Turkish Archives of Pediatrics

SCIENTIFIC LETTER
DOI: 10.5152/TurkArchPediatr.2024.23270

Periodic Lateralized Epileptiform Discharges: A Child with a Rare Manifestation of Posterior Reversible Encephalopathy Syndrome and Literature Review

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Posterior reversible encephalopathy syndrome (PRES) is a distinctive neuroradiological disorder characterized by the abrupt onset of neurological symptoms, including severe headache, altered levels of consciousness ranging from drowsiness to coma, seizures, and visual impairments.[1] The underlying cause of PRES typically arises from endothelial dysfunction triggered by factors such as fluctuating blood pressure, acute renal failure, drug toxicity, immunosuppressive agents, electrolyte imbalances, infections, and autoimmune disorders.[1,2] Electroencephalography (EEG) plays a crucial role in evaluating encephalopathy and identifying nonconvulsive status epilepticus in patients with PRES.[3] However, definitive EEG findings specific to PRES have not been established. A high prevalence of certain EEG abnormalities, such as generalized or posterior focal background slowing, nonconvulsive electrographic status epilepticus, and periodic discharges, has been observed in individuals with PRES.[3-5] Despite this, there is a limited number of reported cases, particularly in the pediatric population, focusing on PRES-associated periodic lateralized epileptiform discharges (PLEDs).[3-16] Therefore, our objective is to present a rare and noteworthy pediatric case involving PRES-associated PLEDs, along with comprehensive clinical information, and to review the existing literature.

A 10-year-old girl, previously monitored in the pediatric intensive care unit for acute extremity compartment syndrome following an earthquake, presented with symptoms including blurred vision, sudden-onset agitation, confusion, gaze deviation, and focal motor and sensory seizures. She was born following an uneventful pregnancy and delivery, with the nonconsanguineous marriage of her parents. She achieved normal developmental milestones.

On physical and neurological examination, she appeared lethargic with the following vital signs: temperature 37.5°C, blood pressure 145/90 mm Hg, heart rate 102 beats/min, and respiratory rate 22 breaths/min. Mid-dilated pupils, lack of eye contact, and an inability to follow light sources were noted. In addition, intermittent bilateral gaze deviation and a positive Babinski sign were observed. Spontaneous and symmetrical movement of both the upper and lower extremities was evident.

Laboratory tests revealed the followings: leukocytosis (23.2 × 10^9/L), anemia (hemoglobin: 7.8 g/dL), thrombocytosis (platelet: 645 × 10^9L), hyponatremia (sodium: 127 mEq/L), hypocalcemia (calcium: 7.4 mg/dL), and hypomagnesemia (magnesium: 1.2 mg/dL). Kidney function tests, including blood urea nitrogen (BUN; 2 mg/dL) and creatinine (0.21 mg/dL), were unremarkable. In addition, the erythrocyte sedimentation rate was normal (20 mm/h), whereas the level of C-reactive protein was elevated (25 mg/dL). Serological tests for viral infections and polymerase chain reaction tests on both nasopharyngeal swabs and cerebrospinal fluid (CSF) were negative. Cerebrospinal fluid examination showed no evidence of central nervous system (CNS) infection, with normal cell count, color, and sugar and protein values. Moreover, cultures from blood, urine, and CSF samples demonstrated no signs of microbial growth.

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Received: November 21, 2023
Revision Requested: December 10, 2023
Last Revision Received: December 28, 2023
Accepted: January 7, 2024
Publication Date: February 2, 2024

Cite this article as: Yıldırım M, Çiçek S, Havan M, Kendirli T, Teber S. Periodic lateralized epileptiform discharges: A child with a rare manifestation of posterior reversible encephalopathy syndrome and literature review. *Turk Arch Pediatr.* 2024;59(3):321-324.

