Persistent neurophysiological abnormalities in Posterior Reversible Encephalopathy Syndrome: a three-month EEG and VEP follow-up in 5 children with acute lymphoblastic leukemia

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Abstract:

Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a well described complication of cancer chemotherapy.

Case series

We have recently observed PRES in 5 children affected with acute lymphoblastic leukaemia. All children presented with altered mental status; visual disturbances, headache and seizures were other common clinical features. Magnetic resonance imaging showed cortical and subcortical hyperintensities on fluid-attenuated inversion recovery and diffusion weighted sequences, mainly located in the occipital and parietal regions, strongly consistent with PRES. All patients completely recovered from their neurologic deficits in about six days. Electroencephalograms (EEG) were performed at onset and three months after syndrome recovery in all patients. Visual evoked potentials (VEPs) were recorded only three months after syndrome onset. Primary objective of this case series was to determine the potential role of neurophysiological investigations in a three-month follow-up of young patients with PRES.

In our small cohort, acute lymphoblastic leukemia, hypertension and immunosuppressants played a crucial role in pathogenesis of PRES. Clinical and radiological features allowed excluding methotrexate-induced encephalopathy. Despite a complete clinical recovery, we could detect residual neurophysiological abnormalities in four patients. Both EEG and VEP abnormalities were observed in 1 patient; 1 patient had only altered EEG and 2 patients exhibited only altered VEPs. VEP anomalies usually consisted of bilateral increased latencies and durations of main waveforms.

Conclusions

EEG and VEPs proved to be effective to define residual neurological dysfunction in patients with PRES. In view of high incidence of visual disturbances and occipital involvement, we observed that VEPs might show some demyelinating features and could arrange with occipital distribution of radiological findings in patients with history of PRES.

Key words: Posterior Reversible Encephalopathy Syndrome; Acute Lymphoblastic Leukemia; electroencephalography; Visual Evoked Potentials; methotrexate.

1. Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical and neuroradiological entity, often accompanied by high blood pressure.[1] Clinical features include headache, seizures, nausea, vomit, altered consciousness, motor transient deficit, visual impairment which may consist of amaurosis, scotomas, hemianopsia, visual hallucinations, visual neglect or cortical blindness.[2] It's related to several conditions such as chronic and acute renal failure,[3] organ transplantations,[4] pre-eclampsia, tumors,[5] uremic-hemolytic syndrome, immunosuppressant,[6] anticonvulsant and cytostatic therapies. Pediatric cases of PRES are more often related to renal and oncohaematological disorders.[6] Magnetic resonance imaging (MRI) typically shows a transient increased intensity signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences that stays for vasogenic edema generally distributed in parieto-occipital lobe, cerebellum, brainstem and basal ganglia.[7,8] Furthermore, diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps are also necessary, helping to differentiate vasogenic from cytotoxic edema.[9] Severe high blood pressure, liberation of endogenous toxic substances, action of toxic drugs can lead to an autoregulation failure, endothelial dysfunction with cellular damage, alteration of haemato-encephalic barrier and vasogenic edema. Reversibility of this syndrome relies on rapid management of hypertension and removal of triggering factors, avoiding permanent deficits or death. Aim of this study was to describe the diagnostic and prognostic performance of two neurophysiological investigations – Electroencephalogram (EEG) and Visual Evoked Potentials (VEPs) – in 5 young patients with Acute Lymphoblastic Leukemia (ALL) who were diagnosed with PRES.

2. Case series

From December 2011 to February 2012, 5 young patients (3 M, 2 F; mean age 8.6; IQR 7-11 years) with ALL admitted to Pediatric Hematology and Oncology Unit (ARNAS Ospedale Civico, Palermo) received diagnosis of PRES. Clinical evaluation included neurological examination, highest creatinine level, blood pressure and drug regimen. Radiological assessment consisted of 1,5 T MRI, performed at symptoms onset and after three months. According to a previous study by Siebert et al.,[7] lesions distribution (left/right, frontal, parietal, occipital, temporal, striatum, pallidum, brainstem, cerebellum), extent, contrast enhancement, diffusivity (decreased or increased ADC), intraparenchymal or subarachnoid bleeding were analyzed. EEG and pattern

reversal-VEPs were used for neurophysiological assessment. EEG recording was performed within 24 hours of seizure onset and after three months. EEG were recorded using Micromed Matrix with 19 electrodes referring to International 10-20 System. Three months after syndrome recovery, pattern reversal-VEPs were recorded three months after syndrome recovery. VEPs were registered using Micromed Matrix with derivations Fz-Oz, Fz-O1, Fz-O2, input impedance less than 10 KΩ, pass filters 1-100 Hz, sweep 300 msec, sensibility 50 μV; pattern reversal stimulus with black and white checks subtending a visual angle of 15° (20'-40'/40-60% contrast). We considered amplitude, duration and morphology of the main waveform (P100).

