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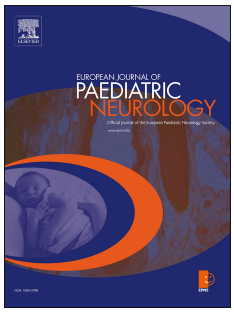

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PII: S1090-3798(20)30202-6

DOI: https://doi.org/10.1016/j.ejpn.2020.10.009

Reference: YEJPN 2744

To appear in: *European Journal of Paediatric Neurology*

Received Date: 27 April 2020

Revised Date: 30 September 2020

Accepted Date: 23 October 2020

Please cite this article as: Cordelli DM, Marra C, Ciampoli L, Barbon D, Toni F, Zama D, Giordano L, Milito G, Sartori S, Sainati L, Foiadelli T, Mina T, Fusco L, Santarone M, Iurato C, Orsini A, Farello G, Verrotti A, Aceti A, Masetti R, Posterior Reversible Encephalopathy Syndrome in infants and young children, *European Journal of Paediatric Neurology* (2020), doi: https://doi.org/10.1016/j.ejpn.2020.10.009.

Posterior Reversible Encephalopathy Syndrome in infants and young children

Duccio Maria Cordelli[a]*, Chiara Marra[a], Lara Ciampoli[a], Davide Barbon[a], Francesco Toni[b], Daniele Zama[c], Lucio Giordano[d], Giuseppe Milito[d], Stefano Sartori[e,f], Laura Sainati[g], Thomas Foiadelli[h], Tommaso Mina[i], Lucia Fusco[j], Marta Santarone[j], Chiara Iurato[k], Alessandro Orsini[l], Giovanni Farello[m], Alberto Verrotti[m], Arianna Aceti[n] and Riccardo Masetti[c].

a. Unit of Child Neurology and Psychiatry, Department of Medical and Surgical Sciences (DIMEC), S. Orsola Hospital, University of Bologna, Italy.

b. IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Neuroradiologia, Bologna, Italia

c. Unit of Pediatric Oncology and Haematology "Lalla Seràgnoli", Department of Pediatrics, Sant'Orsola Hospital, University of Bologna, Bologna, Italy

d. Child Neurology and Psychiatry Unit, Spedali Civili, Brescia, Italy

e. Pediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University Hospital of Padua, Italy;

f. Neuroimmunology Group, Pediatric Research Institute “Città della Speranza”, Padova, Italy

g. Clinic of Pediatric Hematology Oncology, Department of Woman's and Child Health, Azienda Ospedale Università di Padova, Padova, Italy;

h. Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, University of Pavia,

i. Oncoematologia Pediatrica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

j. Department of Neuroscience, Bambino Gesù Children's Hospital, Rome, Italy

k. University of Pisa, Department of Clinical and Experimental Medicine, Paediatric Unit, Pisa, Italy

l. Paediatric Neurology, Department of Paediatrics, University Hospital of Pisa, Pisa, Italy

m. Department of Pediatrics, University of L’Aquila, Italy

n. Department of Medical and Surgical Sciences, Neonatal Intensive Care Unit, AOU Bologna, University of Bologna, Italy

Correspondence:

Dr. Duccio Maria Cordelli, Associate Professor; Unit of Child Neurology and Psychiatry, Department of Medical and Surgical Sciences (DIMEC), S. Orsola Hospital, University of Bologna, Italy; Via Massarenti 11, 40138, Bologna, Italy
ducciomaria.cordelli@unibo.it

