CASE REPORT

Posterior Reversible Encephalopathy Syndrome in children/ adolescents with hematologic malignancies: Case reports

Syndrome d'encéphalopathie postérieure réversible chez les enfants/ adolescents atteints d'hémopathies malignes: Cas cliniques

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Abstract

Introduction: Posterior Reversible Encephalopathy Syndrome (PRES) is one of the most common neurological complications in pediatric onco-hematology. Hematologic malignancies and cytotoxic chemotherapy are involved in its pathogenesis. It's a clinical and radiological entity: the diagnosis of PRES is based on both clinical symptoms and neuroimaging data.
Observation: Here we reported a series of four cases of children/ adolescents treated by cytotoxic chemotherapy for hematologic malignancies who developed neurologic disorders and their magnetic resonance imaging findings were in favor of PRES.
Conclusion: In onco-hematology, children/ adolescents who present with new seizures, visual deficits, or other neurologic signs, PRES should be considered as a part of the differential diagnosis as a good outcome relies on rapid management of this complication.

Key words: case report; chemotherapy; children; hematologic diseases; posterior leukoencephalopathy syndrome

Résumé

Introduction: Le syndrome d'encéphalopathie postérieure réversible (PRES) est l'une des complications neurologiques les plus fréquentes en onco-hématologie pédiatrique. Les hémopathies malignes et la chimiothérapie cytotoxique sont impliquées dans sa pathogenèse. Il s'agit d'une entité clinique et radiologique : le diagnostic du PRES repose à la fois sur les symptômes cliniques et sur les données de la neuroimagerie.
Observation: Nous présentions ici une série de quatre cas d'enfants/ adolescents traités par une chimiothérapie cytotoxique pour des hémopathies malignes qui ont développé des troubles neurologiques et leurs résultats d'imagerie par résonance magnétique étaient en faveur du PRES.
Conclusion: En onco-hématologie, les enfants/ adolescents qui présentent de nouvelles convulsions, déficits visuels ou autres signes neurologiques, le PRES doit être évoqué vu qu'une évolution favorable dépend d'une prise en charge rapide de cette complication.

Mots clés: cas clinique ; chimiothérapie ; enfants ; hémopathies ; leucoencéphalopathie postérieure

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Introduction

Posterior reversible encephalopathy syndrome (PRES) is a diagnosis within a group of disorders known as leukoencephalopathies (1). They are characterized by a constellation of symptoms accompanied by specific radiographic findings (1–3). PRES was first characterized by Hinchey and al (4), and it is described as a phenomenon of transient cerebral vasogenic edema occurring preferentially in posterior circulation (4). It is recognized as one of the most common neurological complications in hematology-oncology pediatric patients who are considered as high risk patients (5) . The diagnosis of PRES is usually made based on both clinical symptoms and radiological data in the context of a known precipitating etiologic condition (4,6). According to the literature, it was suspected in cases where a sudden onset of neurological symptoms such as headache, seizures, visual disturbances, or confusion was observed, along with the presence of focal regions of brain vasogenic edema on radiological imaging (7,8). Complete resolution of the symptoms is typically obtained, by combining supportive treatment, along with antihypertensive and antiepileptic therapy. In our paper, we focused on PRES occurring in a specific group of high-risk patients: children/adolescents with hematological disease after receiving chemotherapy. Our Objective was to present four clinical cases of children/ adolescents who developed PRES and to discuss the associated risk factors for PRES occurrence and related outcomes in such patients.