Brain MRI demonstrated cortical and subcortical hyperintensities in the left dominant bilateral temporal, parietal, and occipital lobes on T2-weighted and fluid attenuation inversion recovery (FLAIR) sequences, suggestive of potential vasogenic cerebral edema. Additional investigations using apparent diffusion coefficient (ADC) mapping indicated increased signal intensity, whereas diffusion-weighted imaging (DWI) revealed isointensity in these specific regions (Figure 1A). Electroencephalography showed a predominant slowing of posterior background activity on the left side and left-dominant bilateral PLEDs plus fast activity (Figure 1B).

Based on these findings, the patient was diagnosed with PRES-associated PLEDs due to hypertension and electrolyte imbalances. We postulated that these conditions could be associated with limb ischemia and sepsis resulting from extremity compartment syndrome, rather than renal dysfunction. The patient presented with focal sensory seizures, such as visual hallucinations and focal tonic seizures. Antiseizure medication (30 mg/kg/day, levetiracetam) and antihypertensive agents were started. Concurrently, replacement therapies were initiated to correct hyponatremia, hypocalcemia, and hypomagnesemia. Within a day, notable improvement in the patient's neurological deficit was observed. While epileptic discharges persisted on EEG, clobazam (0.5 mg/kg/day) effectively prevented seizures recurrence. Follow-up EEG on day 6 demonstrated mild unilateral slowing of the posterior background activity. After 1 month, a control brain MRI showed complete resolution of the abnormalities initially identified. The dose of clobazam was gradually tapered, and seizures did not recur for the subsequent 3 months. She exhibited remarkable improvement in motor and cognitive skills, including attention and perception abilities.

The underlying pathophysiology of PRES remains controversial, with multiple theories including impaired cerebrovascular autoregulation (disrupted cerebral perfusion regulation) and endothelial dysfunction.[1,3] The diagnosis of PRES involves a combination of clinical evaluation, imaging, and electrophysiological studies, with the exclusion of other potential causes. These causes include ischemic or hemorrhagic stroke, meningitis, infectious or autoimmune encephalitis, uremic or hepatic encephalopathy, primary angiitis of the CNS, malignancies such as lymphoma and gliomatosis cerebri, and epileptic disorders.[1,17] Ischemic stroke typically manifests with focal neurological deficits such as hemiparesis/hemiplegia and facial asymmetry. In contrast, PRES often presents with reversible symptoms, including headaches, altered mental status, and focal seizures. Acute ischemia reveals restricted diffusion on DWI and ADC, appearing as hyperintensity on DWI with corresponding hypointensity on ADC. Conversely, typical findings for PRES involve hyperintensity on FLAIR images and ADC mapping, with isointensity on DWI in the parieto-occipital or posterior frontal cortical/subcortical regions.[17,18] CNS infections can lead to symptoms similar to PRES, and CSF analysis can help rule out infectious causes. Moreover, metabolic encephalopathies such as uremic or hepatic encephalopathy and primary angiitis of the CNS can induce similar neurological symptoms. Differentiating these conditions from PRES requires additional blood tests and neuroimaging studies.[17,18]

Periodic lateralized epileptiform discharges are frequently observed in acute neurological conditions, but its association with PRES is rare. To date, PLEDs on EEG have been documented in a limited number of PRES cases: 13 in adults and 6 in children (Supplementary Table 1).[3-16] Posterior reversible encephalopathy syndrome is predominantly identified in young to middle-aged adults, with a higher prevalence in females.[1] In the existing literature, gender information was provided for 11 of the 19 patients with PRES-associated PLEDs, of which 9 (82%) were female. Similarly, our patient was also female.

A comprehensive analysis of PLEDs on EEG was meticulously detailed for 10 of the 19 patients. Among these cases, unilateral PLEDs were evident in 60% of patients, whereas bilateral PLEDs were observed in 40%. In addition, a combination of PLEDs plus fast activity was noted in just 1 patient.[12] Notably, our patient exhibited a similar pattern with PLEDs plus fast activity. Follow-up EEG was documented for 8 of the 19 patients, revealing EEG abnormalities, including background slowing (n = 2), interictal spikes (n = 1), generalized rhythmic discharges (n = 1), and