Demographic data, predisposing diseases, toxicity associations, laboratory and clinical features, radiological findings are summarized in *table 1*. The most common neurological manifestation was altered alertness, occurring in all patients; seizures, headache and visual disturbances were found in three patients. In patients presenting with seizures, the tonic-clonic subtype was the most frequent. Mean arterial blood pressure at PRES onset was 148/99 mmHg (IQR systolic 143-152, diastolic 90-102). Mean creatinine level was 0,98 mg/dl (IQR 0,41-1,7 mg/dl). In our case series, PRES had a mean duration of 5,6 days (IQR 3-4). After three months, neurological examination was normal in all patients.

Patient No	Age(yr)/Sex	Diagnosis and drug treatment	Clinical symptoms and findings at onset	Clinical findings at discharge and at a three-month follow-up	Highest blood pressure (mmHg) and treatment	Lesions on MRI on the admission	Lesions on MRI after three months	Highest blood creatinine level	Duration of PRES (days)
1	11/M	ALL, renal failure, treatment with cyclosporine and tacrolimus	Lethargy, headache, blurred vision	None	150/104 Treated with enalapril	High-intensity signal in right vermian and paravermian, bilateral parahyppocampal and parasagittal parietal white matter on FLAIR sequences; increased diffusivity on DWI/ADC.	Recovery of high signal lesions	1,9 mg/dl	9
2	9/F	ALL, chemotherapy with daunomycin and VCR, intrathecal chemotherapy with MTX	Dizziness, seizures, headache	None	151/110	Hyperintense lesions in cortico-subcortical fronto-parietal zone and in the occipital region on FLAIR sequences; increased diffusivity on DWI/ADC.	Recovery of high signal lesions	0,42 mg/dl	3
3	7/M	ALL, renal failure, chemotherapy with cyclophosphamide and prednisone, intrathecal chemotherapy with MTX	Altered level of consciousness, headache, visual hallucinations	None	154/91 treated with amlodipine and Nifedipine	Hyperintensities of left periventricular white matter on T2-weighted sequences; increased diffusivity on DWI/ADC.	Mild reduction of high T2-signal in the peritrigonal zone.	1,5 mg/dl	6
4	11/M	ALL, chemotherapy with L-asparaginase and prednisone, intrathecal chemotherapy with MTX	Altered level of consciousness, tonic-clonic seizures, right hemiparesis	None	146/100 treated with nifedipine	High signal areas on T2-weighted in cerebellum, temporo-parieto-occipital, ponto-mesencephalic and left thalamo-capsular region; restricted diffusion on DWI/ADC in right temporal-parietal lobe and thalamus.	Recovery of high signal lesions	0,7 mg/dl	7
5	5/F	ALL, intrathecal chemotherapy with MTX, corticosteroid treatment	Altered level of consciousness, tonic-clonic seizures, status epilepticus, mydriasis	None	140/90 treated with nifedipine	Bilateral altered intensity signal lesions in fronto-parieto-occipital and in the left posterior callosal region on FLAIR sequences; increased diffusivity on DWI/ADC.	Recovery of high signal lesions	0,4 mg/dl	3

Table 1: Clinical and MRI features of our cohort

MRI studies showed consistent findings with PRES. Parieto-occipital distribution was seen in four patients, cerebellar involvement was demonstrated in two patients. None of our patients developed hemorrhage. Vasogenic edema with increased ADC values was observed in four patients and restricted diffusion on DWI was detected in only one patient in right-temporal-parietal region. In a three-month follow-up, persistent white matter hyperintensities were found in only one patient.

At the onset of PRES, EEG showed theta/delta slowing and focal sharp waves in four patients. After three months, persistent EEG anomalies were detected in two patients, consisting of slow

anomalies, especially in the parieto-temporo occipital derivations (*Ref. Table 2*).

Patient No.	EEG recorded during the hospitalization and synopsis of EEG findings	EEG recorded at a three-month follow-up and synopsis of EEG findings
1	Normal	Normal background activity, infrequent sharp waves in posterior derivations Normal
2	Delta slowing and bilateral occipital slow waves Altered	Normal background activity, sporadic spikes in the right derivations, theta rhythm in left derivations Altered
3	Increased theta slowing, focal sharp waves in parieto-occipital derivations Altered	Normal background activity, sharp waves and theta rhythm in temporal derivations Altered
4	Theta slowing, diffuse focal sharp waves Altered	Normal background activity Normal
5	Theta slowing Mildly altered	Normal background activity, infrequent theta rhythm in left derivations Normal

Table 2EEG findings during the hospitalization and three months after syndrome recovery

VEPs were altered in 3 patients who showed mild abnormalities such as increased latency, low amplitude and increased duration (*Ref. Table 3*).

