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Prognostic factors and seizure outcome in posterior reversible encephalopathy syndrome (PRES) in children with hematological malignancies and bone marrow failure: A retrospective monocentric study

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ABSTRACT

Purpose: The aim of this study was to evaluate seizure outcome in children with hematological malignancies and PRES and to identify prognostic factors that could help manage the syndrome.
Method: We retrospectively reviewed the report data of 21 patients diagnosed with hematological malignancy or aplastic anemia and PRES between 2008 and 2018. Basic demographic data, oncology treatment, presymptomatic hypertension before PRES manifestation, neurological status, seizure type, and EEG and MRI findings at PRES onset and at the one-year follow-up visit were studied. Patients who developed remote symptomatic seizures or epilepsy were identified.
Results: We included 21 children (11 females and 10 males) in the study. Sixteen patients (76.2%) were diagnosed with ALL and the rest individually with AML, CML, T-lymphoma, Burkitt lymphoma, and severe aplastic anemia. Presymptomatic hypertension (PSH) was evaluated in 19 patients and was present in 18 (94.7%). The duration was 9 h and more in 16 patients (88.8%); the severity was grade II in 12 patients (66.7%). Seizures as the initial symptom of PRES were present in 17 patients (80.9%). Four patients (19.0%) were assessed with remote symptomatic seizures. Two of them (9.5%) had ongoing seizures at the one-year follow-up visit and were diagnosed with epilepsy. The presence of gliosis on follow-up MRI indicated worse outcome with development of epilepsy (without statistical significance).
Conclusions: PRES syndrome has an overall good prognosis and the evolution to epilepsy is rare. The severity and duration of PSH or seizure severity and EEG findings at PRES onsetwere not associated with worse neurological outcomes in this study.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES), as defined by Hinchey et al., is a phenomenon of transient cerebral vasogenic edema occurring preferentially in posterior circulation [1]. Clinically, PRES is characterized by headaches, seizures, reduced consciousness, and visual and other focal neurological symptoms [2,3]. PRES is a clinicoradiological syndrome; a characteristic radiologic finding is vasogenic edema in the bilateral parietal-occipital lobes, which might be related to the lower concentrations of sympathetic innervation of the posterior intracranial arteries in comparison with other cerebral regions, resulting in lower autoregulatory capacity in these vessels [4]. However, other cerebral areas can be involved, and focal areas of PRES vasogenic edema may also be seen in the basal ganglia, brainstem, and deep white matter [5]. Systemic lupus erythematosus, sickle cell disease, sepsis, use of cytotoxic medications (for malignancy or immune suppression), renal failure, and organ transplantation are some of the conditions that have been associated with PRES [6,7]. There is still controversy concerning the pathophysiologic mechanisms of the syndrome; however, the mechanism that produces vasogenic edema (arterial hypertension and endothelial dysfunction) seems to be associated with loss of integrity of the blood-brain barrier [8]. Moderate-to-severe

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hypertension is seen in approximately 75% of patients with PRES [9].

There are many detailed studies regarding the clinical and radiologic aspects of PRES in adults or children. However, the data regarding electroencephalographic changes and seizure outcome are very limited. Furthermore, few studies have yet focused on the very specific group of high-risk pediatric patients: children with hematopoietic or lymphoid tissue tumors or bone marrow failure.

The aim of this study was to retrospectively evaluate neurological status and EEG and MRI findings in children with hematological malignancies or bone marrow failure and PRES. The neurological outcome beyond the acute phase and the development of remote symptomatic seizures (RSS) in these patients was evaluated.

The secondary aim was to correlate these data with the severity and duration of presymptomatic hypertension (PSH) in this group of patients. Arterial hypertension is considered to be an important pathophysiological mechanism of PRES and can be influenced in order to achieve more favorable outcomes in these patients.

2. Material and methods

We retrospectively analyzed 24 patients diagnosed with PRES from 2008 to 2018 at the University Hospital Brno, Czech Republic, from the hospital database. All patients were diagnosed with malignancy or bone marrow failure and treated at the Pediatric Oncology Department, University Hospital Brno, according to appropriate protocols.

The inclusion criteria were: 1) acute clinical symptoms of PRES – alteration of consciousness, encephalopathy, seizures, headache, and visual disturbances and/or other focal neurological deficit; 2) PRES on MRI as diagnosed by a neuroradiologist; and 3) clinical agreement by treating physicians whose reports also were relied upon to determine the etiology.

We collected and analyzed clinical, radiographic, and encephalographic data from the institutional database.

Demographic data were analyzed: sex, age at the manifestation of malignancy, and PRES.

Each patient's clinical manifestation and causal factors were identified: oncological diagnosis, protocol treatment, and phase of treatment with medication in the last 4 weeks. We retrospectively evaluated PSH. Every patient admitted for hospitalization was measured by BP cuff in 3 -h intervals; if hypertension was present, the measurements were taken in 1-h intervals. We evaluated the severity and duration of the PSH prior to PRES clinical manifestation. The blood pressure was classified as normal, prehypertension, hypertension grade I, and hypertension grade II according to the age- and height-related standardized percentile graphs for pediatric populations. All patients were hospitalized at the time of PRES manifestation for various reasons (protocol treatment, febrile neutropenia, infection, *etc.*) so the collection of arterial pressure measurements were complete from the beginning of the PSH. Patients for whom the data were incomplete, *e.g.* PSH onset after admission with hypertension, were excluded from the analysis.

Neurological examination was established by the institutional neurologist at PRES manifestation – up to 3 h from the manifestation and then every 3 months, or more often if needed. We evaluated the neurological status at PRES manifestation and after one year of follow-up care.

Neurological status was classified as follows: 1 – normal; 2 – focal deficit without loss of consciousness; 3 – qualitative disturbance of consciousness (hypoactive or hyperactive delirium: confusion, disorientation, memory disturbance, illusions, or hallucinations); 4 – quantitative disturbance of consciousness – somnolence; 5 – quantitative disturbance of consciousness – sopor; 6 – quantitative disturbance of consciousness – coma.