Authors: email address if available

- Chiara Marra; chiara.marra3@studio.unibo.it
- Lara Ciampoli; lara.ciampoli@studio.unibo.it
- Davide Barbon, davide.barbon@studio.unibo.it
- Francesco Toni; francesco.toni@isnb.it
- Daniele Zama, daniele.zama@aosp.bo.it
- Ivan Giordano, lucio.giordano@asst-spedalicivili.it
- Giuseppe Milito, gmilito78@gmail.com
- Stefano Sartori, stefano.sartori@unipd.it;
- Laura Sainati, laura.sainati@unipd.it
- Thomas Foiadelli, ; t.foiadelli@smatteo.pv.it
- Tommaso Mina, t.mina@smatteo.pv.it
- Lucia Fusco, lucia.fusco@opbg.net
- Marta Santarone, marta.santarone@opbg.net
- Alessandro Orsini, aorsini.mg@gmail.com
- Chiara.Iurato, chiara.iurato@gmail.com
- Alberto Verrotti, alberto.verrottidipianella@univaq.it
- Giiuseppe Farello, giuseppe.farello@univaq.it
- Arianna Aceti, arianna.aceti2@unibo.it
- Riccardo Masetti, riccardo.masetti5@unibo.it

Key words: PRES; Status epilepticus; seizures; infants; EEG monitoring; ICU admission

ABSTRACT

Aim: The aim of this study was to describe the characteristics of Posterior Reversible Encephalopathy Syndrome (PRES) in infants and young children (< 6 years) and to compare them with the older pediatric population affected by PRES.

Methods: we retrospectively reviewed records of 111 children (0-17 years) diagnosed with PRES from 2000 to 2018 in 6 referral paediatric hospitals in Italy. The clinical, radiological and EEG features, as well as intensive care unit (ICU) admission rate and outcome of children aged <6 years were compared to those of older children (6-17 years). Factors associated with ICU admission in the whole paediatric cohort with PRES were also evaluated.

Results: Twenty-nine patients younger than 6 years (26%) were enrolled with a median age at onset of PRES of 4 years (range: 6 months – 5 years). Epileptic seizures were the most frequent presentation at the disease onset (27/29 patients). Status epilepticus (SE) was observed in 21/29 patients: in detail, 11 developed convulsive SE and 10 presented nonconvulsive SE (NCSE). SE was more frequent in children < 6 years compared with older children (72% vs 45%) as well as NCSE (35% vs 10%). Seventeen children aged < 6 years required ICU admission. Prevalence of ICU admissions was higher within younger population compared to older (59% vs 37%). In the whole study population SE was significantly associated with ICU admission (p=0.001).

Conclusions: PRES in children < 6 years differs from older children in clinical presentation suggesting a more severe presentation at younger age.

1. INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinical and neuroradiologic entity that is becoming increasingly well documented in pediatrics (1). PRES is usually diagnosed in association with other clinical conditions, namely infections, autoimmune, renal, oncological or hematological disorders and after transplantation. Its incidence is largely unknown; however, in selected populations such as transplanted children it is reported ranging from 1 to 10% (1). PRES is characterized by a variable association of seizures, headache, altered mental status and visual disturbances, as well as imaging suggesting white-gray matter edema involving the posterior regions of the central nervous system in most cases (1,2). Although PRES is typically considered to have a benign clinical outcome, the presentation of PRES can be associated with life-threatening complications (3,4). The pathogenesis of PRES is not entirely clarified, but it has been etiologically related to many different causes, most commonly acute hypertension, the use of immunosuppressive agents inducing endothelial damage, pre-eclampsia/eclampsia, cancer and renal disorders (5,6).
Although some studies evaluated the characteristics of PRES in the pediatric population (7-9), few cases of children < 6 years have been reported. In particular there is no study specifically focused on the evaluation of the clinical and radiological characteristics of young children affected by PRES and on their long-term outcome.
The aim of this study is to describe clinical and neuroradiological characteristics of infants and young children with PRES and to compare them with the older pediatric population affected by PRES for the identification of any age-related differences.

2. METHODS

2.1 Patients

We retrospectively reviewed records of 111 children (0-17 years) diagnosed with PRES from 2000 to 2018 in 6 referrals paediatric hospitals in Italy (Bologna, Brescia, Padova, Pavia, Pisa, Roma).
In each hospital, patients were identified by electronical database query.
Inclusion criteria were:

- diagnosis of PRES established on the basis of typical neuroimaging finding of vasogenic edema associated with at least one classical clinical sign and symptom including seizures, headache, visual disturbance and mental status changes.
- Age < 18 years

The study was approved by the local Ethics committee (343/2017/O/Oss). The requirement for informed consent was waived by the board.

