

A study on clinical and radiological features and outcome in patients with posterior reversible encephalopathy syndrome (PRES)

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Abstract Posterior reversible encephalopathy syndrome (PRES) is characterized clinically by headaches, seizures, vomiting, nausea, visual abnormalities, and altered mental function and is often (but not invariably) accompanied by parieto-occipital imaging features. The aim of this study is to describe the clinical and radiological features and outcome following PRES in a paediatric cohort. From a retrospectively identified cohort, case records were studied to confirm a diagnosis of PRES. Neuroimaging was reviewed again to

assign to recently described radiological subtypes parieto-occipital pattern, holohemispheric watershed pattern, dominant superior frontal sulcus pattern, and asymmetrical or partial expression of the three primary patterns (A/P). Patient outcome was measured by the modified Rankin scale (mRS) scores. Nine boys and three girls with mean age of 12 were identified. Hypertensive episodes ($n=11$), tacrolimus toxicity ($n=4$), and autoimmunity ($n=1$) were identified as potential risk factors/etiologies. Their median mRS at the peak of

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PRES in children NO MS helped collecting data and preparing initial draft. NO, SW, and MS reviewed the data and helped in preparing the initial draft, and MS helped in subsequent reviews. AS and JU reviewed all the images independently. AS, JU, RS, and ML reviewed all the images to reach to a consensus. ML, MS, and RS assigned mRS scoring and in preparing the final draft and submission.

What is known about this condition and what is new? PRES is a reversible condition, and there has been no report of quantitative measurement of outcome in this group of children at the time of illness and on complete recovery. We report that irrespective of the lesion load and distribution of lesion, the outcome on modified Rankin scale (mRS) is good.

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illness was 2 (range 2–5); three children required intensive care support. After mean follow-up of 35 months (median 37 months; range 3–60 months), all patients improved significantly with mean mRS of 1 (median 1; range 0–1). **Conclusion:** PRES is easily recognizable by the clinical and radiological features. Although severe at presentation, the outcome from this condition is favorable.

Keywords PRES · Hypertension · Tacrolimus · Modified Rankin scale · Parieto-occipital

Abbreviations

AI	Autoimmune
A/P	Atypical or partial expression
CNI	Calcineurin Inhibitors
CKD	Chronic kidney disease
DWI	Diffusion-weighted imaging
EEG	Electroencephalogram
ESRF	End stage renal failure
FLAIR	Fluid-attenuated inversion recovery
HSP	Henoch-Schölein purpura
HbSS	Sickle cell anemia
HH	Holohemispheric
HT	Hypertension
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
Non T	Non-transplant
PO	Parieto-occipital
PRES	Posterior reversible encephalopathy syndrome
SFS	Superior frontal sulcus
SLE	Systemic lupus erythematosus
TT	Tacrolimus toxicity

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity characterized by a variable combination of consciousness impairment, seizure activity, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs. Hinchey and colleagues described patients with headache, altered sensorium, seizures, vomiting, and abnormalities in visual perception, with edema involving the white matter in the posterior portion of the cerebral hemispheres, especially bilaterally in the parieto-occipital regions, and these patients were reported as having a “reversible posterior leukoencephalopathy syndrome” [11]. In recognition of cortical (frontal lobe) and subcortical (basal ganglia) involvement, this distinct clinical radiological syndrome has now been revised to PRES [14].

Among potential triggers, malignant or rapid onset of hypertension, immunosuppressive therapy, and transplantation

are commonly identified [4, 9, 17]. PRES may occur as a result of either breakdown of cerebral autoregulation and disruption of blood brain barrier, causing vasogenic edema [8, 11] or endothelial dysfunction resulting from circulating toxic mediators (CNI), sepsis, autoimmune conditions, or eclampsia [4, 15, 16].

Overall, the reported prognosis is favorable; timely recognition is essential with removal of potential triggering factors although there have been isolated case reports of permanent sequelae and associations with mesial temporal sclerosis but with no medium- to long-term follow-up [1, 2].

Here, we report the clinical and radiological features of 12 children with PRES who improved significantly after medium- to long-term follow-up.

Material and methods

Twelve patients with clinical and radiological findings consistent with PRES were identified at two tertiary pediatric hospitals in South London, over an 8-year period 2006–2013. In this cohort, we included all children with clinico-radiological findings in keeping with PRES based on the most contemporary criteria.