The interpretation of EEGs was established by epileptologists from the Department of Child Neurology, University Hospital Brno. EEG were recorded digitally using a standard 10–20 system with standard 20-minute recordings with or without activations. All patients had EEG at PRES manifestation or in the first 12 h and then follow-up EEG every 3 months, or more often if needed. We evaluated the EEG at PRES manifestation and after one year of follow-up care.

EEGs were classified as follows: 1 – normal; 2 – focal slowing; 3 – diffuse slowing; 4 – focal epileptiform discharges; 5 – generalized epileptiform activity; 6 – LPDs.

Epileptic seizures were classified as follows according to the 2017 ILAE classification: 1 – no seizures; 2 – focal – aware; 3 – focal – impaired awareness; 4 – focal to bilateral tonic-clonic seizure (FBTCS); 5 – generalized tonic clonic seizure (GTCS); 6 – non-convulsive status epilepticus (NCSE); 7 – convulsive status epilepticus (CSE).

Acute symptomatic seizures were defined as seizures occurring in direct association with the PRES syndrome and/or within 6 weeks of its termination. Seizures that occurred later in the course of the oncological disease but still in possible association with PRES syndrome and with no other identified cause were defined as *remote symptomatic seizures (RSS)*. We arbitrarily determined *one year from the manifestation of PRES* as the borderline for another assessment: the one-year follow-up visit.

2.1. Statistics

Categorical variables were summarized using absolute and relative frequencies. To summarize the continuous characteristics, mean, standard deviation (SD), median, minimum and maximum were used.

Testing was carried out using Fisher's exact test. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Basic data

We identified 24 patients out of 1627 (1.4%) diagnosed with PRES and treated at the Pediatric Oncology Department at the University Hospital Brno between 2008 and 2018. Three patients were lost to follow-up care; they died due to the complications of treatment of malignancy. Therefore, 21 patients (11 females and 10 males) with PRES syndrome were included in the study. All patients had been diagnosed with malignancies; one patient was diagnosed with bone marrow failure. The average patient age at presentation was 6.6 ± 4.0 years (ranged from 2 to 16 years). Sixteen out of 21 patients (76.2%) were diagnosed with acute lymphoblastic leukemia (ALL), one patient (4.8%) had a diagnosis of acute myeloid leukemia (AML), one patient (4.8%) was diagnosed with chronic myeloid leukemia (CML), two patients (9.4%) were diagnosed with non-Hodgkin lymphoma (NHL - T-lymphoma and Burkitt lymphoma), and one patient (4.8%) was treated for severe aplastic anemia (Table 1). The incidence of PRES for each diagnosis for 10 years (2008–2018) can be expressed as follows: 16 out of 174 patients with ALL (9.2%), one out of 33 patients with AML (3.0%), one out of 15 patients with CML (6.6%), two out of 74 patients with NHL (2.7%), and one out of 9 patients with severe aplastic anemia (11.0%).

The time from the diagnosis of malignancy to the manifestation of PRES was 4.4 ± 4.9 months (ranged from 0.1 to 19.7 months). All patients received some form of chemotherapy according to the appropriate treatment protocol. The most common drugs used at the onset of PRES were intrathecal methotrexate (N = 18; 85.7%), corticosteroids (N = 16; 76.2%), L-asparaginase (N = 15; 71.4%), vincristine (N = 14; 66.7%), doxorubicin (N = 13; 61.9%), and cytarabine (N = 9; 42.9%); fewer than five patients used other drugs. In accordance with the treatment protocol, all patients were using polytherapy; see Table 1 and Table 3. Intrathecal methotrexate is used at the child oncology clinic in the treatment of hematological malignancies, and it is known for possible neurotoxicity. PRES syndrome developed in 18 patients out of 248 (7.2%) treated with intrathecal methotrexate between 2008 and 2018.

Table 1
Factors involved in the pathogenesis of PRES.

Factors involved in the pathogenesis of PRES			
oncological diagnosis: 21 patients			
ALL	16	76.2%	
AML	1	4.8%	
CML	1	4.8%	
T-lymfoma	1	9.4%	
Burkitt lymfoma	1		
severe aplastic anemia	1	4.8%	
blood pressure: 19 patients			
normotension	1	5.3%	not included in the evaluation of PSH
presymptomatic hypertension: 18 patients			
hypertension grade I	6	33.3%	
hypertension grade II	12	66.7%	
duration (hours)			
6	2	11.2%	
9	8	44.4%	
12	6	33.4%	
15	1	5.5%	
18	1	5.5%	
protocol treatment at the PRES onset and /or 4 weeks before			
methotrexat	18	85.7%	
corticosteroids	16	76.2%	
L-asparaginase	15	71.4%	
vincristine	14	66.7%	
doxorubicine	13	61.9%	
cytarabine	9	42.9%	
puri-nethol	6	28.6%	

PSH was assessed in 19 patients; data from 2 patients were incomplete. Only 1 patient out of 19 (5.3%) had normal blood pressure in the presymptomatic period and prehypertension at PRES manifestation; this patient was not included in the statistical evaluation. Two patients out of 18 (11.2%) had 6 -h long PSH, 8 patients out of 18 (44.4%) had 9 -h long PSH, and another 8 patients out of 18 (44.4%) had more than 9 -h long PSH with 18 h as maximum.

The PSH severity was as follows: 1 patient out of 19 (5.3%) had normal pressure, 6 patients out of 18 (33.3%) had hypertension grade I, and 12 patients out of 18 (66.7%) had hypertension grade II. Factors involved in the pathogenesis of PRES (oncological diagnosis and treatment and PSH) are summarized in Table 1.

We compared the number of antihypertensives used to achieve normotension and the duration of antihypertensive therapy in *non-RSS patients* and *RSS patients*. In the first group, 236 ± 1.33 antihypertensive drugs (ranged from 1 to 5 drugs) were used for 2.14 ± 2.88 months (ranged from 0 to 12 months). In the second group, 3.75 ± 0.83 antihypertensive drugs (ranged from 3 to 5 drugs) were used for 4.25 ± 4.49 months (ranged from 1 to 12 months). Although higher values in the second group are obvious, results in such a small sample size are not statistically significant.