2.2 Evaluation

The clinical, radiological and EEG features of children with PRES aged <6 years were evaluated, as well as intensive care unit (ICU) admission rate and outcome and compared to those of older children (aged 6-17 years) with PRES. We collected data regarding demographics, underlying diseases and risk factors. Hypertension was defined as systolic blood pressure and/or diastolic blood pressure ≥95th percentile. Status epilepticus (SE) was defined as 30 minutes of continuous seizure activity; nonconvulsive SE (NCSE) was defined using clinical and EEG criteria (10). During the study period EEG practice in our institutions was to record as early as possible after the onset of alteration of mental status or other neurological signs or symptoms. Serial EEGs were performed in the cases of detection of abnormalities during the first recording. When antiepileptic therapy was administered for seizure activity or SE, EEG was continued until the end of the seizure to monitor the effects of treatment. Our imaging practice was to perform urgent neuroimaging (usually CT scan) in the case of focal neurological signs and/or prolonged alteration of consciousness and/or unexplained seizures. Brain magnetic resonance imaging (MRI) was performed as early as possible over the following days or as first neuroimaging evaluation when rapidly available. MRI techniques included fast spin echo (FSE) and fluid attenuated inversion recovery (FLAIR) T2 weighted images, pre- and post-contrast T1 weighted images, gradient-echo (GE) T2 weighted images and diffusion weighted images (DWI). Localization of edema was evaluated. All patients had a follow-up period of at least 2 years and data regarding outcome and long-term complications (epilepsy, permanent neurological deficits) were collected.

2.3 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics v 20.0.0 (Armonk, NYC, US). Differences between groups (i.e. study center, age group, etc.) in terms of categorical variables were evaluated using the Fisher exact test. In order to identify factors related to ICU admission, an analysis linking ICU admission to clinical variables, treatment, imaging findings, and study center was performed using the Fisher exact test. *P*-values were corrected using Simes' method (*Q*-values) to control for false discovery rate related to multiple testing. The significance level was set at 5%.

3. RESULTS

3.1 Patients demographics and risk factors for PRES

A total of 111 patients with PRES were identified: out of them, 29 patients (26%) were aged <6 years. In Table 1 characteristics concerning demographics, underlying diseases, risk factors for PRES, clinical presentation, EEG, neuroimaging features, evolution and outcome are reported.

The underlying disease included oncological disease in 73/111 cases (20 aged < 6 years), haematological non-oncological disease in 22/111 cases (6 < 6 years), autoimmune disease in 8/111 cases (2 < 6 years) and kidney disease in 7/111 children (1 aged < 6 years). Details about underlying diseases are shown in Table 2. Hypertension was the most common risk factor (83/111 patients, 23 < 6 years) followed by chemotherapy (58/111 patients, 16 < 6 years). Sixty patients developed PRES after transplantation, of whom 15 were aged less than 6 years .

Statistical comparison of preschool children and older children showed no significant difference in gender, underlying disease and risk factors between groups (Table 1).

3.2 Clinical presentation

Epileptic seizures were the clinical presentation at the onset in 105/111 children. In particular 27/29 patients aged less than 6 years presented with seizures (93%). SE was observed in 58/111 patients (21 aged < 6 years): 40 with convulsive SE and 18 with NCSE (11 and 10 in children aged < 6 years, respectively). SE was more frequent in children < 6 years compared with older children (72% vs 45%) as well as NCSE (35% vs 10%). Mental status changes not related to epileptic seizures were signalled in 26/111 patients (10 patients < 6 years) while 14/111 patients presented visual disturbances (5 patients < 6 years) and 7/111 patients reported headache (4 patients < 6 years).