We collected data including demography, underlying primary disease and associated co-morbidities, relevant clinical features, and details regarding medications and management (NO, RS). Hypertension was defined as blood pressure above the 95th percentile using the Task Force report (group (revised [10])). Tacrolimus was suspected to be a trigger factor in patients, who were on tacrolimus, in absence of any identifiable trigger factors, like hypertension, autoimmune, or infective triggers.

Modified Rankin scale (mRS) scoring adapted for children is the most widely used outcome measure of the degree of disability or dependence, in patients with stroke [6]. We used mRS scores for our children during acute illness and at the time of their last clinic follow-up (RS, ML, and MDS).

Imaging studies were reviewed by two neuroradiologists (AS, JU) independently, and discrepancies were reviewed (AS, JU, RS, ML) to reach a consensus. As a minimum, all patients had MRI imaging with T2 weighted, T2 FLAIR, T1-weighted, and diffusion-weighted imaging (DWI) sequences and these were reviewed in all children. Additional sequences like contrast enhanced T1 weighted ($n=2$) and time-of-flight intracranial MR angiography ($n=3$) were reviewed. A diagnosis of PRES confirmed if typical imaging findings were found as described by Bartynski and Boardmann: dominant parieto-occipital (PO) pattern, holohemispheric (HH) watershed pattern, dominant superior frontal sulcus (SFS) pattern, and asymmetrical or partial expression (A/P) of the three primary patterns [5]. The imaging findings were also described according to their location, i.e., frontal, parietal,

Table 1 Demographic profile all 12 children, including primary disease, suspected etiology for PRES, and neurological outcome as measured by modified Rankin scale

Case	Demographics	Primary disease, transplant status	Possible etiology for PRES (tacrolimus level), stage of HT (I, II)	Follow-up (months), median 37 months (3–60)	mRS at nadir median 2 (1–5)	mRS at latest follow-up median 1 (0–2)
1	14 years, M	Wilson disease, liver T	TT (18.6), HT I	24	2	1
2	6 years, M	Biliary atresia, liver T	(12), HT II	22	4	2
3	12 years, F	Nephropathic cystinosis, renal T	TT (27), N	46	2	1
4	10 years, M	Prune belly syndrome, renal T	TT (16), HT II	46	2	1
5	11 years, M	Nephronophthisis, renal T	(10), HT, II	48	2	1
6	5 years, M	Bilateral renal dysplasia, renal T	TT (10), HT I	52	2	1
7	7.5 years, M	HSP, Non T	HT, II	24	1	0
8	10 years, F	ESRF due to pANCA positive vasculitis, Non T	HT, II	44	4	1
9	14 years, M	SLE, Non T	AI, HTI	60	2	1
10	14 months, M	Tubular interstitial nephritis, Non T	HT, II	30	5	1
11	6 years, M	Post meningococcal CKD, Non T	HT, I	3	2	1
12	11 years, M	SLE-related hepatitis, Non T	HT, I	24	2	1

1 mean median, range; 2 mean median, range; 3 mean median, range

AI autoimmune, CKD chronic kidney disease, ESRF end stage renal failure, HSP Henoch-Scholein purpura, HT hypertension, mRS modified Rankin scale, SLE systemic lupus erythematosus, Non T non-transplant, I stage I hypertension, II stage II hypertension, N normotensive, TT tacrolimus toxicity

occipital, temporal, deep white matter, basal ganglia/thalami, brain stem, and cerebellum.

As the data collection was retrospective with no additional data being collected beyond what was required for the standard medical care of the patients, a full ethics review was not deemed necessary by the authors.

Results

Twelve children (nine boys) with a median age of 10 years, range 14 months to 14 years, were identified with PRES based on contemporary criteria. Four children had a recent renal transplant, and two had recent liver transplant. The non-

Table 2 Neuroimaging features and radiological outcome

Case	MRI	Location of change	Diffusion characteristic	IV contrast	MRA	Follow-up scan
1	HH	P, O, F, CBLL	F	ND	ND	ND
2	PO	P, O, F, DWM, CC	F	SSE	ND	Re
3	PO	P, O, F	F	ND	SMNP	ND
4	PO-P/A	P	F	ND	ND	ND
5	SFS	P, O, F	F (minimal R)	ND	ND	ND
6	SFS	P, O, F, T, CBLL	F (minimal R)	PSCE	ND	ND
7	PO	P, O, F, T, DWM, CC	F (minimal R)		Normal	ND
8 ^a	PO	First episode: P, O, F Second episode: T, BG, BS, CBLL	F	PSCE ND	Normal SMNP	PR Re
9	PO-P/A	P, O, F, T	F	ND	ND	Re
10	HH	P, O, F, T, BG, DWM, CC, BS, CBLL	F (minimal R)	ND	Normal	ND
11	PO	P, O, DWM, CC, BS	F	ND	ND	ND
12	PO	P, O, F, CBLL	F	ND	ND	Re

