

Posterior reversible encephalopathy syndrome: Malaysian haemato-oncological paediatric case series

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Abstract

Background & Objective: Posterior reversible encephalopathy syndrome (PRES) is associated with immunosuppressive agents used in children with haemato-oncological diseases. There are no reports to date from the South Asia and South East Asia region. We report a Malaysian tertiary centre case series of children with haemato-oncological disease who developed PRES. **Methods:** Retrospective study of children seen with haemato-oncology diseases seen at the University Malaya Medical Centre Kuala Lumpur who developed PRES from 2011 – 2013. Clinical details were obtained from medical records and brain neuroimaging was reviewed. **Results:** Five patients met the inclusion criteria. All 5 patients had significant hypertension acutely or subacutely prior to neurology presentation. Four presented with acute seizures and the remainder 1 presented with encephalopathy. Three patients were on chemotherapy, 1 had renal impairment and 1 had prior immunosuppression for bone marrow transplantation. A full recovery was seen in 4 patients and 1 patient had mild residual quadriplegia. **Conclusion:** Our case series expands the clinico-radiological spectrum of PRES in children with underlying haemato-oncological disorders. It is the first to show that prior cyclosporin intake as long as 2 months is a potential risk factor for PRES. Clinicians need to be vigilant for development of PRES and closely monitor the blood pressure in these children who are receiving or recently had immunosuppressive drugs and present with acute neurological symptoms.

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological condition. It is characterized by neurological symptoms including headache, altered mental function, seizure and cortical blindness associated with typical neuroimaging findings. The topographic distribution of neuroimaging features of PRES is divided into 4 characteristic patterns; i) *Holohemispheric watershed pattern*: confluent involvement extending through frontal, parietal and occipital lobes; ii) *Superior frontal sulcus pattern*: frontal lobe along the superior frontal sulci +/- parietal and occipital lobes; iii) *Dominant parietal-occipital pattern*: posterior part of parietal and occipital lobe; iv) *Partial or asymmetric expression of primary patterns*: defined as unilateral or bilateral absence of involvement or oedema in either parietal or occipital lobes.¹

PRES was first described by Hinchey *et al.* in 1996 by reviewing clinical and imaging findings

of 15 patients over a 6 year period.² At the time of first report the authors presented the syndrome as reversible posterior leukoencephalopathy syndrome. Prior to this there have been reports from the 1980s of clinico-radiological descriptions of probable PRES.^{3,4} The first possible paediatric case of PRES was reported in 1931.⁵ However recently, the reversible aspect has been questioned as neurological impairment and up to 15% mortality rate have been reported.^{6,7}

Exposure to toxic agents including the use of immunosuppressive agents in haemato-oncological diseases and hypertension are commonly associated with PRES. Other known associations are organ or bone marrow transplants, acute or chronic renal diseases, high dose corticosteroids and hemodialysis.^{6,8-14} To date, there are only a total of 42 paediatric patients reported with PRES associated with haemato-oncological disease with no reported case series from the South Asia and South East Asia region. In this study, we report a

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single centre case-series of 5 Malaysian children with haematological-oncological disease who developed PRES managed in University Malaya Medical Centre, Kuala Lumpur.

METHODS

This retrospective study was undertaken at the University Malaya Medical Centre Kuala Lumpur, Malaysia. Children with haematological-oncological diseases who developed PRES were identified by searching the paediatric haematology patient database from January 2011 – December 2013. Brain computed tomography (CT) and / or magnetic resonance imaging (MRI) studies were reviewed in the identified patients. MRI protocol included T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR), diffusion-weighted (DWI) and apparent diffusion coefficient (ADC) sequences using a 1.5T MR scanner. Criteria for confirmation of PRES included features of the typical PRES pattern; and a clinical presentation consistent with PRES such as encephalopathy, seizures, cortical visual impairment or headache.