3.2. Clinical-radiological diagnosis of PRES

The PRES clinical manifestations were as follows: seizures with or without disturbance in consciousness, in 17 patients out of 21 (80.9%); quantitative or qualitative disturbance of consciousness without seizures, in 4 patients out of 21 (19.0%); headache, in 4 patients out of 21 (19.0%); and visual disturbances, in 3 patients out of 21 (14.3%). Headache and visual disturbances were not the first symptoms of PRES reported by the patient but they were often immediately described after seizure or restoration of consciousness. Patients who reported headache as one of the first symptoms of PRES were 8.50 ± 4.50 years of age (ranged from 5 to 16 years). Visual disturbances at PRES onset were reported at 8.33 ± 1.36 years of age (ranged from 7 to 10 years). This is in accordance with the fact that small children often have difficulty describing their symptoms, so these symptoms could have been overlooked.

The neurological examination at PRES onset was normal in 4 patients out of 21 (19.0%); 1 patient out of 21 (4.8%) had only focal deficit without disturbance of consciousness; 8 patients out of 21 (38.1%) had qualitative disturbance of consciousness; 1 patient out of 21 (4.8%) had somnolence; 4 patients out of 21 (19.0%) were in sopor; and 3 patients out of 21 (14.3%) were in coma state; see Table 2.

In the *non-RSS* group, the neurological status normalized in 4.75 ± 8.82 days (ranged from 1 to 28 days). In the RSS group of patients, the neurological status normalised in 69.25 ± 105.81 days (ranged from 1 to 252 days); see Table 2.

All patients underwent a structural examination of the brain, either CT or MRI. Two patients out of 21 patients had only a CT scan, with hypodense lesions in the posterior regions correlating with the image of vasogenic edema; 19 patients out of 21 had MRI scans in correlation with the radiologic diagnosis of PRES; 15 patients out of 21 (71.4%) had lesions typically in the parieto-occipital region; 2 patients out of 21 (9.5%) had pathology in the parieto-occipital region, but also with frontal involvement; 4 patients out of 21 (19.1%) had severe diffuse involvement in bilateral fronto-temporo-parieto-occipital regions, including the cerebellum or brainstem in 2 of them; see Table 2. Follow-up MRI was performed in all patients after 43.1 ± 29.6 days (ranged from 12 to 90 days): 19 patients out of 21 (90.5%) had normal follow-up MRI; 2 patients out of 21 (9.5%) had persisting gliosis in the parieto-occipital region on MRI at the one-year follow-up visit (Table 2, Figs. 1–4).

3.3. Seizures at PRES manifestation and RSS

Seventeen patients out of 21 (80.9%) had seizures as the clinical manifestation of PRES (Table 2). Focal seizures were described in one patient out of 17 (5.9%); focal seizures with impaired awareness in 5 patients out of 17 (29.4%); focal seizures with evolution to tonic-clonic seizure in 1 patient out of 17 (5.9%); generalized tonic-clonic seizures were described in 4 patients out of 17 (23.6%); nonconvulsive status epilepticus in 3 patients out of 17 (17.6%); and convulsive status epilepticus also in 3 patients out of 17 (17.6%).

Four patients out of 21 (19%) were assessed as having *RSS*; 2 of them (9.5%) had ongoing seizures at the one-year follow-up visit.

Antiepileptic drugs (AEDs) used in the management of acute symptomatic seizures at PRES onset and chronic AEDs are presented in Table 3. All patients with RSS took levetiracetam (LEV) at the one-year follow-up visit. Three patients out of 17 (17.6%) from the *non-RSS* group were also on AEDs at the one-year follow-up visit (see Table 3). GBP was used in the treatment of neuropatic pain. All AEDs in these patients were tapered off in the course of the second year after PRES onset. We have to take into consideration that this fact could possibly mask the development of RSS in these patients during the one-year follow-up period. However, these patients arbitrarily met the study inclusion criteria, so they were included in the non-RSS group of patients.

3.4. EEG findings (*Table 2*)

All patients had EEG recorded directly at PRES manifestation or within no more than 12 h (24/7 EEG availability is provided). Follow-up EEG were performed every 3 months in all patients, or often if needed.

Normal EEG at PRES manifestation was described in 4 patients out of 21 (19.0%); focal or regional slowing was present 9 patients out of 21 (42.8%); and diffuse slowing was present in 2 patients out of 21 (9.6%). Three patients out of 21 (14.3%) had focal epileptiform discharges on EEG, and 3 patients out of 21 (14.3%) had LPDs on EEG.

Localization of focal slow waves or epileptiform discharges on EEG was predominantly in the parieto-occipital region (for details, see Table 2).

Table 2
Clinical characteristics and EEG and MRI findings of patients with PRES.