Case reports

Case 1: M.R

An 8-year-old boy with T-cell acute lymphoblastic leukemia (ALL) in relapse was admitted to our service. The patient presented with generalized tonic-clonic seizures and post-critical coma on day 29 of reinduction chemotherapy, after receiving methotrexate (5g/m2) on day 8, cyclophosphamide (1g/m2) on day 9 and vincristine (1.5 mg/m2), daunorubicin (40 mg/m2) and l-asparaginase (10000 UI/m2) on day 29. Upon clinical examination, the child was afebrile and had normal metabolic checkup results. Protein c-reactive was negative, and the patient had a platelet count of 1 G/L [150-450 G/L]. A cerebral computed tomography (CT) scan was performed to rule out cerebral venous thrombosis or cerebral hemorrhage. It showed multiple secondary intracerebral lesions, which were confirmed by brain magnetic resonance imaging (MRI). The patient was diagnosed with PRES and was transferred to the intensive care unit, where he received antiepileptic treatment with clonazepam. A control brain MRI performed one week later showed a marked reduction in brain damage. The patient received a bone marrow transplant from his sister and is currently in remission.

Case 2: A.Y

An 8-year-old boy, diagnosed with nasopharyngeal Burkitt lymphoma stage IV (disseminated disease with extra-nodal invasion), with tumoral involvement of the facial bone and the base of the skull with orbital and maxillary extension, was admitted to the hospital. He presented with revulsion of the eyeballs, followed by a tonic crisis with post-critical coma lasting more than 30 minutes on day 7 of COPADM1 chemotherapy cycle (cyclophosphamide, vincristine, prednisolone, Adriamycin and methotrexate). After the resolution of the crisis, the clinical examination revealed no fever, a Glasgow Coma Scale score of 13/15, weak osteotendinous reflexes, and abolished Achilles reflexes. A cerebral CT scan and a lumbar puncture were performed to rule out meningoencephalitis, however no abnormalities were detected. The electroencephalogram (EEG) showed diffuse slowing with no paroxysmal abnormalities. Brain MRI showed abnormalities in T2 and Fluid Attenuated Inversion Recovery (FLAIR) cortical-subcortical fusito-parieto-occipital bilateral and symmetrical diffuse patches, suggestive of PRES. The patient received antiepileptic treatment with clonazepam and anti-hypertensive treatment with captopril. His lymphoma is currently in complete remission.

Case 3: K.A

A 9-year-old boy with B-cell ALL was admitted during the induction chemotherapy cycle. On day 36, he presented with tonic focal epileptic seizure with deviation of the head and eyes and loss of contact, followed by post-critical confusion. The clinical examination revealed tachycardia at 180 bpm, arterial hypertension at 140/110 mmHg, and desaturation at 80%. The patient received oxygen therapy, captopril, and valproic acid. The complete blood count showed no detectable abnormalities. The cerebral CT scan showed right parasagittal hypodensity without peripheral enhancement nor mass effect. The brain MRI showed ranges in T2, FLAIR hypersignal of white matter predominantly subcortical asymmetric biparietal, suggestive of PRES. The child was in molecular remission following chemotherapy.

Case 4: G.S

A 16-year-old boy, diagnosed with stage IV (disseminated disease with extra-nodal invasion, for example bone marrow or central nervous system invasion) medullary T-cell lymphoblastic lymphoma, presented with right hemiparesis 10 days after receiving his fourth methotrexate dose of 5g/m2. The neurological examination revealed a decrease in muscle strength of the right upper limb and the right lower limb, with conservation of sensitivity, abolished osteotendinous reflexes, and an unsteady gait. The clinical examination did not reveal any other specificities. The brain MRI showed abnormalities of the signal of the bilateral and symmetrical semi-oval center, more marked on the left side, of rounded shape, in hypersignal diffusion, with restriction of the apparent diffusion coefficient, in discreet

hyposignal T1, isosignal T2, without uptake of contrast after injection of gadolinium. Brain lesions suggested PRES. The patient received levetiracetam and foldine. After 15 days, he fully recovered, and cerebral MRI showed the disappearance of previously described abnormalities. However, the patient died two years after PRES from meningeal relapse of his lymphoblastic lymphoma.