Medical records of the patients' were comprehensively reviewed and the following were ascertained: symptoms at clinical presentation, known clinical associations with PRES (including details of immunosuppression medications, infection, sepsis, transplantation, blood pressure prior and during symptomatic neurotoxicity) and clinical outcome. Hypertension was defined as elevated systolic or diastolic blood pressure (BP) greater than the 95th centile for the specific age categories.¹⁵ Children with systolic BP > 179mmHg or diastolic BP greater than 109 mm Hg was defined as having a hypertensive crisis.¹⁶

RESULTS

Five paediatric patients with PRES from January 2011 to December 2013 were admitted to University Malaya Medical Centre with underlying hemato-oncological diseases. Two patients were male and 3 patients were female with age range from 6 – 17 years old (mean age: 11.5 years). Four of the 5 patients were inpatients prior to the development of clinical symptoms of PRES.

Table 1 shows the clinical characteristics of the case series. All patients had underlying hematologic-oncological disease. Four patients were immunocompromised receiving prior chemotherapeutic or immunosuppressive drugs and 1 patient had undergone allogenic bone marrow

transplant (for underlying beta thalassaemia major) and was weaned off immunosuppressive drugs 2 months prior to clinical symptoms. All of the 5 patients had significant hypertension either acutely or subacutely (several hours to days) prior to neurological symptoms. Of these patients, 1 experienced a hypertensive crisis. Acute antihypertensive treatment was given to all patients.

Investigations performed on all 5 patients included: blood for full blood count, renal profile, liver function test, coagulation profile, C-reactive protein, and blood culture; urine for microscopy and culture. Cerebrospinal fluid (CSF) was performed on 4 patients (Patient 2, 3, 4, 5) for microscopy, bacterial culture and cytospin. Bone marrow examination was performed on 2 patients (patient 2,3). Patient 5 had additional investigations performed including serum for cortisol, renin, aldosterone; urine for catecholamines; and CSF culture for viruses (paired with Herpes IgM and JE IgM), fungus and tuberculosis.

Brain neuroimaging findings of the patients are summarized in Table 2 and Figure 1. Patient 4 had widespread PRES lesions on neuroimaging corresponding with cytotoxic oedema (Figure 2) and intraparenchymal haemorrhage (Figure 3). The majority of patients (4/5) made a complete clinical recovery apart from patient 4 who had residual quadriplegia (MRC power grade 4/5 bilaterally) 1 year after clinical presentation.

Clinical summary prior and during PRES episode

Patient 1: 17-year-old girl diagnosed with renal cell carcinoma at 12 years old. She underwent a right nephrectomy and subsequently completed chemotherapy with adjunctive radiotherapy at 14 years old. She represented at 17 years old with recurrence of renal cell carcinoma with acute on chronic renal failure. She had a laparotomy for debulking of the tumour and post-operatively stayed in the Paediatric Intensive Care Unit. Whilst in intensive care she developed persistent hypertension and 2-days after that she became encephalopathic for 6 hours followed by an 18-day period of cortical blindness. She did not receive 2nd line chemotherapy during the period of her relapse of renal cell carcinoma.

Patient 2: 10-year old boy with newly diagnosed Acute Lymphoblastic Leukemia was commenced on chemotherapy (IV vincristine, IT methotrexate, IM asparaginase) with prednisolone using the

Table 1: Clinical characteristics of patients

Patient (age)	Underlying disease	Presenting symptoms	Maximal BP mmHg (BP 95 th centile for age)	Duration of hypertension pre-symptoms	Additional potential precipitating factors	Clinical outcome (treatment given)
1 (17 years)	Renal cell carcinoma	Encephalopathy, cortical blindness	180/114 (130/85)	2 days	Renal impairment	Complete recovery (ventilated for 4 days, antihypertensive for 1 month)
2 (10 years)	Acute lymphoblastic leukemia	Seizure, headache	160/98 (120/79)	8 days	Induction chemotherapy, Tumor lysis syndrome	Complete recovery (antihypertensive and antiepileptic drug for 1 month)
3 (7 years)	Non-Hodgkin lymphoma	Seizure	150/100 (116/76)	On the same day	Induction chemotherapy	Complete recovery (ventilated for 1 day, antihypertensive for 3 months, antiepileptic drug for 1 month)
4 (7 years)	Biphenotypic (predominant myeloid) leukemia	Status epilepticus, cortical blindness	150/98 (116/76)	6 days	Induction hemotherapy, febrile neutropenia, sepsis	Residual quadriplegia with power 4/5 (antihypertensive for 3 months, antiepileptic drug for 1 month)
5 (6.6 years)	Beta thalassaemia major	Seizure, cortical blindness	170/120 (110/73)	On the same day	Prior cyclosporine intake, bone marrow transplantation	Complete recovery (antihypertensive)