PO parieto-occipital, HH holohemispheric, SFS superior frontal sulcus, P/A partial/asymmetric expression, O occipital, P parietal, F frontal, T temporal, DWM deep white matter, CC corpus callosum, BG basal ganglia, BS brainstem, CBLL cerebellum, F free diffusion, R restricted diffusion, PSCE partial sulcal/cortical enhancement, SSE smooth sulcal enhancement, MRA magnetic resonance angiogram, SMNP subtle multifocal narrowing posteriorly, Re resolved, PR partial resolution but not progressed, ND not done/not indicated

^a This patient had relapse of PRES following initial resolution

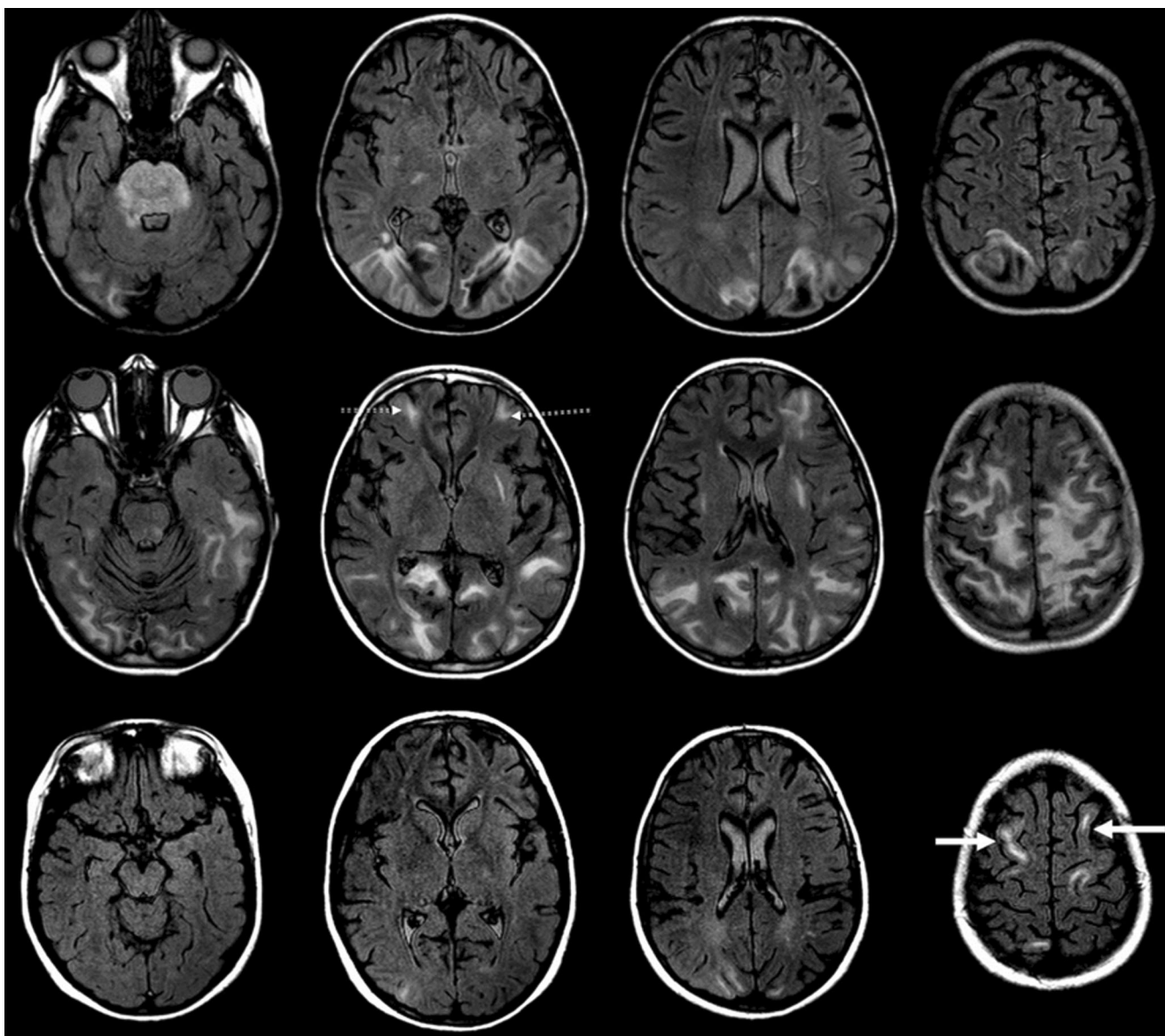


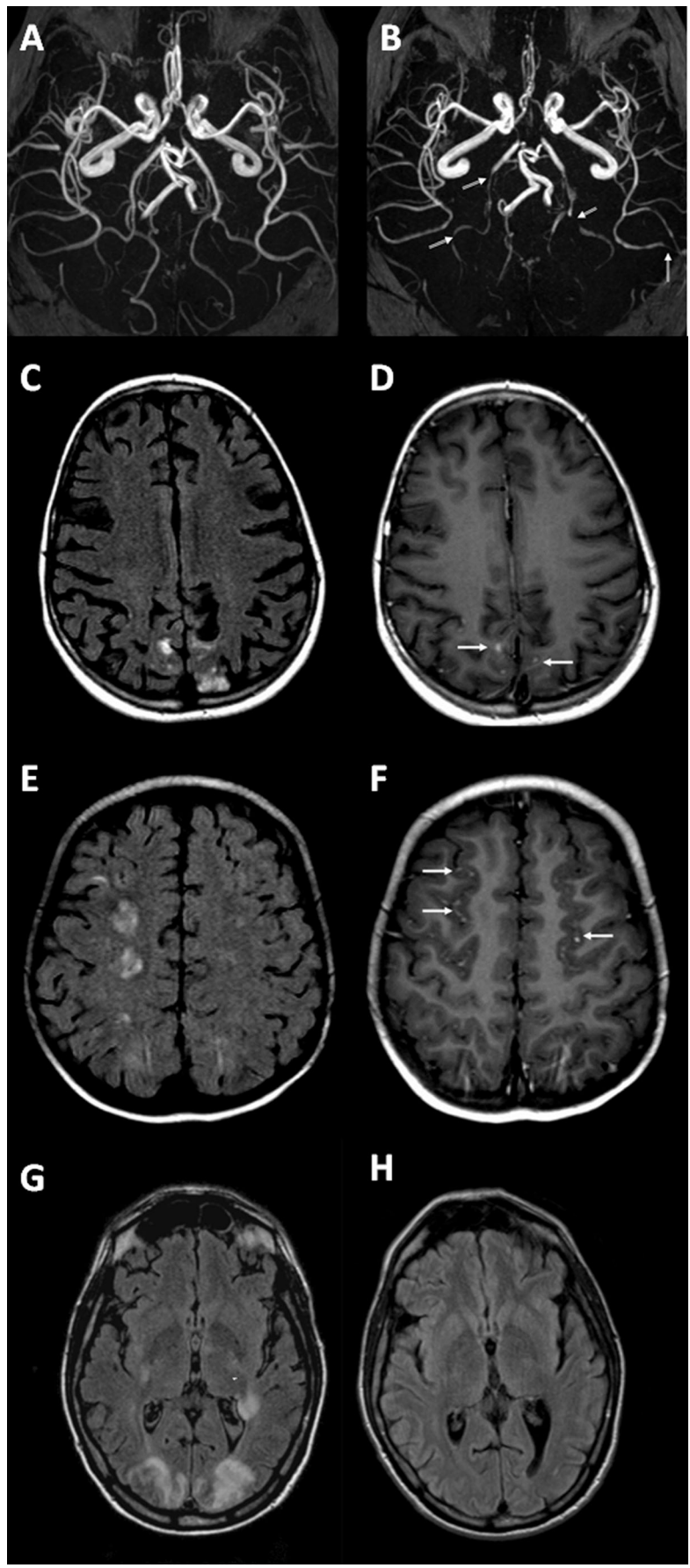
Fig. 1 Axial T2 FLAIR images at various levels in three patients with PRES showing the different imaging patterns. *Top row* (case 11) shows the dominant parieto-occipital (PO) pattern in a 6-year-old boy with acute renal failure with past history of meningococcal septicemia. *Middle row* (case 8) shows the dominant holohemispheric (HH) watershed pattern with changes extensively in both hemispheres but predominantly in the