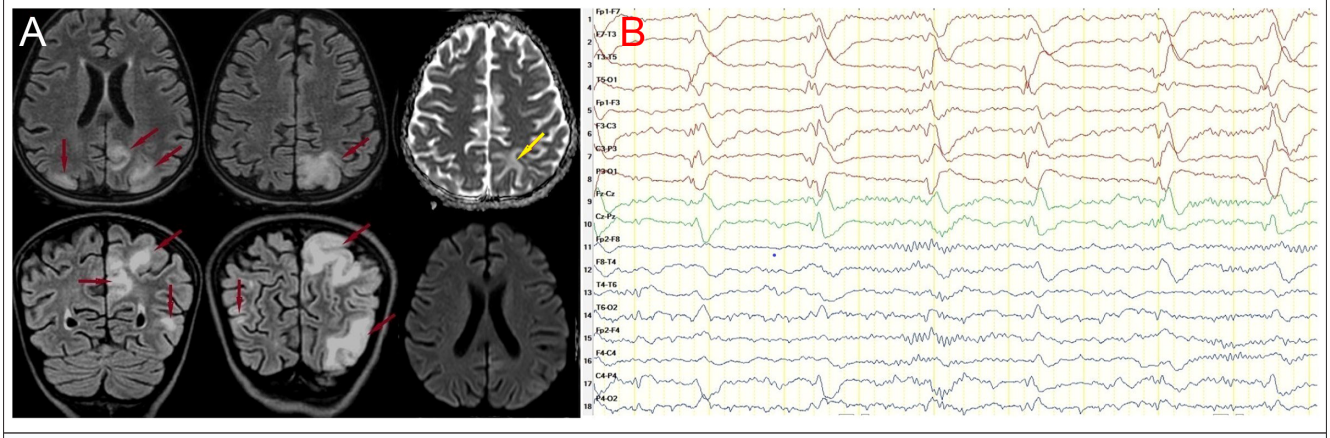

Figure 1. (A) Sixteen hours after the onset of typical symptoms, a fluid-attenuated inversion recovery (FLAIR) MRI sequence revealed abnormal subcortical and cortical hyperintensities consistent with vasogenic edema in the bilateral temporal, parietal, and occipital lobes, with more prominent in the left hemisphere (red arrows). Apparent diffusion coefficient (ADC) mapping demonstrates cortical/subcortical vasogenic edema with hyperintensity (yellow arrow). Diffusion-weighted imaging (DWI) showed isointensity in these areas. (B) Twenty-two hours after the onset of typical symptoms, the electroencephalography demonstrated mild slowing of the background rhythm, left dominant slowing of the posterior background activity and posteriorly left dominant bilateral PLEDs plus fast activity.

PLEDs (n = 1) in 50% of this subgroup. However, the time intervals for these follow-up EEGs varied considerably, ranging from 10 to 50 days, and were often not reported for most patients.

Electroencephalography patterns associated with PRES encompass diffuse or focal slowing of the background rhythm, generalized and/or focal epileptiform discharges, electrographic status epilepticus, and PLEDs.[4] Reiher et al[19] proposed a classification for PLEDs, dividing them into 2 primary categories: "PLEDs proper" (involving PLEDs without rhythmic discharges) and "PLEDs plus" (encompassing PLEDs with rhythmic discharges). The "PLEDs proper" category was further subdivided into 3 subcategories labeled as classes 1, 2, and 3. In addition, "PLEDs plus" was classified into 2 distinct classes: class 4 (encompassing PLEDs with brief rhythmic discharges lasting 1 second or less) and class 5 (characterized by more prolonged rhythmic discharges). Notably, the "PLEDs plus" category carried a higher risk of seizure recurrence when compared to "PLEDs proper."[19] Despite our patient being classified as class 5 "PLEDs plus," an absence of seizure recurrence was observed during follow-up, leading to the decision for early discontinuation of antiseizure medication.

Outcomes were documented in 9 of the 19 patients with PRES-associated PLEDs. Among this group, seizures persisted beyond the acute phase of PRES in 44% of patients, whereas no recurrence was observed in the remaining patients. Moreover, 2 patients (22%) experienced persistent neurological deficits such as aphasia and motor weakness.[9,14] Unfortunately, 1 patient died because of progression of the primary disease.[11] In contrast, in our patient, seizures did not recur over the subsequent 3 months, and no neurological deficits were observed.