Table 2: Neuroimaging details of patients

Patient	Imaging finding (characteristic imaging pattern)	Timing of imaging at presentation (imaging modality)	Timing of repeat imaging (imaging modality)	DWI and ADC findings
1	Bilateral occipital, parietal, temporal and frontal (<i>dominant parietal-occipital pattern</i>)	Day 0 (CT)	Day 20 (CT)	Not done
2	Bilateral frontal, parietal and occipital (<i>dominant parietal-occipital pattern</i>)	Day 1 (CT)	2 months (MRI)	Not done
3	Right posterior temporal, bilateral parietal-occipital (<i>dominant parietal-occipital pattern</i>)	Day 2 (MRI)	1 month (MRI)	Vasogenic oedema
4	Vertex, left frontal, bilateral posterior parietal and occipital (<i>Holohemispheric watershed pattern</i>)	Day 2 (MRI)	7 months (MRI)	Cytotoxic oedema
5	Bilateral cerebellar, occipital, frontal and high parietal regions (<i>dominant parietal-occipital pattern</i>)	Day 2 (MRI)	3.5 months (MRI)	Vasogenic oedema

MASPORE 2010 protocol and developed a tumour lysis syndrome. He was hypertensive for an 8-day period during the induction phase of chemotherapy. He then woke on day 8 of induction chemotherapy with acute onset severe headache followed by a cluster of left sided focal seizures.

Patient 3: 7-year old girl newly diagnosed

with Non-Hodgkin Lymphoma. Induction chemotherapy was commenced using the ALCL 1999 protocol (IT methotrexate, IT cytarabine, IV dexamethasone, IV cyclophosphamide, IV doxorubicin). Day 4 after induction chemotherapy he developed hypertension and on the same day he developed a cluster of focal right sided head versive seizures with bilateral upper limb convulsions.

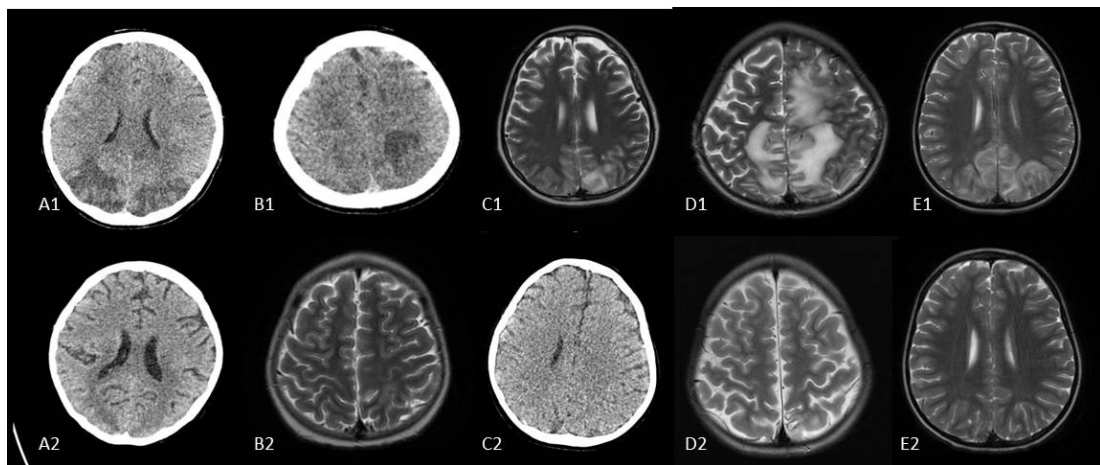


Figure 1: Serial axial neuroimaging of patient 1-5 (initial imaging on top and repeated imaging bottom) showing distribution of lesions on presentation and subsequent resolution of lesion.