Patient No.	oncological diagnosis	treatment protocol	age at oncological diagnosis (years)	PRES onset - from oncological diagnosis (months)	acute PRES onset					
					neurological examination	seizure type	EEG	localisation on EEG	MRI	duration of PSH (hours)
1	T-ALL	ALL-IC 2002	17	10	3	1	1	normal	PO bilat.	0
2	praeB-ALL	ALL-IC BFM 2002	8	1	6	5	2	slowing PO bilat.	PO bilat.	9
3	cALL	ALL-IC BFM 2002	6	2	1	5	2	slowing O bilat.	PO bilat. (CT)	9
4	praeB-ALL	ALL-IC BFM 2002	7	1	1	3	1	normal	F right, O left	6
5	ALL	ALL-IC BFM 2002	4	10	5	3	2	slowing O bilat.	PO bilat.(CT)	NA
6	cALL	AIEOP-BFM ALL 2009	2	11	3	3	2	slowing TPO right	PO bilat.	NA
7	cALL	AIEOP-BFM ALL 2009	4	2	3	6	6	LPDs PT right	FTPO bilat., cerebellum	15
8	praeB-ALL	ALL-IC BFM 2002	3	0	5	1	1	normal	PO bilat.	9
9	T-ALL	AEIOP- BFM ALL 2009	6	1	6	5	2	slowing O bilat.	O bilat.	12
10	cALL	ALL-IC BFM 2002	16	1	3	1	2	slowing O bilat.	O bilat.	9
11	AML	AML BFM 2012	5	2	3	1	3	diffuse slowing	FTPO bilat., brain stem	9
12	preB-ALL	ALL-IC BFM 2002	7	2	4	7	6	LPDs PO right	PO bilat.	12
13	cALL	AIEOP-BFM ALL 2009	4	7	3	6	4	SWC TPO left	PO bilat.	6
14	cALL	AIEOP BFM ALL 2009	3	7	5	4	1	normal	FP bilat.	9
15	NHL	AIEOP-BFM ALL 2009	7	5	5	3	2	slowing TO left	PO bilat.	18
16	AA	EWOG SAA 2010	5	1	3	6	4	SWC FTPO right, max F	PO bilat.	12
17	BL	INT BNHL 2010	8	1	1	7	2	slowing right P	P right	12
patients with remote symptomatic seizures										
1	praeB-ALL	AIEOP-BFM ALL 2009	13	8	1	2	2	slowing PO bilat.	FTPO bilat.	12
2	CML	CML paed 2006	10	19	3	5	3	diffuse slowing	FPO bilat.	9
3	cALL	AIEOP-BFM ALL 2009	7	1	2	3	6	LPDs TO right	O bilat.	12
4	praeB-ALL	AIEOP BFM ALL 2009	3	1	6	6	4	SWC TO right	FTPO bilat. cerebellum	9

Patient No.	acute PRES onset	restoration after acute state			one-year follow-up visit				
	severity of PSH (grade)	neurological examination (days)	EEG (days)	duration of anti-HT therapy (months)	neurological examination	EEG	AEDs	MRI	time to follow-up MRI (days)
1	normal	1	NA	NA	1	1	0	normal	12
2	2	1	1	0	1	1	0	normal	12
3	2	1	1	0	1	1	0	normal	60
4	2	1	NA	3	1	1	0	normal	60
5	NA	1	3	NA	1	1	0	normal	14
6	NA	1	28	NA	1	1	0	normal	60
7	2	28	NA	12	1	3	LEV	normal	60
8	2	NA	NA	1	1	1	0	normal	14
9	2	3	3	2	1	1	0	normal	14
10	1	1	1	1	1	1	GBP + VPA	normal	14
11	2	3	28	3	1	1	0	normal	90
12	2	1	90	1	1	1	GBP	normal	14
13	1	1	90	1	1	1	0	normal	21
14	1	1	NA	3	1	1	0	normal	60
15	2	3	90	1	1	1	0	normal	28
16	2	28	NA	1	1	2	0	normal	14
17	1	1	90	1	1	1	0	normal	90
patients with remote symptomatic seizures									
1	2	1	3	1	1	1	LEV	normal	28

(*continued on next page*)

Table 2 (*continued*)

	acute PRES onset	restoration after acute state			one-year follow-up visit				
Patient No.	severity of PSH (grade)	neurological examination (days)	EEG (days)	duration of anti-HT therapy (months)	neurological examination	EEG	AEDs	MRI	time to follow-up MRI (days)
2	1	3	3	12	1	1	LEV	normal	60
3	1	21	NA	2	1	2	LEV	O bilat. gliosis	90
4	2	252	90	2	1	1	LEV	PO bilat. gliosis	90

Neurological examination: 1 – normal; 2 – focal deficit without loss of consciousness; 3 – qualitative disturbance of consciousness (hypoactive or hyperactive delirium: confusion, disorientation, memory disturbance, illusions or hallucinations); 4 – quantitative disturbance of consciousness – somnolence; 5 – quantitative disturbance of consciousness – sopor; 6 – quantitative disturbance of consciousness – coma. **Seizure type:** 1 – no seizures; 2 – focal – aware; 3 – focal – impaired awareness; 4 – focal to bilateral tonic-clonic seizure (FBTCS); 5 – generalized tonic clonic seizure (GTCS); 6 – non-convulsive status epilepticus (NCSE); 7 – convulsive status epilepticus (CSE). **EEG:** 1 – normal; 2 – focal slowing; 3 – diffuse slowing; 4 – focal epileptiform discharges; 5 – generalized epileptiform activity; 6 – LPDs.
Oncological diagnosis: ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, NHL-Non-Hodgkin lymphoma, AA – aplastic anemia, BL – Burkitt lymphoma, CML – chronic myeloid leukemia; **localization on EEG and MRI:** F- frontal, P-parietal, T-temporal, O-occipital; **anti-HT** - antihyperensive, **AEDs** – antiepileptic drugs: LEV – levetiracetam; GBP – gabapentine; VPA – valproate.

In the non-RSS group, EEG was normalized in 38.64 ± 39.96 days (ranged from 1 to 90 days), in the RSS group, EEG was normalised in 32.67 ± 40.55 days (ranged from 3 to 90 days); see Table 2.

At the one-year follow-up visit, 18 patients out of 21 (85.7%) had normal EEG; 2 patients out of 21 (9.5%) had focal slowing; and 1 patient out of 21 (4.8%) had diffuse slowing on EEG. No epileptiform discharges were recorded.

3.5. Findings in patients with RSS

Four patients out of 21 (19%) were assessed as having with *RSS*. The small sample size prevents a statistically significant analysis, but it is possible to describe these patients' important characteristics. There were 3 girls and 1 boy in this group, ages 13, 10, 7, and 3 years respectively at the PRES onset. Three of them were diagnosed with ALL and one had CML. PSH took 9 h in 2 patients and 12 h in 2 patients; PSH was grade I in 2 patients and grade II in two patients. The seizure type at PRES onset was different in each patient: focal aware, GTCS, focal with impaired awareness, or NCSE. Acute EEG findings were different in each patient as well: focal slowing, diffuse slowing, LPDs, or focal epileptiform discharges. All patients started treatment with levetiracetam at a dose of 40–50 mg/kg/day after acute symptomatic seizures.