In a retrospective analysis of 46 adult patients who experienced PRES, Kamiya-Matsuoka et al[3] demonstrated a correlation between the location of radiological lesions and the specific region displaying focal abnormalities on routine EEG. However, our patient did not exhibit an obvious correlation. Interestingly, despite 3 patients with PRES-associated PLEDs in the literature showing bilateral hemispheric involvement on MRI, their EEG revealed unilateral PLEDs. A similar observation was noted in a study by Kastrup et al,[4] involving the assessment of EEGs from 49 adult patients with PRES, where no distinct correlation was established between MRI involvement and EEG findings. The occurrence of PRES-associated PLEDs in children was initially documented by Cordelli et al.[16] In this retrospective analysis of 111 children diagnosed with PRES, 61.9% of children showed slowing of background activity in the posterior regions, while 5.7% exhibited PLEDs.

In conclusion, to the best of our knowledge, this report represents the first documented pediatric case of PRES-associated PLEDs, including information on prognosis in the current literature. Further studies are needed to determine the prevalence and eventual outcomes of PLEDs in children diagnosed with PRES.

Informed Consent: Written informed consent for publication of this case report were obtained from the patient's parents in compliance with the national ethics regulation.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – M.Y., S.Ç.; Design – M.Y., M.H.; Supervision – T.K., S.T.; Materials – M.Y., M.H., T.K.; Data Collection and/or Processing – M.Y., S.Ç.; Analysis and/or Interpretation – M.Y., S.Ç., S.T.; Literature Review – M.Y., S.Ç., M.H.; Writing Manuscript – M.Y., M.H.; Critical Review – T.K., S.T.

Declaration of Interests: The authors have no conflicts of interest to declare.

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Supplementary Table 1. Clinical summary and characteristics of our patient and previously reported patients with PRES-associated PLEDs

Patient	Age (years)	Sex	Brain MRI involvement	EEG	Accompanying disorder/Etiology	Seizure type(s)	Treatment (and ASMs)	Follow-up EEG (time)	Outcome
Fitzpatrick et al. [6]	ND	ND	Bilateral involvement (details ND)	PLEDs (details ND)	Hypertension	ND	ND	ND	ND
Fitzpatrick et al. [6]	ND	ND	Bilateral involvement (details ND)	PLEDs (details ND)	Hypertension	ND	ND	ND	ND
Bhatt et al. [7]	47	F	Bilateral temporo-occipital lobes	PLEDs (details ND)	Non-small cell carcinoma of the lung on etoposide treatment	No seizure	Discontinuation of etoposide	Normal (10th day)	Good (seizure free)
Skiba et al. [8]	28	M	Bilateral parieto-occipital lobes	Posteriorly dominant bilateral PLEDs, slowing of the posterior background rhythm	Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, hypertension, chronic renal failure	Generalized tonic-clonic, focal-nonmotor-sensory	Intravenous antihypertensives, valproic acid, phenytoin and levetiracetam	Normal (time ND)	Recurring several generalized tonic-clonic seizures
Kastrup et al. [4]	60	F	Bilateral frontal, temporal and parieto-occipital lobes	Left dominant bilateral PLEDs, slowing of the posterior background rhythm	Facioscapulohumeral dystrophy, electrolyte imbalance	Generalized and focal motor	Correction of electrolyte imbalance, clonazepam, valproic acid	Normal (21th day)	Good (seizure free)
Choi et al. [9]	54	F	Unilateral medial temporal, parieto-occipital lobes	Posteriorly dominant unilateral PLEDs, slowing of the posterior background rhythm	Subacute encephalopathy with seizures in alcoholics syndrome	Focal to bilateral tonic-clonic	Levetiracetam	ND	Poor (persisting aphasia and motor weakness)
Cherian et al. [10]	32	F	Bilateral parieto-occipital (left dominant) and frontal lobes	Unilateral (right) occipital PLEDs, slowing of the posterior background rhythm	Crohn's disease on mesalamine treatment (immunomodulator), pulmonary tuberculosis	Convulsive status epilepticus	Valproic acid	Slowing of the posterior background rhythm (time ND)	Good (seizure free)
Kandemir et al. [11]	60	F	Bilateral parieto-occipital lobes	Left dominant bilateral temporo-parieto-occi pital PLEDs, slowing of the posterior background rhythm	Metastatic lung cancer, usage of carboplatin and paclitaxel therapy	Generalized tonic-clonic, focal-nonmotor-sensory	Dexamethasone, phenytoin infusion, levetiracetam	Slowing of the background and PLEDs on both temporo-parieto -occipital regions (17th and 50th days)	Recurring seizures, death secondary to cardiopulmonary arrest due to cancer progression
Silveira et al. [12]	20	F	Bilateral frontal, posterior temporal, and parietooccipital lobes	Unilateral (right) tempo ro-parieto-occipital PLEDs plus fast activity	Acute intermittent porphyria, hypertension	Generalized tonic-clonic	Antihypertensives, lorazepam, levetirasetam, high dose steroids	ND	Good (seizure free)