3.3 Neuroimaging and EEG

Neuroimaging showed supratentorial involvement in all 111 children.

Parietal lobe was involved in 82/111 patients (22 in patients < 6 years), occipital lobe in 76/111 patients (22 in patients < 6 years), frontal lobe in 45/111 patients (9 in patients < 6 years), temporal lobe in 35/111 patients (8 in patients < 6 years).

Infratentorial involvement was documented in 17/111 children of whom 6 were aged < 6 years. In detail, cerebellum was involved in 17/111 children (6 in patients < 6 years) and brainstem in only 1 child aged < 6 year.

Compared with older population, infratentorial involvement in neuroimaging was more frequent in younger children (21% vs 13%), even if this difference was not statistically significant. EEG was performed in 105/111 patients: ictal abnormalities were recorded in 34/105 patients, of whom 14 < 6 years. We observed EEG slowing in the posterior regions in 65/105 (12 in patients <6 years) and periodic lateralized epileptiform discharges (PLEDs) in 6/105 (2 in patients <6 years). In only 2 patients EEG was normal. In all cases of NCSE, EEG showed continuous or near-continuous rhythmic epileptic discharges in the posterior regions. EEG results are summarized in Table 3.

3.4 ICU admission and outcome

Forty-seven children (17 < 6 years) required admission to intensive care unit (ICU).

Prevalence of ICU admissions was higher among younger children compared to older (59% vs 37%), although this difference failed to achieve statistical significance (Figure 1). Considering

the whole study population, SE and in particular convulsive SE were significantly associated with ICU admission. In Table 4 we summarize factors by ICU admission.

Concerning long-term outcome, 37/111 children died during the follow-up period; out of them 9 were aged <6 years and only in 1 case death was caused directly by PRES (cerebral haemorrhage). Moreover, 7/111 children (3 aged < 6 years) developed epilepsy after PRES and 2 children, both aged < 6 years, presented permanent neurological deficits at last follow-up. None of these children presented any disease other than PRES predisposing to epilepsy and/or neurological deficits.

Mortality rate did not significantly differ between preschool and older children.

4. DISCUSSION

This study is the first attempt to investigate the features of PRES in infants and young children. In our large multicentric series, 29 out of 111 pediatric patients with PRES (26 %) were aged < 6 years. Although some authors found relevant clinical and radiological differences between pediatric and adult PRES patients (7,8), no studies have focused so far on young children and compared clinical and radiologic presentation between younger and older subgroups of children. A study on children with renal disorders (11) found that younger children with PRES were more prone to severe neurological symptoms, due to the greater recurrence of seizures, but there were no patients under the age of 5. Moreover, only few case reports described PRES in infants (12,13). In our pediatric population, PRES in children < 6 years differed from PRES occurring in older children in clinical presentation and severity: a difference was documented in the rate of SE, NCSE and in the need of ICU admission.

SE and especially NCSE were more frequent in younger children. Seizures and SE are common presenting signs of PRES in children and some studies report high frequency of seizures and SE in the pediatric population (14). Interestingly, Yamada et al. reported an increased susceptibility to seizures in younger children with PRES (11). The higher frequency of SE and NCSE in younger children detected in our study may be due to a more severe neurotoxicity related to the permeability of the immature blood-brain barrier (15) and/or to an increased susceptibility to seizures and SE in the developing brain (16). EEG is mandatory for a correct diagnosis and management of NCSE. Based on our results, we underline that EEG monitoring is a fundamental tool to properly diagnose and treat NCSE particularly in younger children with definite or suspected PRES.

In our experience, infratentorial involvement was more frequent in younger children. A few case series studies investigated the differences in brain edema location found in children respect to adult patients. In keeping with our results these authors showed that infratentorial involvement was more common in children (8, 17). Little sympathetic innervation of the posterior circulation has been proposed as a possible explanation of the more frequent posterior region involvement (18). Infratentorial involvement of PRES can predispose to potential life-threatening complications such as cerebellar herniation that require a correct and prompt diagnosis and treatment (3). Hence, we suggest that the execution of an urgent neuroimaging study has to be considered in all children with signs and symptoms fitting with PRES.