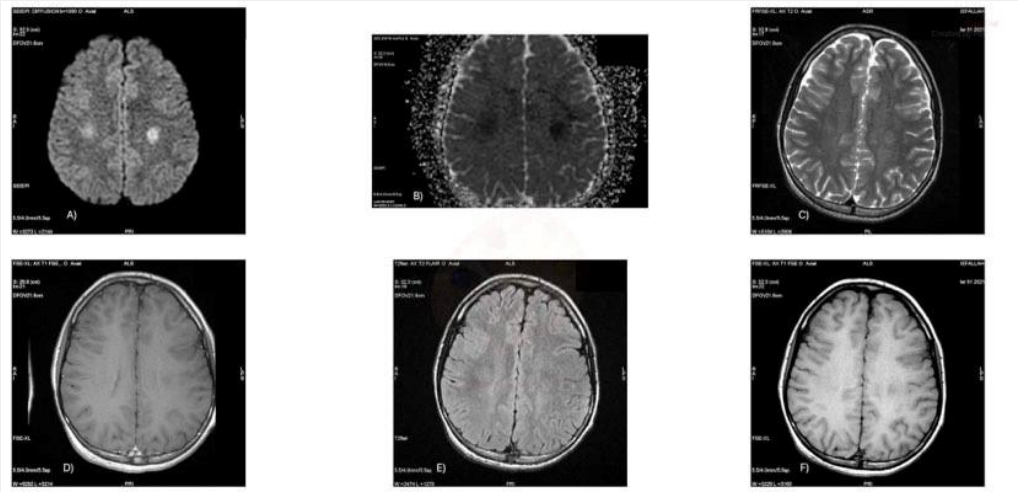

Figure 1. Brain magnetic resonance imaging findings for patient in case 4

(A,B) Rounded shape bilateral and symmetrical lesion in hypersignal diffusion with low ADC1 values

(C,D) Axial Spin. Echo T1 and T2 -weighted show discreet hyposignal on T1, isosignal on T2

(E) Axial FLAIR2 -weighted shows a discreet hypersignal

(F) No enhancement is seen post Gadolinium

[1]Apparent diffusion coefficient

[2]Fluid Attenuated Inversion Recovery

Discussion

Hematologic diseases and their treatments are a major cause of PRES in children (9). While PRES is generally considered a reversible condition, it can lead to long-term neurological sequelae, most commonly epilepsy, or even mortality in some cases (4). The underlying pathophysiology of PRES remains unclear, but two main hypotheses have been proposed. The first hypothesis suggests that cerebral blood perfusion abnormalities result in blood-brain barrier dysfunction and subsequent cerebral vasogenic edema (10). In this theory, severe arterial hypertension disrupts autoregulation, leading to hyperperfusion and endothelial injury/vasogenic edema (11). The second theory proposes that vasoconstriction and hypoperfusion cause brain ischemia, followed by vasogenic edema (6). The hypoperfusion hypothesis may be particularly relevant to cases of PRES associated with cytotoxic therapy (12). Regardless of the underlying mechanism, PRES can result in serious neurological sequelae, including epilepsy, and it can be even fatal (11,12). Among pediatric patients treated for hematologic diseases developing PRES, death, more linked to PRES causes than to PRES itself, happens in 17% of cases (13). Only one of the cases presented resulted in the death of the patient, which occurred 2 years after the development of PRES due to meningeal relapse of the lymphoma.

Some of the chemotherapeutic agents most commonly associated with PRES include methotrexate high dose, cyclophosphamide, vincristine, cisplatin, and interleukin2 (13). Corticosteroids and l-asparaginase have also been implicated in PRES (13), which is the case in our four patients presented above.

PRES typically presents with subacute symptoms such as headache, visual disturbances, confusion, and seizures. Arterial hypertension is commonly observed in patients with PRES, but it is not always present (6). Therefore, clinicians should consider PRES in any patient with hematologic diseases or receiving cytotoxic therapies who presents with neurological symptoms and signs, particularly in the presence of arterial hypertension.