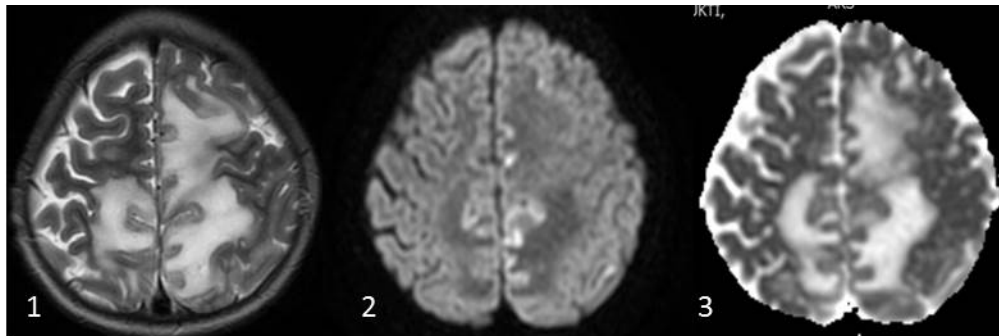


Figure 2: Patient 4 axial neuroimaging (1: T2-weighted, 2: DWI, 3: ADC sequences) showing cytotoxic oedema.

Patient 4: 7-year old boy newly diagnosed Biphenotypic (predominant myeloid precursors) leukemia. Induction chemotherapy was commenced (high dose IV cytarabine, IV daunorubicin, IV etoposide) for 5 days. He was hypertensive from day 3 of induction chemotherapy. Four days after the high dose IV cytarabine he developed status epilepticus. He subsequently developed a febrile neutropenia with sepsis requiring antibiotic treatment.

Patient E: 6-year 7-month old girl diagnosed with beta thalassaemia major at age of 5-year 4-month old. She subsequently undergone successful matched-sibling donor haematopoietic stem cell transplantation (HSCT). Her immunosuppression regimen post-HSCT included oral mycophenolate and oral cyclosporin. She was off mycophenolate for 6 months and cyclosporin for 2 month prior to presentation. On presentation, she had an episode of vomiting followed by a cluster of 3 left sided focal seizures over 3 hours. On admission she was hypertensive and developed cortical blindness

DISCUSSION

In our study we describe the detailed clinical course, imaging features and potential PRES risk factors in children who presented to our unit with PRES. To our knowledge, this is the first cohort of children with PRES from South Asia and South East Asia, and expands the clinical spectrum of these children.

In our case series, hypertension was present in all patients and seizures were the most common presenting symptom which was seen in 4/5 patients. Similar findings have been reported in other studies with frequency of hypertension ranging between 42-100% of patients.^{10,11,14,17-20} Our study reiterates that children presenting with acute neurological symptoms in particular seizures, visual impairment or encephalopathy in the combination with risk factors of PRES should be a red flag of a possible PRES diagnosis.

Exposure to immunosuppressive and chemotherapy agents have been shown to be associated with PRES. These agents might act through the direct toxic effect on the