The first patient had two focal aware RSS 3 months after PRES onset, leading to an increase in the dose of levetiracetam to 60 mg/kg/day. Acute MRI showed diffuse lesions in the fronto-temporo-parieto-occipital region correlating with edema. Control MRI was normal after one month. The patient was seizure free at the one-year follow-up visit with normal neurological examination and EEG, still taking levetiracetam.

The second patient had one RSS with headache and visual illusion + ns 9 months after PRES onset, while tapering off levetiracetam. Acute MRI correlated with PRES syndrome with fronto-parieto-occipital lesions. A follow-up MRI 3 months later was normal. The patient was seizure-free at the one-year follow-up visit with normal neurological examination and EEG; the patient was still taking levetiracetam.

The third patient had repeated seizures, continuing at one-year follow-up visit. The patient described positive visual symptoms and headache while fully aware. The dose of levetiracetam was increased to 60 mg/kg/day and the seizures reduced in frequency (1/month). The patient and his parents preferred not to change medications; the seizures did not disturb him. The patient had occipital lesions on acute MRI with right-sided predominance; gliosis in the same region persisted on MRI at the one-year follow-up visit (Figs. 1 and 2). Neurological examination was normal after one year, with focal slowing on EEG (occipital right).

The fourth patient had focal aware repeated seizures, continuing at the one-year follow-up visit. The dose of levetiracetam was increased with partial effect, eslicarbazepine was added at the one-year follow-up visit with effect and the patient became seizure-free. Acute MRI was with diffuse cortico-subcortical fronto-temporo-parieto-occipital findings and with cerebellum involvment; these lesions persisted with occipital predominance as gliosis on MRI at the one-year follow-up visit (Figs. 3 and 4). Neurological examination and EEG was normal after one year.

3.6. Statistics

Statistical analysis did not reveal a statistically significant difference between sex or age at PRES onset (patients younger than 6 years *vs*. 6 years and older) in terms of duration and severity of PSH, clinical manifestation, seizure type, or EEG findings at PRES onset and at the one-year follow-up visit and the occurrence of RSS.

Statistical analysis also did not reveal a statistically significant difference between the group of patients with PSH grade I and those with grade II in terms of neurological status, seizure type, or EEG findings at PRES onset and at the one-year follow-up visit and the occurrence of

Table 3
Characteristics of oncological, antihypertensive and antiepileptic treatment.

Patient No.	oncological diagnosis	treatment protocol	oncological treatment 6 weeks before and/or at PRES manifestation	antihypertensive treatment	No. of anti-HT drugs	acute AEDs i.v.	chronic AEDs
1	T-ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, vincritsine, doxorubicin, asparaginase	NA	NA	0	0
2	praeB-ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	furosemide	1	DZP	0
3	cALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, vincritsine, doxorubicin, cyclophosphamide	enalapril	1	DZP	0
4	praeB-ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	captopril, isradipine	2	0	0
5	ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, vincritsine, doxorubicin, asparaginase	NA	NA	DZP	0
6	cALL	AIEOP-BFM ALL 2009	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, asparaginase	NA	NA	DZP	0
7	cALL	AIEOP-BFM ALL 2009	i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine	enalapril	1	DZP,LEV	LEV
8	praeB-ALL	ALL-IC BFM 2002	corticosteroids	furosemide	1	0	0
9	T-ALL	AEIOP-BFM ALL 2009	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	enalapril, furosemide, propranolol, esmolol	4	DZP,LEV	0
10	cALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, vincritsine, doxorubicin, asparaginase	captopril, furosemide	2	DZP,VPA	GBP, VPA
11	AML	AML BFM 2012	i.th. MTX, i.th. cytarabin, i.th. prednisone, cytarabin, etoposid	dihydralazine, furosemide, clonidine, enalapril, amlodipine	5	0	0
12	preB-ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	captopril, isradipine	2	DZP,CLZ	GBP
13	cALL	AIEOP-BFM ALL 2009	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	dihydralazine, furosemide, enalapril	3	DZP,PB,LEV	0
14	cALL	AIEOP BFM ALL 2009	i.th. MTX, cytarabine, thioguanine, cyklophosphamide, asparaginase	enalapril	1	DZP,LEV	0
15	NHL	AIEOP-BFM ALL 2009	i.th. MTX, vincristine, asparaginase	dihydralazine, clonidine, enalapril, metoprolol	4	LEV, VPA	0
16	AA	EWOG SAA 2010	Atgam, cyclosporine A, corticosteroids	dihydralazine, furosemide, clonidine, enalapril, amlodipine	5	LEV	0
17	BL	INT BNHL 2010	corticosteroids, i.th. and i.v. MTX, i.th. cytarabin, cyclophosphamide, vincritsine, doxorubicin, rituximab	enalapril	1	LEV	0
patients with remote symptomatic seizures							
1	praeB-ALL	AIEOP-BFM ALL 2009	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, vincritsine, doxorubicin, erwinase	clonidine, metipranolol, enalapril	3	CLZ,LEV	LEV
2	CML	CML paed 2006	Atgam, melphalan, cyclophosphamide, thiotepa, fludarabine	dihydralazine, lercanidipine, perindopril, metoprolol, captopril	5	CLZ,LEV	LEV
3	cALL	AIEOP-BFM ALL 2009	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	dihydralazine, enalapril, furosemide	3	CLZ, LEV	LEV
4	praeB-ALL	AIEOP BFM ALL 2009	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	dihydralazine, clonidine, enalapril, propranolol	4	DZP, LEV	LEV

Oncological diagnosis: ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, NHL-Non-Hodgkin lymphoma, AA – aplastic anemia, BL – Burkitt lymphoma, CML – chronic myeloid leukemia.
MTX – methotrexate, i.th. – intrathecal, AEDs – antiepileptioc drugs, anti-HT – antihypertensive, DZP- diazepame, CLZ – clonazepame, PB- phenobarbital, GBP – gabapentine, VPA – valproate, LEV – levetiracetame.