In infants and young children with PRES we observed a higher rate of ICU admissions suggesting a more severe presentation at younger age. Of note, long-term complications were more frequent in young children and the only 2 patients that presented permanent neurological deficits at follow-up experienced PRES in the first years of life. Some factors could favor a more severe clinical course in younger patients with PRES: autoregulatory response improves with increasing age and maturity of the brain region, and immature brain is more susceptible to vasoconstriction during hypertension (19); moreover, exposure to calcineurin inhibitor at a young age could result in much severe neurotoxicity due to a more permeable blood–brain barrier allowing PRES - mediating circulating

substances to induce endothelial damage (8,15). SE was significantly associated to ICU admission in our paediatric population, largely explaining the increased rate of ICU admission in younger children. SE is a frequent indication for ICU admission in PRES patients as documented by Legriel et al (20) who observed SE in 44% of all adult patients admitted to the ICU for severe PRES. These data suggest that a prompt diagnosis and treatment of seizures and SE is needed in children with PRES and that prolonged EEG monitoring is an indispensable tool in this setting to avoid underdiagnosis and delayed interventions.

The main limitation of this study is its retrospective design. Moreover, we considered mainly oncological and transplanted patients.

5. Conclusion

To the best of our knowledge, this is the first study investigating the peculiar picture of PRES in the preschool age. PRES in children < 6 years differs in clinical presentation and neuroimaging features suggesting a more severe presentation at younger age. A careful monitoring of clinical, EEG and neuroimaging evolution is required to properly manage these children.

Acknowledgments

The authors thank AbDeb group and the Neuroncology study group of the Società Italiana di Neurologia Pediatrica (SINP) for their fundamental support.

Declarations of interest: none.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1 Clinical features and outcome in younger and older children with PRES

	All Patients (111)	Patients < 6 years (29)	Patients ≥ 6 years (82)	*Q*-value
Patients demographics				
Gender (male)	67 (60%)	19 (65%)	48 (58%)	1.000
Median age (range)	8 (0-17 y)	4 (0-5 y)	10 (6-17 y)	
Underlying diseases				
Oncological disease	73 (66%)	20 (69%)	53 (65%)	1.000
Hematologic non oncological	22 (20%)	6 (21%)	16 (19%)	1.000
Kidney disease	8 (7%)	1 (3%)	7 (8%)	1.000
Autoimmune disease	7 (6%)	2 (7%)	5 (6%)	1.000
Infectious disease	1 (1%)	0	1 (1%)	1.000
Risk factors for PRES				
Transplantation	60 (54%)	15 (52%)	45 (55%)	1.000
Chemotherapy	58 (52%)	16 (55%)	42 (51%)	1.000
Calcineurin Inhibitors	57 (51%)	12 (41%)	45 (55%)	1.000
Steroids	52 (47%)	14 (48%)	38 (46%)	1.000
Hypertension	83 (75%)	23 (79%)	60 (73%)	1.000
Toxic Etiology	95 (86%)	26 (90%)	69 (84%)	1.000
Clinical presentation				
Seizure	105 (95%)	27 (93%)	78 (95%)	1.000
SE	58 (52%)	21 (72%)	37 (45%)	0.196
Convulsive SE	40 (36%)	11 (38%)	29 (35%)	1.000
NCSE	18 (16%)	10 (35%)	8 (10%)	0.138
Neuroimaging				
Infratentorial Involvement	17 (15%)	6 (21%)	11 (13%)	1.000
Evolution and long-term outcome				
ICU	47 (42%)	17 (59%)	30 (37%)	0.311
Death	37 (33%)	9 (31%)	28 (34%)	1.000
for PRES	3 (3%)	1 (3%)	2 (2%)	1.000
Long-term complications	9 (12%)	5 (25%)	4 (7%)	0.311
Epilepsy	7 (9%)	3 (15%)	4 (7%)	1.000
Permanent neurological deficits	2 (3%)	2 (10%)	0	0.322