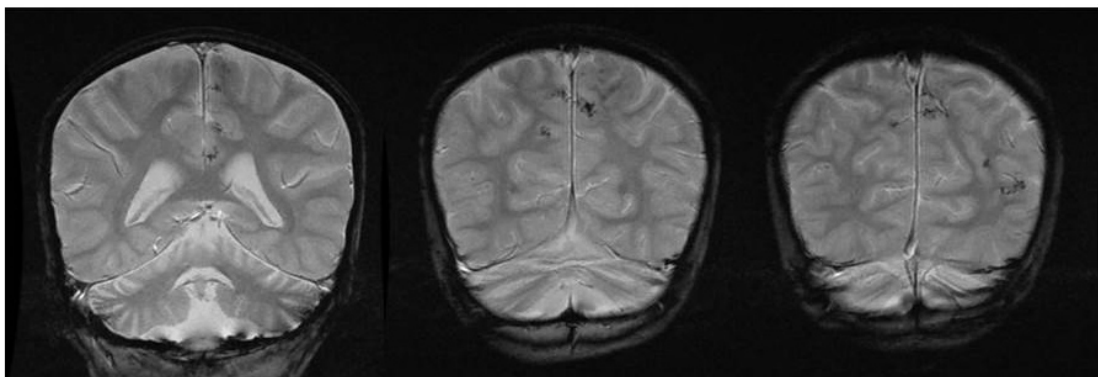


Figure 3: Patient 4 coronal neuroimaging gradient recalled echo (GRE) sequences showing multiple minute haemorrhages (seen as blooming artifacts) over the midline and bilateral parietal lobes.

cerebrovascular endothelium.²¹ Three of our patients (patient 2, 3, 4) developed symptoms after induction chemotherapy for acute lymphoblastic leukemia, non-Hodgkin lymphoma and biphenotypic leukemia. Steroid-based induction chemotherapy with intrathecal methotrexate is known to be a predisposing factor for PRES.^{8,18,21} In methotrexate-induced neurotoxicity, white matter lesions are affected typically involving the periventricular regions.²³ However, in our patient 3 who received prior treatment with intrathecal methotrexate before developing PRES did not show the typical periventricular lesions. One patient (patient 5) with underlying beta thalassaemia major had a history of daily oral cyclosporine for post-haematopoietic stem cell transplantation (HSCT) immunosuppression 2 months before presentation of PRES. HSCT and prior cyclosporin intake appeared to be the risk factors in this patient. Although cyclosporine is also a known predisposing factor for PRES^{9,24,25}, previous reports indicate that cyclosporine-induced PRES is transient with resolution of symptoms when patients ceased cyclosporine therapy.²⁵⁻²⁷ HSCT is another risk factor for PRES as patients are exposed to both myeloablative as well as immunosuppressive therapy.

Although the pathophysiology of hypertensive encephalopathy is still unclear, there are currently two most compelling though competing theories on its pathophysiology: (i) systemic hypertension exceeds cerebral autoregulatory limits resulting in forced cerebral hyperperfusion; and (ii) cerebrovascular endothelial toxicity with cerebral hypoperfusion, with or without compensatory (possibly protective) systemic hypertension. The latter theory may better explain the association of cytotoxic agents with PRES without hypertension. Consequently, disruption of the blood brain barrier and increased vascular permeability occurs resulting in vasogenic oedema.²⁸ Vasogenic oedema can be differentiated from cytotoxic oedema using diffusion weighted images in MRI.^{13,14} In patients with PRES, the typical appearance is high ADC values which represents highly mobile water in the area of vasogenic oedema. This finding suggests a better prognosis. In contrast, restricted ADC values imply cytotoxic oedema and indicate the possibility of irreversible brain damage.⁹ One of the 3 initial MRIs in our series showed cytotoxic oedema (Figure 2). This patient did not show a complete clinical recovery which corroborates with the neuroimaging findings of multiple residual minute focal intraparenchymal haemorrhage (Figure 3)

and initial cytotoxic oedema. There however may be other confounding factors including sepsis that could have contributed to this patient's brain injury rather than just the PRES alone.

We acknowledge there are limitations in our study due to the retrospective methodology used. Similar to other PRES studies, the neuroimaging protocol and timing varied among patients in the acute phase and during follow-up. One of our patients only had serial brain CT which may limit detection of additional brain abnormalities.

In conclusion, our case series expands the clinico-radiological spectrum of PRES in children with underlying haematological-oncological disorders and is the first paediatric series from the South Asia and the South East Asia region. Although cyclosporin therapy has been implicated in PRES²⁴⁻²⁷, our series is the first to show that it is a potential risk factor even after therapy has been discontinued for as long as 2 months. We reiterate that clinicians need to be vigilant for development of PRES and closely monitor the blood pressure in children with underlying haematological-oncological disorders when receiving or recently had immunosuppressive drugs who present with acute neurological symptoms.

DISCLOSURE

Conflict of interest: None

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