 to 2013 were retrospectively analyzed. In the 31 patients, 16 were males, and 15 females, with a median age of 7 years (3-12 years). Patients younger than 10 years accounted for 74.2% of the 31 patients.**

Results: **Seizure, the most common clinical sign, occurred in 29 of the 31 patients. Visual disturbances were also observed in 20 patients. Cerebral imaging abnormalities were bilateral and predominant in the parietal and occipital white matter. In this series, three patients died in the acute phase of PRES. One patient had resolution of neurologic presentation within one week, but no apparent improvement in radiological abnormalities was observed at eight months. One patient showed gradual recovery of both neurologic presentation and radiological abnormalities during follow-up at eight months. One patient developed long-term cortical blindness. All of the PRES patients with hematologic tumor had a worse prognosis than those without hematologic tumor.**

Conclusions: **Seizure is a prevalent characteristic of children with PRES. Poor prognosis can be seen in PRES patients with hematologic tumor.**

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Original article

Introduction

In 1996, Hinchey et al[1] first described posterior reversible encephalopathy syndrome (PRES) as a clinical and radiological disease. PRES is thought to be due to different causes such as acute hypertension, use of immunosuppressive agents, preeclampsia/eclampsia, and renal disorders.[2] A typical imaging findings of PRES, including various distribution patterns, cytotoxic edema, infarction, hemorrhage, and contrast enhancement have been reported.[3] PRES is associated with various symptoms that comprise headache, focal neurological deficits (visual disturbances, dysphasia, paresis, and so on), seizures, and reduced consciousness.

Published studies on PRES before 2010 were mostly case reports. Retrospective studies with large samples were seen just in recent two years.[4] These studies largely focused on disease spectrum, pathogenesis, atypical lesions, and complications.[5] Among them, the occurrence of PRES could be explained by two hypotheses. First, the occurrence of PRES is caused by the sudden increase in blood pressure, which exceeds the cerebrovascular autoregulatory limits. The increase in blood pressure results in vasodilation, followed by disruption of the blood-brain barrier.[6] Second, the occurrence of PRES is the result of the effects of immunosuppressants, chemotherapeutic agents, and inflammatory factors; endothelial damage

may cause the disruption of the blood-brain barrier.[5,7,8] Blood-brain barrier damage causes the extravasation of plasma components and blood cells of the extracellular space and subsequent vasogenic cerebral edema. The sympathetic nervous system has a significant role in regulating cerebral vascular function. Vasogenic brain edema is confined to the posterior area of the brain. This edema may be related to the lack of sympathetic innervation in the posterior vessel.[5] The occurrence and resolution of vasogenic brain edema can be used to explain reversible clinical and imaging findings. Siebert et al[4] showed that PRES is encountered in most patients with autoimmune disorders, followed by patients with hematologic tumor. In addition, Kim et al[8] reported that PRES is usually found in the induction period of chemotherapy for acute lymphoblastic leukemia. Acute lymphoblastic leukemia chemotherapy is the main factor inducing PRES. Thus, to better define this syndrome in a large group of pediatric patients, especially in patients with hematologic tumor, we conducted a retrospective study involving five medical centers in China. The symptoms and outcomes of two PRES groups, one with hematologic tumor and the other without the disorder, were compared.

Methods

Participants

We retrospectively reviewed all pediatric patients diagnosed with PRES from five medical centers between 1 January 2001 and 1 April 2013. We used the information systems of these five medical centers through a keyword search in the diagnosis of "PRES" and "posterior reversible encephalopathy syndrome" to generate a patient database. To fulfill the inclusion criteria, patients should present features of an acute neurological syndrome, including headache, visual change, seizure, altered mental status, or a combination of these symptoms. The diagnosis of PRES was believed reasonable if magnetic resonance imaging (MRI) showed vasogenic edema in posterior region of the brain. Patients were excluded if the diagnosis showed a different result.

Risk factors, symptoms, and MRI results

The clinical records of recruited patients were reviewed. Brain MRI findings of the subjects were checked by neuroradiologists. Baseline data, including the records on first presentation, demographics, follow-up, drug profiles, and risk factors of PRES (use of chemotherapeutic drugs and immunosuppressants, hypertension, sepsis, and autoimmune diseases, and so on) were retrieved. The symptoms, particularly headache, seizure, visual disturbance, and other focal neurological deficits, were recorded. The results of brain MRI studies, including the presence of lesions on diffusion-weighted imaging, distribution of vasogenic edema, and hemorrhage, were obtained.

Statistical analysis

Categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate. Continuous variables were compared using the Mann-Whitney *U* test or Wilcoxon's rank-sum test if appropriate. Age was represented by the median value of the ages (Q1-Q3).