ICU, Intensive Care Unit; NCSE, Non-Convulsive Status Epilepticus; PRES, Posterior Reversible Encephalopathy Syndrome; SE, Status Epilecticus

Table 2 Underlying diseases in younger and older children with PRES

Underlying disease	All Patients (111)	Patients < 6 years (29)	Patients ≥ 6 years (82)
Oncological disease	73 (66%)	20 (69%)	53 (65%)
Leukemia	58 (52%)	16 (55%)	42 (51%)
Myelodysplasia	3 (3%)	0	3 (4%)
Neuroblastoma	3 (3%)	2 (7%)	1 (1%)
Non-Hodgkin lymphoma	3 (3%)	0	3 (4%)
Hodgkin lymphoma	2 (2%)	0	2 (2%)
Medulloblastoma	1 (1%)	1 (3%)	0
Nasopharyngeal carcinoma	1 (1%)	0	1 (1%)
Wilms' tumor	1 (1%)	1 (3%)	0
Rhabdomyosarcoma	1 (1%)	0	1 (1%)
Hematologic non oncological	22 (20%)	6 (21%)	16 (19%)
Thalassemia	8 (7%)	2 (7%)	6 (7%)
Sickle cell disease	5 (5%)	1 (3%)	4 (5%)
Anemia	5 (5%)	1 (3%)	4 (5%)
Immunodeficiency disorders	2 (2%)	2 (7%)	0
Lymphohistiocytosis	2 (2%)	0	2 (2%)
Kidney disease	8 (7%)	1 (3%)	7 (8%)
Nephotic syndrome	4 (4%)	0	4 (5%)
Kidney malformation	1 (1%)	1 (3%)	0
Acute renal failure	1 (1%)	0	1 (1%)
Lupus nephritis	1 (1%)	0	1 (1%)
Alport syndrome	1 (1%)	0	1 (1%)
Autoimmune disease	7 (6%)	2 (7%)	5 (6%)
Systemic Lupus Erythemtaosus	3 (3%)	0	3 (4%)
Rheumatoid arthritis	3 (3%)	2	1 (1%)
Dilatative cardiomyopathy	1 (1%)	0	1 (1%)
Infectious disease	1 (1%)	0	1 (1%)

Table 3 EEG features in younger and older children with PRES

EEG	All Patients (105/111)	Patients < 6 years (28/29)	Patients ≥ 6 years (77/82)
Ictal	34 (32%)	14 (50%)	20 (26%)
Non-ictal	71 (70%)	14 (50%)	59 (77%)
Posterior slowing	65 (62%)	12 (43%)	53 (69%)
PLEDs	6 (6%)	2 (7%)	4 (5%)
Normal	2 (2%)	0	2 (3%)