(*Continued*)

Supplementary Table 1. Clinical summary and characteristics of our patient and previously reported patients with PRES-associated PLEDs (*Continued*)

Patient	Age (years)	Sex	Brain MRI involvement	EEG	Accompanying disorder/Etiology	Seizure type(s)	Treatment (and ASMs)	Follow-up EEG (time)	Outcome
Kamiya-Matsuoka et al. [3]	Adult (detail ND)	ND	Bilateral posterior parieto-occipital lobes, and thalamus	Left dominant bilateral occipital PLEDs	Malignancy (details ND)	ND	ND	Symmetric generalized rhythmic discharges (time ND)	Poor (details ND)
Subramaniam et al. [13]	77	M	Left posterior regions	Unilateral (left) posterior PLEDs	ND	ND	Four ASMs (details ND)	ND	ND
Matsumoto et al. [14]	79	F	Unilateral (left) rectal gyrus, temporo-parietal lobes, insular cortex, and thalamus	Unilateral (left) PLEDs	Epilepsy, chronic phase of subarachnoid hemorrhage	Focal motor	Levetiracetam, general anesthesia, valproic acid, perampanel	Normal (time ND)	Poor, (motor and sensory aphasia and right hemispatial neglect, recurring seizures)
Fisher et al. [15]	40	F	Bilateral parieto-occipital and left frontal (with punctate hemorrhages)	Unilateral (right) occipital and posterior temporal PLEDs, focal occipital electrographic seizures	Liver transplant for alcoholic cirrhosis on prednisone, tacrolimus, and mycophenolate for acute rejection, hypertension	Focal-nonm otor-sensory, focal motor, focal to bilateral tonic-clonic	Antihypertensive, levetiracetam, pregabalin, lacosamide, midazolam, propofol, ketamine, topiramate, clobazam, transcranial direct current stimulation	Interictal temporo-occipital spikes (time ND)	Good (seizure free)
Cordelli et al. [16] (Total six children)	ND	ND	ND	PLEDs (details ND)	ND	ND	ND	ND	ND
Present case	10	F	Left dominant bilateral tempo ro-parieto-occi pital lobes	Left dominant bilateral PLEDs plus fast activity, slowing of the posterior background rhythm	Acute extremity compartment syndrome, hypertension, hyponatremia, hypocalcemia, hypomagnesemia	Focal-nonm otor-sensory, focal motor	Antihypertensive, correction of electrolyte imbalance, levetiracetam, clobazam	Mild unilateral (left) slowing of the posterior background rhythm (6th day)	Good (seizure free)

ASM, antiseizure medication; EEG, electroencephalography; F, female; M, male; MRI, magnetic resonance imaging; ND, not documented; PLEDs, periodic lateralized epileptiform discharges; PRES, posterior reversible encephalopathy syndrome.