Results

Demographics

In 31 patients diagnosed with PRES, the youngest was one year old. The median age of the patients on presentation was 7 years (3-12 years), and 74.2% of the patients were younger than 10 years old. Fifteen patients were female, and 16 were male. The results of the primary diagnoses showed acute lymphoblastic leukemia (*n*=7), lymphoma (*n*=1), renal failure (*n*=8), bone marrow transplantation (*n*=10), hypertension encephalopathy (*n*=1), immune thrombocytopenic purpura (*n*=1), systemic lupus erythematosus (SLE; *n*=1), and intravenous drip anti-inflammatory herbal supplement (*n*=2). Table 1 shows the characteristics of the patients.

Table 1. Clinical data of patients with posterior reversible encephalopathy syndrome (*n*=31)

Variables	*n* (%)
Median age (y)	7 (3-12)
Gender	
Female	15 (48.4)
Male	16 (51.6)
Hypertension	19 (61.3)
Symptoms	
Visual disturbances	20 (64.5)
Blurred vision	15 (48.4)
Cortical blindness	3 (9.7)
Blind	2 (6.4)
Seizure	29 (93.5)
Headache	19 (61.3)
Consciousness disturbances	13 (41.9)
Lesion distribution	
Only occipital lesion	7 (22.6)
Only parietal lesion	1 (3.2)
Parieto-occipital lesion	8 (25.8)
Frontal-parietal lesion	6 (19.4)
Temporal-occipital lesion	1 (3.2)
Parieto-occipital plus temporal lesion	1 (3.2)
Parieto-occipital and fronto-temporal lesion	1 (3.2)
Parieto-occipital plus frontal lesion	6 (19.4)

Symptoms and causes

The following characteristics of PRES symptoms were reported. Seizure was the most common clinical symptom, and it occurred in 29 patients. Among these patients, 25 showed multiple seizures and 4 demonstrated single seizures. Headaches and visual disturbances were reported in 19 and 20 patients, respectively. In this series, 15 patients presented with visual blurring, 2 patients had symptoms of blindness (continuous for 7 days and ongoing for 2 days), and 3 patients presented with cortical blindness. The impairment of consciousness was found in 13 patients, of whom four showed confusion. Eighteen patients had both visual disturbances and seizures. Visual disturbances and loss of consciousness occurred in 7 patients. Initial clinical syndromes associated with PRES included seizures in 23 children, consciousness disturbances in 6, and visual disturbances in 2. Nineteen children demonstrated hypertension during or before the event. The recovery from seizure during hospital stay occurred in 93.5% of the patients, with an average time of 3 days. In our patients, the mean time for resolution of blurred vision was 7 days; one patient had no apparent improvement from cortical blindness after two months. The duration of consciousness disturbances in the patients was 5 days. The causes of PRES are listed in Table 2. A comparison of the clinical symptoms and outcomes of the tumor (n=14) and non-tumor groups (n=17) is shown in Fig. Table 4 shows the list of patient characteristics of the two groups.

Table 2. Causes of posterior reversible encephalopathy syndrome (n=31)

Hypertension (n=19)	Autoimmune diseases (n=2)	Infection (n=5)	Kidney damage (n=8)	Drug toxicity (n=30)	n (%)
				+	7 (22.6)
			+	+	1 (3.2)
		+	+	+	1 (3.2)
		+		+	3 (9.7)
+			+	+	6 (19.4)
+				+	9 (29.0)
+		+		+	1 (3.2)
+	+			+	2 (6.5)
+					1 (3.2)

+: patients with the cause.

Radiological examination

MRI was performed for the 31 patients. All patients demonstrated features of subcortical vasogenic edema and cortical involvement. Cranial MRI showed T1-weighted images of hypointensity and T2-weighted images of hyperintensity, thus suggesting edema. Cerebral imaging abnormalities were mostly bilateral (93.5%). Isolated occipital lesion was found in 7 patients, isolated parietal lesion in 1, parieto-occipital lesion in 8, frontal-parietal lesion in 6, temporal-occipital lesion in 1, parieto-occipital plus temporal lesion in 1, parieto-occipital and fronto-temporal lesion in 1, and parieto-occipital plus frontal lesion in 6. In short, occipital lesions were encountered in most of the patients, followed by parietal lesions and frontal lesions.