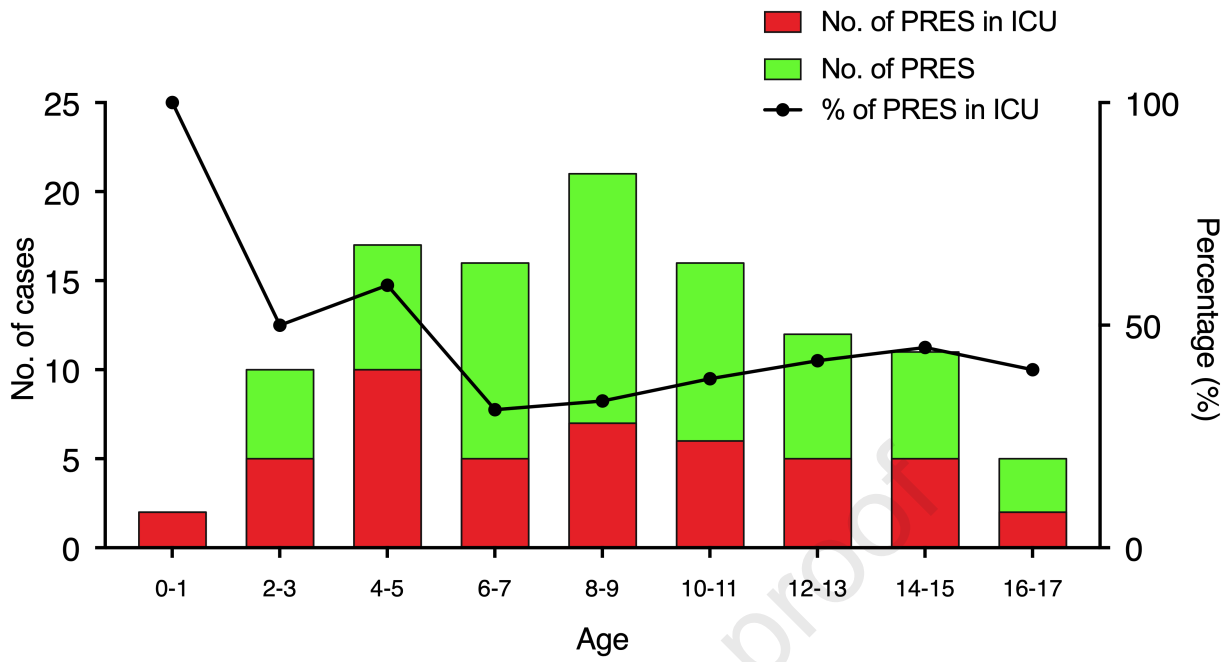
Table 4 Clinical features of children admitted to ICU

	All Patients (111)	ICU admission (47)	No ICU admission (64)	*Q*-value
Patients demographics				
Gender (male)	67 (60%)	29 (62%)	38 (59%)	1.000
Age (< 6 years)	29 (26%)	17 (36%)	12 (19%)	0.300
Underlying diseases				
Oncological disease	73 (66%)	32 (68%)	41 (64%)	1.000
Hematologic non oncological disease	22 (20%)	7 (15%)	15 (23%)	0.995
Kidney disease	8 (7%)	5 (11%)	3 (5%)	0.995
Autoimmune disease	7 (6%)	2 (4%)	5 (8%)	1.000
Infectious disease	1 (1%)	0	1 (2%)	1.000
Risk factors for PRES				
Transplantation	60 (54%)	25 (53%)	35 (55%)	1.000
Chemotherapy	58 (52%)	27 (57%)	31 (48%)	0.995
Calcineurin Inhibitors	57 (51%)	24 (51%)	33 (52%)	1.000
Steroids	52 (47%)	23 (49%)	29 (45%)	1.000
Hypertension	83 (75%)	37 (79%)	46 (72%)	1.000
Toxic Etiology	95 (86%)	40 (85%)	55 (86%)	1.000
Clinical presentation				
Seizure	105 (95%)	44 (94%)	61 (95%)	1.000
SE	58 (52%)	38 (81%)	20 (31%)	**<0.001**
Convulsive SE	40 (36%)	27 (57%)	13 (20%)	**0.001**
NCSE	18 (16%)	11 (23%)	7 (11%)	0.526
Neuroimaging				
Infratentorial Involvement	17 (15%)	9 (19%)	8 (13%)	0.995

ICU, Intensive Care Unit; NCSE, Non-Convulsive Status Epilepticus; PRES, Posterior Reversible Encephalopathy Syndrome; SE, Status Epilecticus

FIGURE 1

Title: Age-related admission to ICU



Highlights

- SE and NCSE are more frequent in children with PRES aged < 6 years
- Prevalence of ICU admissions was increased among younger PRES population
- SE and age < 6 years were associated with ICU admission
- Careful monitoring of clinical, EEG and neuroimaging evolution is required

Declarations of interest: none.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.