The most frequent clinical presentation is epilepsy. It is not uncommon for patients with PRES to present with status epilepticus, EEG is usually abnormal, as mentioned in the study of Cordelli et al (7). In their series of patients, 10 out of 11 had this presentation.

MRI changes are indeed a hallmark of PRES and are usually present in the early stages of the disease. MRI can show various patterns of abnormalities depending on the stage and severity of the disease, including vasogenic edema, cytotoxic edema, and hemorrhage (7). These changes can involve different regions of the brain, including the parietal and occipital lobes, and can be bilateral and symmetrical or asymmetric (7). MRI can also help differentiate PRES from other neurological conditions that may have similar clinical features. In our paper, MRI changes were evident in all cases .

The management of PRES typically involves supportive care, including treating the underlying cause of the syndrome and implementing antihypertensive and/or antiepileptic therapy (14). Additionally, discontinuation of any medication or treatment that may have contributed to the development of PRES is recommended (10,15). When dealing with pediatric PRES cases, there is often a clinical dilemma regarding whether to halt chemotherapy, especially when it occurs during induction chemotherapy for ALL (8).

In addition, these patients typically receive multiple agents, making it challenging to determine which drug is specifically responsible for causing PRES. Therefore, careful consideration and monitoring of the patient's condition are required to determine the appropriate course of action.

In the management of pediatric PRES, antiepileptic drug therapy is commonly used as secondary seizure prophylaxis (14). Valproic acid and clonazepam are preferred over phenytoin, carbamazepine, and phenobarbital because they do not induce cytochrome P450 (14). Morris et al suggested that patients with PRES should receive 3-12 months of seizure prophylaxis, with longer durations recommended for those with recurrent seizures or EEG abnormalities (12).

In a case report by Fukuyama et al (16), prophylactic measures were recommended for the prevention of PRES in a 6-year-old boy with trisomy 21 and recurrent B-cell ALL. The patient received multiagent systemic and intrathecal chemotherapy for recurrence, and subsequently developed systemic inflammatory response syndrome that was treated with methylprednisolone. The patient then developed PRES, which was manifested by seizures and arterial hypertension with a mean arterial pressure of 125 mmHg (16). Diagnosis was suggested by computed tomography scan, and the patient was treated with nifedipine and enalapril as antihypertensive agents. Based on their experience, the authors recommended PRES prophylaxis with antihypertensive agents, magnesium, and antiepileptic therapy in similar cases (16).

Our paper had some limitations. First, the small number of cases restricts the generalizability of the findings. Larger studies would be needed to confirm these observations and provide more robust data on risk factors and outcomes. Second, while we discussed the two primary hypotheses concerning the pathophysiology of PRES syndrome, we did not provide data to support one hypothesis over the other. To enhance understanding in this field, more detailed mechanistic studies are necessary. Third, our paper did not provide follow-up data on neurological sequelae or quality of life which would enhance understanding of the long-term impact oof PRES. More detailed analysis of the risk factors specific of the reported cases would be beneficial. Finally, the paper could benefit from discussing different preventive and curative strategies that could influence the outcomes.

Conclusion

PRES is a rare condition in the pediatric population, most commonly occurring in the context of ALL during induction chemotherapy cycle. The pathogenesis of PRES involves cerebral dys-autoregulation and endothelial dysfunction, likely due to arterial hypertension and/or direct endothelial cytotoxicity from chemotherapy. Clinicians should consider PRES in the differential diagnosis for any patient with hematologic malignancy or undergoing chemotherapy who presents with neurological symptoms. Diagnosis is established based on clinical and radiographic findings, and treatment involves supportive measures such as antihypertensive and/or antiepileptic therapy. The role of specific chemotherapeutic agents in precipitating PRES is not well-defined, and further research is needed to help guide drug selection and prevent recurrences.

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