Follow-up

The mean time of follow-up for the patients was 8

Table 3. Comparison of studies on posterior reversible encephalopathy syndrome in children conducted in Europe and Asia

Variables	Siebert's study in Europe (n=18)	Our study in Asia (n=31)
Demographics		
Male/female	11/7	16/15
Median age (y)	9 (7-12)	3 (7-12)
Primary disease		
Non-tumor group, n (%)	14 (77.8)	17 (54.8)
Tumor group (chemotherapy), n (%)	4 (22.2)	14 (45.2)
Symptoms		
Seizures, n (%)	18 (100)	29 (93.5)
Altered mental status, n (%)	5 (27.8)	13 (41.9)
Imaging of brain lobe lesions		
Frontal, n (%)	17 (94.4)	13 (41.9)
Parietal, n (%)	17 (94.4)	23 (74.1)
Occipital, n (%)	16 (88.9)	24 (77.4)
Clinical prognosis		
Complete remission, n (%)	16 (88.9)	25 (80.6)
Incomplete remission, n (%)	2 (11.1)	3 (9.7)
Death, n (%)	0	3 (9.7)

Table 4. Comparison of studies on posterior reversible encephalopathy syndrome in children with tumor or without tumor

Variables	Without tumor (n=17)	With tumor (n=14)
Male/female	8/9	8/6
Symptoms		
Seizures, n (%)	16 (94.1)	13 (92.9)
Headaches, n (%)	11 (64.7)	8 (57.1)
Visual disturbances		
Visual blurring, n (%)	8 (47.1)	7 (50.0)
Blindness, n (%)	2 (11.8)	0
Cortical blindness, n (%)	1 (5.9)	2 (14.3)
Consciousness impairment, n (%)	9 (53.0)	4 (28.6)
Hypertension, n (%)	12 (70.6)	7 (50.0)
Imaging of brain lobe lesions		
Occipital, n (%)	13 (76.5)	11 (78.6)
Parietal, n (%)	13 (76.5)	10 (71.4)
Frontal, n (%)	7 (41.2)	6 (42.9)
Clinical prognosis		
Complete remission, n (%)	16 (94.1)	9 (64.3)
Incomplete remission, n (%)	0	3 (21.4)
Death, n (%)	1 (5.9)	2 (14.3)

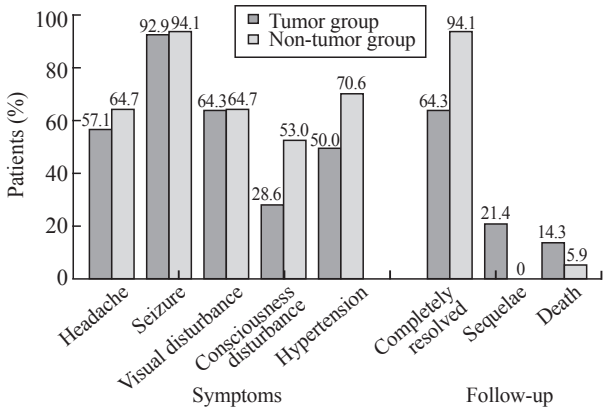

Fig. Comparison of studies on posterior reversible encephalopathy syndrome in children with tumor or without tumor.

months. Follow-up MRI was performed in 28 patients after two to three weeks. Three patients in the acute phase of death were likewise followed up. Clinical and radiological changes were resolved in 25 patients within two weeks. One patient had resolution of neurologic symptoms within one week, but no marked change was observed in radiological abnormalities at 8 months. In one patient both neurologic symptoms and radiological abnormalities were changed gradually during the follow-up at 8 months. Another patient had long-term cortical blindness. We compared the clinical symptoms and outcomes between the hematologic tumor PRES group and the non-hematologic tumor PRES group. The results showed a worse prognosis in PRES patients with hematologic tumor than that in PRES patients without hematologic tumor (Fig.).

Discussion

We reviewed the clinical and imaging features of the 31 patients with PRES. In these patients, 29 patients had seizures, in which single seizure occurred in 4 patients, and multiple seizures (10 times and more) in 25. Thus, seizure was found to be prevalent in children. Moreover, 3 patients died, and three patients manifested sequelae. The most common causes of PRES were drug toxicity and hypertension. A previous study[8] revealed that 3 of 9 patients with recurrent seizures or epileptiform discharges presented with intractable seizures. In 7 patients whose cranial MRI revealed sequelae, 6 patients received a long-term anticonvulsant therapy. Lee et al[5] reported 36 patients with PRES, of whom 7 patients had cortical blindness. In our study, 3 patients had cortical blindness, and 15 had varying degrees of blurred vision. Therefore, cortical blindness is a common clinical manifestation that needs adequate attention from physicians.