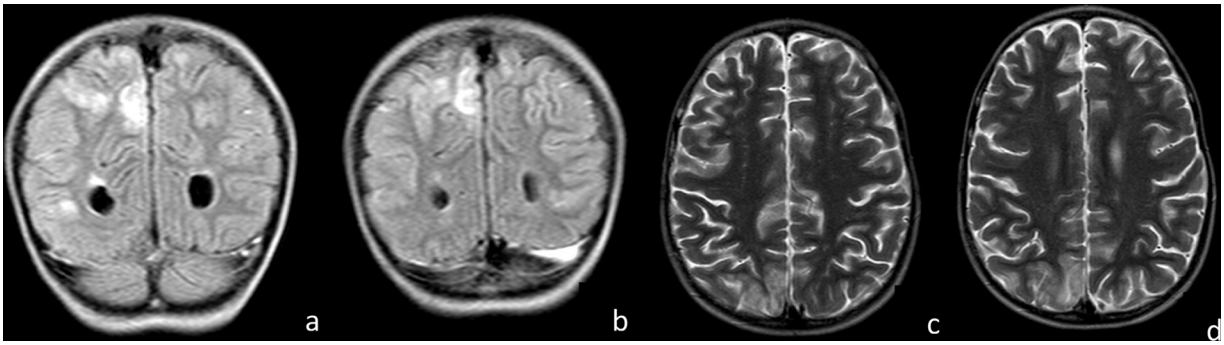

Fig. 1. Patient No. 3 from RSS group: MRI at PRES onset showing FLAIR (a,b) and T2-weighted (c,d) subcortical hyperintensities in occipital regions with right predominance.

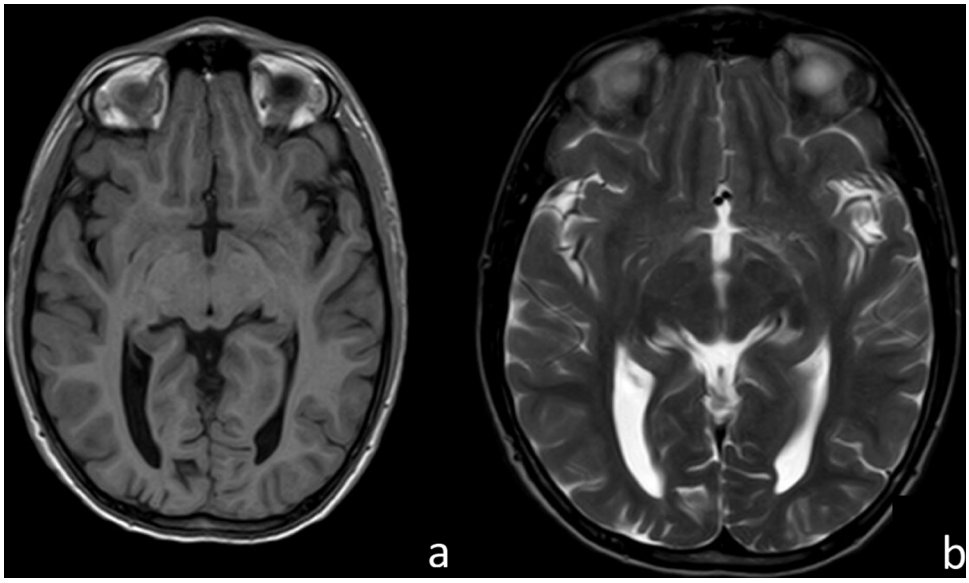

Fig. 2. Patient No. 3 from RSS group: follow-up MRI showing T1-weighted (a) hypointensities and T2- weighted hyperintensities in occipital regions with right predominance correlating to gliosis.

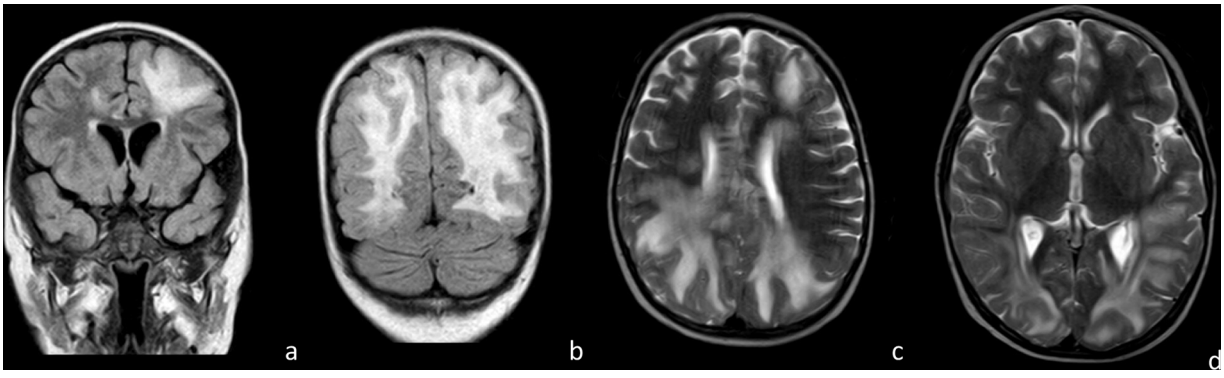

Fig. 3. Patient No. 4 from RSS group: MRI at PRES onset showing FLAIR (a,b) and T2-weighted (c,d) diffuse supratentorial cortical-subcortical hyperintensities with occipital predominance.

RSS. Neither were there statistically significant differences between the group of patients with PSH of duration ≤ 9 h and > 9 h in terms of neurological status, seizure type, or EEG findings at PRES onset and at the one-year follow-up visit and the occurrence of RSS.