watershed distribution with involvement of the frontal poles (*dashed arrows*) in a 10-year-old girl with ESRF secondary to pANCA positive vasculitis who presented with a seizure. *Bottom row* shows MRI of an 11-year-old boy presenting with a seizure 9 days post renal transplant (case 5) showing the dominant superior frontal sulcus (SFS) pattern with linear changes mainly along the superior frontal sulci (*solid arrows*)

transplant cohort included one child each with acute renal failure, chronic kidney disease on hemodialysis, and acute Henoch-Schölein purpura (HSP) nephritis, and two with lupus nephritis of whom one also had sickle cell anemia (HbSS).

Children presented with multiple neurological symptoms, and the most common was seizures (11 of 12 children). Three children were admitted to the pediatric intensive care unit with prolonged seizure and reduced level of consciousness. Seizure pattern was varied with predominantly generalized (8/12), and one child had prolonged post-ictal period and was found to have non-convulsive status epilepticus on EEG. Other

Fig. 2 **a** Time-of-flight MR angiography images in case 8, demonstrating an initial normal study. **b** Subsequent MR angiography on day 10 after onset of PRES shows multifocal narrowing of the intracranial arteries (*solid arrows*), particularly in the posterior circulation, mirroring the distribution of parenchymal changes (not shown). **c–f** Axial FLAIR (**c, e**) and post-gadolinium T1-weighted imaging (**d, f**) in two patients (case 2 (**c–d**) and case 6 (**e–f**)) showing smooth sulcal enhancement (*arrows*) on the post-contrast images, adjacent to areas of parenchymal signal changes on FLAIR. **g, h** Axial FLAIR images in a patient (case 3) showing typical parieto-occipital changes (**g**) which later resolved completely on follow-up imaging (**h**)



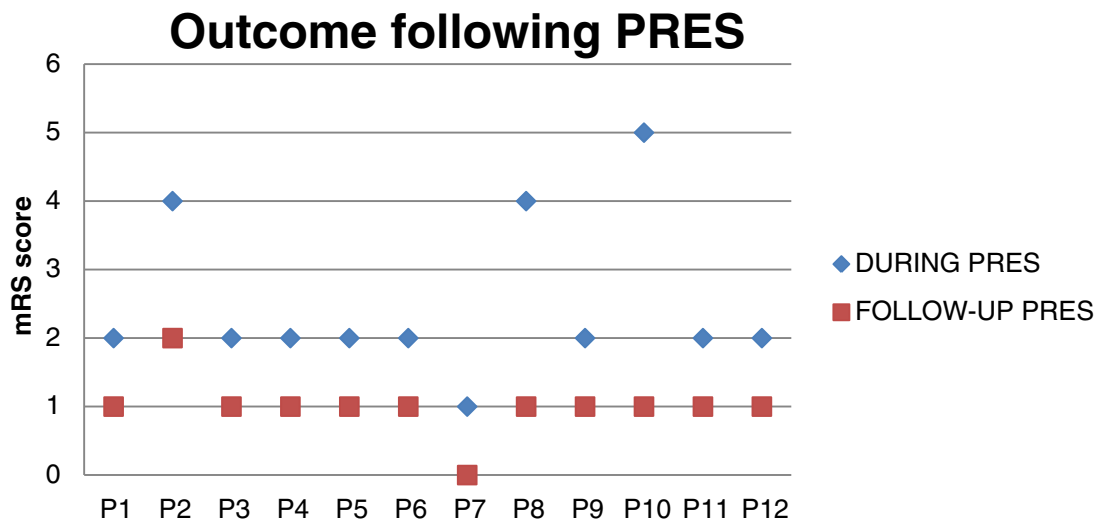


Fig. 3 Modified Rankin scale (mRS) score for 12 children with PRES. *Top line* representing the score during PRES and *bottom line* at follow-up

symptoms included confusion (3/12), irritability, and vomiting (3/12) visual symptoms (3/12). None of the children had any evidence of septicemia.