Patients who developed anomalies in EEG or VEP three months after syndrome onset were comprehensively 4: 1 patient showed both EEG and VEP abnormalities, 1 only altered EEG, 2 only altered VEP. Three months after PRES beginning, pattern reversal-VEPs were altered in 3 patients with increase of latency and duration (*Ref. Table 3*). Neurophysiological investigations contributed to establish prognosis in our patients, improvement of such findings helped us to suggest a good prognosis.

Patient No.	VEP (40% contrast)				VEP (60% contrast)				Conclusions
	Latency	Amplitude	Duration	Morphology	Latency	Amplitude	Duration	Morphology	
1	Normal (left>right)	Normal	Normal	W on the left	Normal	Normal	Normal	W on the left	Normal
2	Normal	Normal	Increased on the right	Irregular	Normal	Normal	Increased on the right	Irregular	Abnormal
3	Normal	Normal	Normal	Regular	Normal	Normal	Normal	Regular	Normal
4	Increased bilaterally	Low on O2	Increased bilaterally	Regular	Increased bilaterally	Low on O2	Increased bilaterally	regular	Abnormal
5	Normal	Normal	Normal	Regular	Increased on the	Normal	Normal	Regular	Abnormal

					right				

Table 3: VEP findings referred to main peak P100. VEPs were recorded in a three-month follow-up.

We evaluated symptoms, duration of PRES, blood pressure and brain MRI performed during the hospitalization and neurophysiological findings three months after PRES onset (*Ref. Table 4*). EEG alterations (n=2) couldn't arrange with other clinical or radiological variables. VEP alterations (n=3) matched with an occipital distribution of T2-hyperintensities on first MRI and intrathecal administration of MTX.

Patient No.	Intrathecal Methotrexate	Age (years)	Symptoms at PRES onset	Blood pressure (mmHg) at PRES onset	Follow-up EEG	Three-month VEPs	Duration of PRES (days)	Distribution of lesions on first MRI
1	No	11	Altered level of consciousness, visual disturbance	150/104	Normal	Normal	9	Parietal bilaterally, cerebellum, hippocampus
2	Yes	9	Seizures, short blackouts	151/110	Altered	Altered	3	Frontal, parietal and occipital bilaterally
3	Yes	7	Altered level of consciousness, visual hallucinations	154/91	Altered	Normal	6	Periventricular white matter
4	Yes	11	Tonic-clonic seizures, right hypoesthesia, altered level of consciousness	146/100	Normal	Altered	7	Temporal, parietal, occipital bilaterally, cerebellum, brainstem and thalamus
5	Yes	5	Tonic-clonic seizures, status epilepticus, mydriasis.	140/90	Normal	Altered	3	Frontal, parietal, occipital bilaterally

Table 4: Main clinical and neurophysiological findings in our small cohort

3. Discussion

PRES is a clinical-radiological syndrome related to several diseases and clinical conditions. Although its name, if not adequately treated, it can lead to irreversible damage,[11] even if in the majority of cases, it has a favorable prognosis. Its symptoms can range from headache, visual loss, altered mental status to seizures. Brain imaging allows detecting vasogenic edema in white matter, compatible with the diagnosis of a leukoencephalopathy. Leukoencephalopathy often encompasses posterior regions in a symmetric and bilateral fashion. Lesions tend to localize in watershed regions, often involving the vascular territory between medium and posterior cerebral arteries.[8] In the occipital lobe, calcarin and paramedial areas are often spared, being this feature necessary to differentiate PRES from posterior cerebral artery infarction, generally caused by rostral basilar artery embolism. Brainstem, cerebellum, basal ganglia and frontal lobe involvement has been also described in

typical cases of PRES.[8] Pathophysiology of PRES is still debated but two main theories have been used to elucidate its mechanisms. The former theory is based on the central role of hypertension in provoking loss of cerebral perfusion autoregulation and vasogenic edema predominantly in posterior areas, maybe due to paucity of sympathetic innervation in vertebrobasilar vessels.[12,13] The latter theory was proposed because 20-30% patients suffering with PRES have normal blood pressure[14] and is focused on the role of endothelial dysfunction, driven by several triggers such as immunosuppressants. Immunosuppressants can induce toxic effects on vascular endothelium, release of endothelins and formation of microtrombi.