We tested the relationship between the seizure type and EEG or MRI findings at PRES onset and the occurrence of RSS. There was not a statistically significant difference between these variables.

4. Discussion

4.1. Pathophysiology of PRES in children with malignancy or bone marrow failure

PRES is a possible complication in children undergoing chemotherapy [6,10]. The overall incidence of PRES in child malignancies

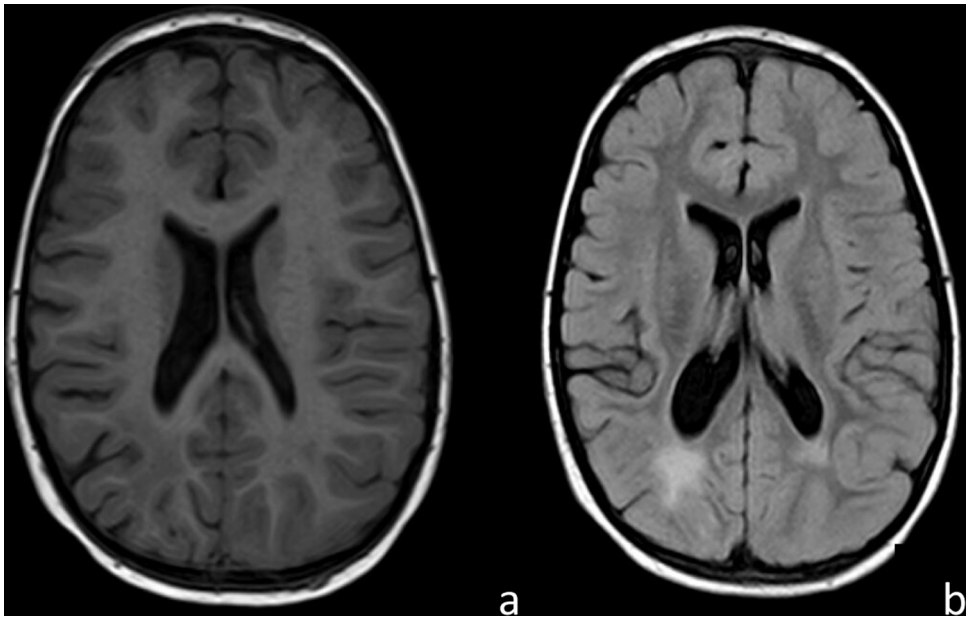

Fig. 4. Patient No. 4 from RSS group: follow-up MRI showing T1-weighted (a) hypointensities and T2- weighted hyperintensities in parietooccipital regions with right predominance correlating to postischemic lesions and gliosis.

in our series is 1.4%, which makes this diagnosis very rare. According to the literature, it affects mainly patients with ALL (55%), and less frequently patients with AML (9%), which is also due to the different incidence of these diagnoses [11]. There are also reports of PRES associated with Langerhans histiocytosis, Hodgkin's lymphoma, non-Hodgkin's lymphoma [12], and aplastic anemia [13]. In our series, the majority of patients in the study had ALL (76.2%) individual patients were also diagnosed with AML, CML, lymphoma, or severe aplastic anemia.

Corticosteroid treatment, L-asparaginase, cyclosporin A, and intrathecal methotrexate are suggested to have an important role in the development of PRES [6,14]. In total, 85.7% of patients were treated with intrathecal methotrexate, 76.2% of patients with corticosteroids, and 71.4% of patients with L-asparaginase. Intrathecal methotrexate is known for its neurotoxicity, and case reports with acute polyradiculoneuropathy [15], acute myelopathy [16] or MTX-induced stroke-like neurotoxicity [17] after intrathecal methotrexate administration have been published. Recent studies with animal models indicate possible late cognitive deficits induced by methotrexate [18,19]. In our study, PRES syndrome developed in 7.2% of patients with malignancy treated with intrathecal methotrexate over a 10-year period. It has been hypothesized that endotheliotoxic effects of both immunosuppressive as well as cytostatic drugs may lead to blood-brain barrier disturbances as well as to the impairment of cerebral vascular autoregulation [20] with the development of brain vasogenic edema. In addition, corticosteroids may play an indirect role in the development of PRES due to the higher risk of steroid-related hypertension [11].

Hypertension is considered to be another key risk factor of PRES. Severe hypertension leads to failed autoregulation and subsequent hyperperfusion, again with the development of vasogenic edema [21]. Hypertension is often seen in children with PRES (100% according to Morris [12]; 68% according to Kim [6]. We observed hypertension in all patients except one (94.7%) and the hypertension was severe: grade II in the majority of patients. The duration of PSH was 9 h or longer in almost all patients. The clinical manifestation of PRES was observed most often between 9 and 12 h of the PSH.

The effect of PSH on PRES severity was studied in 65 patients with PRES by Lee et al. [22]. The brain lesion distribution degree, or lesion scoring point (LSP) on MRI was numerically calculated and compared with presymptomatic blood pressure. The LSP was significantly correlated with pre-MAP (mean arterial pressure before the clinical manifestation of PRES). The authors concluded that patients with PRES who have relatively higher blood pressure in the presymptomatic period could have worse degrees of impaired cerebral autoregulation and are more likely to have wider lesion distributions than patients with lower blood pressure. A possible limitation is that only the distribution of edematous lesions was studied (number of brain regions affected), which does not necessarily correlate with their severity. In our study, we examined the relationship between PSH and neurological outcomes in children with PRES: neurological status, type of seizures, and EEG at PRES onset and at the one-year follow-up visit. We did not find any statistically significant relationship.

We can conclude that hypertension is not the only causative factor in the pathogenesis of PRES, especially in this specific group of patients with hematological malignancies, in whom it is necessary to consider the endothelial dysfunction caused by the cytotoxic and immunosuppressive drugs used. It is also necessary to highlight the hypertensive effect of corticosteroids used in most patients. However, targeted and prompt blood pressure control can be crucial in the management of PRES and should not be underestimated in the context of the multifactorial etiology of this syndrome.