The suspected etiology at the time of the presentation is displayed in Table 1 and commonly included multiple factors including hypertension in 11 patients, tacrolimus toxicity in four, and autoimmunity induced in one patient. Six post-transplant patients were on tacrolimus and one on cyclosporine, and the median onset of PRES was 17.6 days (range, 6–41 days) following transplantation.

PRES was managed with a combination of anti-hypertensive medications, reduction of steroid dose (one child), and reduction of calcineurin inhibitor (CNI) dose (three children) or change of CNI agent to alternative immunosuppressant (one child).

Eight children had MRI changes, predominantly parietal and occipital regions (PO pattern) (Table 2), two had holohemispheric involvement (HH), and two had predominantly superior frontal sulcus (SFS) involvement (Fig. 1). On diffusion-weighted imaging, the lesions showed predominantly free diffusion characteristics in all cases, with the observation of minimal foci of diffusion restriction in the cortex and splenium of corpus callosum in four children. In three children who had post-gadolinium imaging, mild smooth sulcal enhancement (Fig. 2d, f) was noticed corresponding to the regions showing parenchymal T2/FLAIR signal change (Fig. 2c, e). MR angiography was done in five children, and three of them showed subtle multifocal narrowing in the posterior circulation (Fig. 2b). Follow-up MRI performed in four children showed resolution in all cases except one child (case 8) had two episodes of PRES with serial imaging and clinical findings confirming resolution of initial episode but with subsequent development 10 days later of PRES with typical clinical and radiological findings.

In both instances, hypertension was identified as triggering etiology and all our children made a complete recovery on formal neurological and visual assessment at a mean follow up of 35 months..

Discussion

In 12 children with radiologically and clinically confirmed PRES, hypertension was the most common but not invariable causative factor, consistent with previous reports. The threshold whereby hypertension would attribute to PRES was lower, if co-occurring associated factors, such as tacrolimus, were present as reported [11, 13]. This finding was also observed in our patients on tacrolimus (in case 3 with high tacrolimus level 27 ug/L and normal blood pressure, also in case 5 with tacrolimus level of 10 ug/L and patient having malignant hypertension). Trough tacrolimus levels of above 12 ug/L was considered toxic, as per our local protocol; however, even lower trough levels were considered to be a trigger in relevant clinical context (case 5). In our children, the level of tacrolimus did not correlate with the severity of PRES, but all patients improved once CNI was reduced or withdrawn.

Most of our children had parieto-occipital lobe involvement as reported in literature. Interestingly, four of our children had involvement of brainstem, which is an uncommon finding. Three of our children who required PICU admissions did not show any specific pattern of involvement or increased lesion load.

Our findings on diffusion imaging were consistent with previously described changes, with predominantly free diffusion indicating vasogenic edema and suggesting reversibility

of changes. Additional novel findings in our case series include the long-term outcome confirming reversibility of acute findings in PRES (Fig. 2g, h). Vascular/angiographic imaging is not routinely performed or required in these patients. In the two of five cases wherein MR angiography was performed in our series (e.g., for underlying sickle cell disease in one case), vasculopathy was identified with multifocal areas of dilatation and narrowing matching the posterior distribution of the changes, similar to previously described findings in literature [3].

Median follow-up for our patients was 37 months (3–60 months). The median mRS score at the peak of their illness was 2 suggesting slight disability and unable to carry out all previous activities, but were able to look after their own affairs without assistance. Three patients had scores of 4–5 at their peak illness, and they required PICU admission. The median mRS score at their last clinic visit was 1, which reflected no significant disability despite of their underlying chronic disease or other conditions except one child (case 7) with Henoch-Schleim purpura. mRS Score of 1 in 11/12 children reflects preceding co-morbidities (Fig. 3). All children had pre-PRES level mRS scores reflecting reversibility of this clinical entity irrespective of the lesion load and extent on MRI studies and hence favorable outcome of this condition. This is likely to reflect the underlying pathophysiology of PRES that is disruption of blood brain barrier and endothelial dysfunction, triggered either by rapid surges in blood pressure, toxic, or autoimmune mediated inflammation, leading to vasogenic edema. Importantly, persisting vasogenic edema may massively compromise local microcirculation leading to cytotoxic injury or irreversible neuronal injury, as reported [7, 12].

Our study, being a retrospective one, is subject to selection and recall bias. Nevertheless, our study with 12 children shows good neurological outcome, without any long-term sequelae. Importantly, prompt diagnosis and the empirical modification of all identifiable risk factors are ultimately the determinants of outcome in these children.

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