PRES is thought to be reversible and cannot cause sequelae.[1,6,7] However, there are contradictory reports. Residual abnormalities or recurrence has been reported, particularly in cancer patients.[8-12] This finding is consistent well with the result of our patients during acute lymphoblastic leukemia induction chemotherapy. This finding, which was associated with the pathogenesis of patients who developed PRES during induction chemotherapy, could be deemed as one of the various factors. We compared the clinical symptoms and outcomes of the PRES patients with or without hematologic tumor. PRES patients with hematologic tumor showed a worse prognosis than those without hematologic tumor. Children with tumors have a poor prognosis because of difficulty in treating the underlying condition and limitation of treatments caused by cancer-related issues.

The interaction of multiple risk factors is similar to the relationship of "seed, insects, and soil". Studies[9,10] found long-term hypertension in patients with kidney disease or SLE. The main predisposing factor for PRES was hypertension, but blood pressure was within normal range in patients with PRES. This was found in the treatment of acute childhood leukemia. Endothelial damage caused by chemotherapeutic agents and tumor lysis syndrome are the main predisposing factors for PRES. Fluid retention and increased fluid volume are often related to kidney dysfunction. Besides cyclosporine and hypertension, other factors including low serum albumin level, generalized edema, increased vascular permeability, unstable fluid status, and renal insufficiency appear to predispose the development of PRES.[13] The relationship between lesion distribution and PRES etiology should be elucidated. We suggest that lesions may be atypical under damaged blood vessel endothelium and other factors may lead to PRES. PRES is likely to occur in the posterior area of the brain if vascular autoregulation dysfunction plays a role in PRES patients with hematologic tumor. We also compared the clinical symptoms and outcomes of our patients with those from Europe.[4] The prognosis of our PRES patients was poorer than that of the patients reported by Siebert et al[4] because patients with hematologic tumor accounted for 45% in our study.

The limitations of this study include incomplete data and retrospective nature. Nevertheless, the results of our study may be helpful to clarify pediatric PRES. Pediatricians should recognize the clinical features of PRES to prevent the occurrence of irreversible neurological lesions.

In conclusion, poor prognosis can be observed in PRES patients with hematologic tumor. Pediatricians should recognize the clinical features of PRES to prevent the occurrence of irreversible neurological lesions.

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References

1 Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494-500.
2 Dillon WP, Rowley H. The reversible posterior cerebral edema syndrome. AJNR Am J Neuroradiol 1998;19:591.
3 Trullemans F, Grignard F, Van Camp B, Schots R. Clinical findings and magnetic resonance imaging in severe cyclosporine-related neurotoxicity after allogeneic bone marrow transplantation. Eur J Haematol 2001;67:94-99.
4 Siebert E, Spors B, Bohner G, Endres M, Liman TG. Posterior reversible encephalopathy syndrome in children: radiological and clinical findings-a retrospective analysis of a German tertiary care center. Eur J Paediatr Neurol 2013;17:169-175.
5 Lee VH, Wijdicks EF, Manno EM, Rabinstein AA. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Arch Neurol 2008;65:205-210.
6 Liman TG, Bohner G, Heuschmann PU, Endres M, Siebert E. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: the retrospective Berlin PRES study. J Neurol 2012;259:155-164.
7 Young GB. Encephalopathy of infection and systemic inflammation. J Clin Neurophysiol 2013;30:454-461.
8 Kim SJ, Im SA, Lee JW, Chung NG, Cho B, Kim HK, et al. Predisposing factors of posterior reversible encephalopathy syndrome in acute childhood leukemia. Pediatr Neurol 2012;47:436-442.
9 Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. AJNR Am J Neuroradiol 2008;29:1043-1049.
10 Panis B, Vlaar AM, van Well GT, Granzen B, Weber JW, Postma AA, et al. Posterior reversible encephalopathy syndrome in paediatric leukaemia. Eur J Paediatr Neurol 2010;14:539-545.
11 Won SC, Kwon SY, Han JW, Choi SY, Lyu CJ. Posterior reversible encephalopathy syndrome in childhood with hematologic/oncologic diseases. J Pediatr Hematol Oncol 2009;31:505-508.
12 Lucchini G, Grioni D, Colombini A, Contri M, De Grandi C, Rovelli A, et al. Encephalopathy syndrome in children with hemato-oncological disorders is not always posterior and reversible. Pediatr Blood Cancer 2008;51:629-633.
13 Ishikura K, Ikeda M, Hamasaki Y, Hataya H, Nishimura G, Hiramoto R, et al. Nephrotic state as a risk factor for developing posterior reversible encephalopathy syndrome in paediatric patients with nephrotic syndrome. Nephrol Dial Transplant 2008;23:2531-2536.

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