4.2. Seizure outcome in patients with PRES

Many studies describe the clinical and radiological features of PRES in adults and in children. However, studies concerning the electroencephalographic findings and seizure occurrence and prognosis are rare and are mostly designed for the adult population.

Seizures are significantly more frequent in pediatric PRES patients as an initial PRES-related symptom than in adults [11,20]. Experimental data suggest that exposure to calcineurin inhibitors causes more severe neurotoxicity at a young age due to an increased permeability of the immature blood-brain barrier, allowing PRES-mediating circulating substances to act on the brain [5,23]. These factors might contribute to the high incidence of seizures observed in pediatric PRES, possibly sharing pathophysiological similarities with pediatric febrile seizures, a common pediatric condition that might also be partially triggered by fever-associated circulating proinflammatory cytokines [24].

Seizure occurrence in patients with PRES suggests that this syndrome is not just a subcortical pathology. Cortical irritation resulting from the adjacent vasogenic edema that follows disruption of the blood brain barrier is the most probable implicating factor [9].

Seventeen patients out of 21 (80.9%) had seizures as the clinical manifestation of PRES. Almost half of the patients had severe seizure manifestation at PRES onset: GTCS was observed in 4 patients out of 17 (23.6%), NCSE was observed in 3 patients out of 17 (17.6%), as was convulsive SE. Only one patient of this group – the patient with NCSE – developed RSS.

EEG patterns are not well described, but common patterns are reported and include diffuse and focal (mostly posterior) slowing with or without epileptiform discharges [9,10,25] as we found in our series. Lateralized periodic discharges (LPDs) are not commonly associated with PRES [11,13,26] but when they occur, they are associated with a worse prognosis and the development of ongoing seizures or epilepsy [26]. In our study, 3 patients out of 21 (14.3%) had LPDs on acute EEG; only one of them developed RSS.

The results from our study showed that neither the severity of seizure type at PRES onset nor the severity of acute EEG findings are associated with worse neurological prognosis in patients with PRES syndrome. But we have to take into consideration relatively small number of patients in the study.

RSS or the development of epilepsy after PRES syndrome is rare. Recurrent seizures were observed in 4 adult patients out of 46 (8.7%); 3 of those patients had atypical PRES pattern on MRI (involvement of the basal ganglia, thalamus, corpus callosum, and periventricular white matter, in addition to typical lesions) [27]. Sha et al. published a series of 75 adult patients with PRES: 4 of them (5.3%) developed RSS, 2 patients (2.6%) developed epilepsy with seizures occurring more than one year after the PRES [25]. An interesting Swedish study of 52 children with ALL and PRES syndrome was recently published. According to this study, 7 patients out of 52 (13.4%) had epilepsy after PRES and the same number of patients had neurocognitive difficulties as a consequence of ALL diagnosis and treatment [28]. In our study, almost one fifth of patients (19%) had RSS beyond the acute phase of PRES syndrome. Statistical analysis in such a small cohort is not strong enough to trace common factors provoking RSS after PRES syndrome. If this group of patients is studied more closely, it emerges that patients with persisting gliosis on MRI had ongoing seizures at the one-year follow-up visit. According to the definition of epilepsy (ILAE 2017), these 2 patients can be classified as having epilepsy (9.5%). It seems that a persisting structural lesion on MRI is important prognostically. In a study by Sha et al. in which 4 patients out of 75 developed RSS, two patients had post-ischemic lesions on MRI, one patient had focal atrophy, and one patient had normal MRI at the follow-up visit [25]. To date, the correlations between imaging findings and seizure outcome have been poorly described [25,29]. Yamamoto et al. (2015) studied a group of 40 children with PRES; 10% developed focal epilepsy [30]. The same study examined cytotoxic edema on MRI, represented by ADC reduction, which can lead to irreversible cerebral damage; vasogenic edema is likely to be reversible. Almost half of the studied patients had focal gliosis or atrophy on follow-up MRI; this finding was associated with ADC reduction during the acute period. Three of four patients with focal epilepsy had gliosis or atrophy on follow-up MRI. The study concluded that cytotoxic edema with ADC reduction during the acute period and subsequent focal lesions could lead to epileptogenic focus. Recently, atypical neuroimaging findings such as cytotoxic edema, infarction, hemorrhage, contrast enhancement, and a non-reversible clinical course including subsequent epilepsy, have been highlighted [29,31,32]. The pathogenesis of cytotoxic edema in PRES syndrome is not clear. A comparative study of 19 pediatric versus 100 adult patients with PRES proved ADC reduction was statistically significant in children as compared to adults [33]. Further studies are needed to clarify the cause of persistent lesions on MRI and their relationship to PRES syndrome, its neurological outcome, and possible epileptogenesis.

4.3. Study limitations

The results of this study have to be assessed in the context of the following facts. The study is retrospective and the cohort is not large; we included 21 patients in the study. Comparing the data with the literature, this is one of few studies assessing EEG and MRI findings and seizure outcome in children with PRES. Other studies are designed for the adult population. Literature concerning clinico-radiologic findings in children with PRES often describe small series: 7 patients [11], 5 patients [14], 19 patients [15], and 8 patients [16]. Nevertheless, the number of patients in this study limits the statistical analysis. MRI data are inconsistent. We have CT scans in the acute phase of only two patients and MRI was performed on various machines with different protocols between 2008 and 2018 (0.2 T, 1 T, and 1.5 T). For these reasons, the MRI data cannot be studied more precisely (the extent of lesions, ADC maps, *etc*.).

5. Conclusion

PRES is a rare complication in the treatment of children with hematological malignancies and bone marrow failure. It is considered to be a reversible condition, but RSS or epilepsy can develop. Persisting structural lesions on follow-up MRI can be associated with a worse prognosis, but further studies are needed to explain the pathophysiology of these MRI changes and their epileptogenesis. The severity and duration of PSH does not correlate with the neurological and seizure outcomes, but the study nevertheless encourages the prompt and targeted treatment of hypertension in patients with PRES.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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