Several diagnostic criteria have been proposed but clinical judgement is essential for diagnosis of PRES.[15] MRI is the gold standard even if computed tomography may show vasogenic edema. High signal lesions are found on T2-weighted and FLAIR sequences. DWI is mandatory to differentiate PRES (increased diffusivity on ADC maps) from hypoxic-ischemic damage (restricted diffusivity).[16] There is no specific therapy for PRES: treatment of hypertension or discontinuation of toxic drugs are common therapeutic strategies. Mean time to full recovery is usually 2-8 days.[17] Although PRES has been considered a benign condition, some life-threatening complications can occur, including cerebral hemorrage,[18] cerebellar herniation or refractory status epilepticus.[19] Persistent neurological sequelae (hemiparesis, decreased visual acuity, seizures) are reported in 10-20% of patients but are not well characterized.[20] As a matter of fact, recent evidence showed that one negative determinant of PRES recovery is time to causative-factor control.[21]

Our five patients were diagnosed PRES because of clinical features suggesting cortical and posterior involvement (seizures, altered consciousness and visual disturbances) and MRI findings showing edema in pathognomonic regions.

In this case series, ALL, intrathecal therapy with MTX, hypertension and renal impairment were the most important factors concerned with the pathogenesis of PRES. Three of our patients were administered prednisone which contributed to hypertension because of its mineralocorticoid effect. Pediatric PRES is usually associated with lower mean blood pressure values than adults probably because cerebral blood flow autoregulation threshold is lower:[22] according to a German review, mean blood pressure value at pediatric PRES presentation was 140/85 mmHg.[7] In our cohort, mean blood pressure values were comparable to those observed in other pediatric

cohorts. Mean time to full recovery was 5 days in agreement with previous reports.[17]

In 4 of our patients, differential diagnosis consisted of MTX-induced encephalopathy. As already revealed by the Ponte di Legno consortium,[23] acute toxic effects for childhood ALL comprise both methotrexate encephalopathy and PRES although several cases of PRES have been related to MTX. MTX-induced encephalopathy and PRES share some features such as transient symptoms or DWI altered signals on MRI. MTX-encephalopathy is a stroke-like syndrome with a waxing and waning clinical course, occurring within 2 or 3 weeks after MTX administration and resolving within 1 week; white matter changes are usually observed, indicating a leukoencephalopathy.[24] In our cohort, radiological findings standing for vasogenic edema contributed to diagnose PRES. Moreover, although visual disturbances are described in MTX-induced encephalopathy, they're not as common as in PRES.

Main aim of our work was to describe neurophysiological abnormalities and underline the potential role of EEG and VEPs in the follow-up of patients who suffered from PRES. Indeed, neurological examination and neuroimaging tended to normalize in few days. To our knowledge, this is the first work evaluating the role of both EEG and VEPs in PRES follow-up.

With respect to EEG studies, Kastrup et al. (2012)[25] affirmed the role of EEG in classifying the degree of encephalopathy, monitoring epileptic activity and diagnosing status epilepticus. The authors couldn't find a worse prognosis in patients with altered EEG. Nevertheless, in a recent case-report, recurrent seizures were observed despite resolution MRI lesions, showing that EEG could play a guiding role in the follow-up of PRES.[26] In our report, EEG changes consisted of diffuse slowing and focal sharp waves in posterior derivations, maybe due to proneness of immature occipital lobe to injury. According to our data, even if EEG was recorded within 24 hours of seizure onset, epileptic discharges on EEG could have been missed at the onset of PRES. In the present case series, we confirmed that diffuse theta slowing is the most frequent electrographic pattern observed in PRES and that EEG findings don't have any association with MRI findings.[27]

Since the relevance of parieto-occipital involvement in PRES, we used visual evoked responses and recognized increased latencies and durations, indicating demyelination of visual pathways within three months of syndrome onset. Altered responses arranged with a posterior distribution of MRI findings. Despite total recovery of visual disturbance, in three of our patients, a dissociation between VEP anomalies and normal vision was detected. As

we have already seen in one young woman suffering from eclampsia, persistence of VEP anomalies should be considered in patients who developed PRES.[28] However, one limitation of this study is that we could not record VEPs at the onset of symptoms.

Neurophysiological investigations, as our data show, seem to be very sensitive to reveal functional abnormalities even in case of clinical and radiological recovery. Further studies are needed to explore VEPs usefulness in acute setting or in longer follow-up of PRES.

Abbreviations:

PRES: Posterior Reversible Encephalopathy Syndrome; MRI: Magnetic Resonance Imaging; FLAIR: Fluid Attenuated Inversion Recovery; DWI: Diffusion-Weighted Imaging; ADC: Apparent Diffusion Coefficient; EEG: Electroencephalogram; VEP: Visual Evoked Potential; ALL: Acute Lymphoblastic Leukemia; IQR: Interquartile Range; MTX: Methotrexate.

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Conflict of interest:

Nothing to report.

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