

Atypical Manifestations of Posterior Reversible Encephalopathy Syndrome (PRES) Complicating Cytotoxic Chemotherapy during the Treatment of Acute Lymphoblastic Leukemia in a Child

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a rare cause of acute encephalopathy but can be observed in children under chemotherapy. We herein report a case of PRES in a 13-year-old boy with an acute lymphoblastic leukemia following treatment with intrathecal and intravenous chemotherapy. On Magnetic Resonance Imaging (MRI) the thalamic nuclei and cortex involvement accompanied the classical subcortical localization in parietal and occipital lobes. In addition, cytotoxic edema, instead of the vasogenic edema classically occurring in PRES, was observed. Cortical atrophy was seen after regression of other MRI findings. This case shows that PRES with an atypical appearance on MRI should be considered in children in case of acute encephalopathy occurring during chemotherapy treatment.

Keywords: PRES; Restricted diffusion; Chemotherapy

Introduction

Posterior reversible encephalopathy syndrome (PRES) is clinically characterized by headache, confusion, seizure, altered consciousness and visual disturbances with a typical Magnetic Resonance Imaging (MRI) appearance [1]. Diagnosis of PRES is based on both clinical presentation and imaging. On MRI, usual presentation consists of vasogenic edema in the subcortical white matter of the parieto-occipital lobes with relative sparing of the cortex [2,3]. The global incidence of PRES is unknown. According to retrospective studies of cases seen between 1988 and 2008, PRES has been reported in patients aged 4 to 90 years with a significant female predominance [4]. Many patients have comorbidities including severe conditions such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension [4]. We present a case of a 13-year-old boy with PRES due to chemotherapy administration and with atypical involvement of thalamic nuclei and cortex and with presence of cytotoxic edema.

Case Report

A 13-year-old boy with T cell lymphoblastic leukemia was treated with a combination of intrathecal (methotrexate, cytarabine) and intravenous (vincristine, L-asparaginase, daunorubicine, cyclophosphamide) chemotherapy as well as a high dose of corticosteroids. A few hours after the first intrathecal chemotherapy administration, the patient developed abrupt headaches and status epilepticus. The blood pressure was normal. He was treated for his status epilepticus and for his post-dural-puncture headache with intravenous caffeine administration.

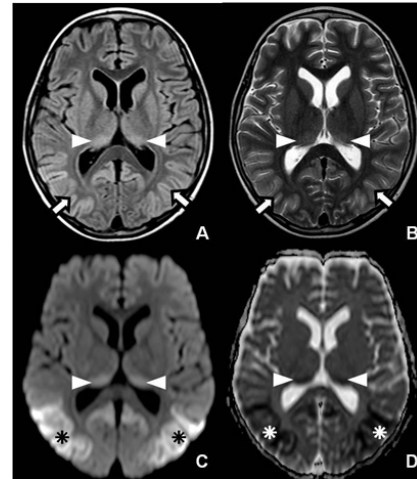


Figure 1: (A-D) Brain MRI performed one day after onset of symptoms detected discrete increased signal on Flair (A) and T2-weighted imaging (B) in the subcortical and cortical regions of the parieto-occipital areas (arrows A,B) and the posterior parts of the thalami (pulvinar) (arrowheads A,B). Diffusion sequences showed more obvious restricted diffusion with high signal on DWI trace (stars, C) and low signal on ADC maps (stars, D) at the corresponding areas due to cytotoxic edema.

MRI demonstrated symmetric and bilateral abnormal high signal intensity on FLAIR (fluid-attenuated inversion recovery) and T2-weighted imaging sequences, located in the parietal and occipital cortex, involving subcortical white matter such as the pulvinar nuclei

and associated with slight gyral swelling and sulcal effacement (Figure 1A and 1B). Diffusion weighted imaging (DWI) showed more obvious high signal on DWI b1000 with low signal on apparent diffusion coefficient (ADC) images typical for diffusion restriction in these locations (Figure 1C and 1D). There was no pathological enhancement after gadolinium injection.

The diagnosis of early PRES was made on the basis of symptoms, clinical history (intrathecal and intravenous chemotherapy) and abnormal findings on MRI. Two weeks later, the follow-up MRI showed loss of grey-white matter differentiation with extension of signal changes into the subcortical and deep white matter and increased gyral swelling and sulcal effacement predominating in the parieto-occipital lobes. Furthermore, some cavitory lesions appeared in the deep white matter, especially in the left parietal region next to the collateral trigone (Figure 2). A follow-up MRI was performed two months later because of the persistence of delirium with transient visual disturbances. The control MRI showed even more extensive signal abnormalities in the parieto-occipital lobes with decreased cortical thickness compared to the acute stage presumably due to a combination of diffuse cortical atrophy with some remaining cortical swelling (Figure 3). The five months follow-up MRI revealed an important regression of signal abnormalities. However, the cortical atrophy was very evident, with a slight increase in the size of lateral ventricles and subarachnoid space (Figure 4).

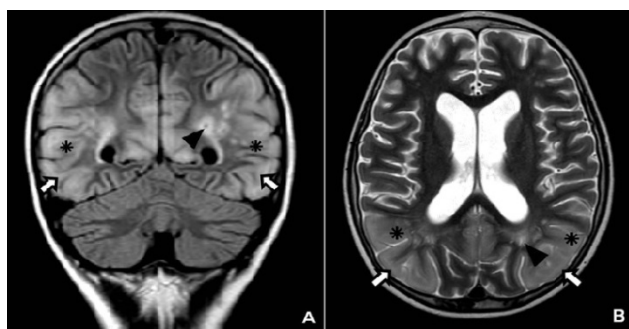


Figure 2: (A, B) Fifteen days later, MRI points out extension of the high signal on Flair (A) and T2-weighted imaging (B) in the subcortical and deep white matter (stars, A, B), increased gyral swelling with sulcal effacement predominating in the parieto-occipital regions with loss of grey-white matter differentiation (arrows A, B) and cavitory lesions in the deep white matter more pronounced in the left parietal region next to the collateral trigone (arrowheads A, B).

Discussion

Posterior reversible encephalopathy syndrome (PRES) is a rare cause of acute encephalopathy in children under chemotherapy including methotrexate administration [5,6]. This condition was first described in adults by Hinckey in 1996, as a syndrome consisting of headache, confusion, seizure and visual disturbance associated with lesions predominating around posterior lobes [1,7]. Hypertension including toxemia of pregnancy is the main condition favoring the appearance of PRES.

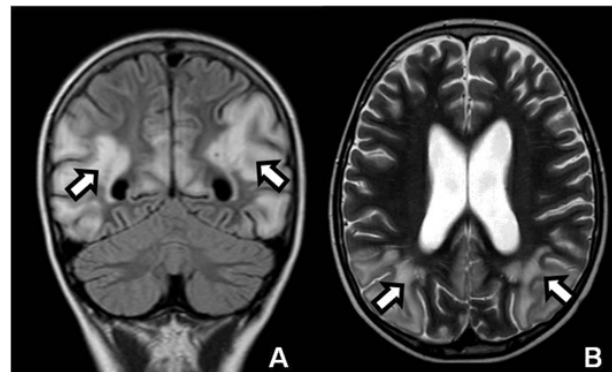


Figure 3: (A, B) Two months later MRI shows further extension of the high signal on Flair sequence (A) and T2-weighted imaging (B) to the deep white matter (arrows A, B).

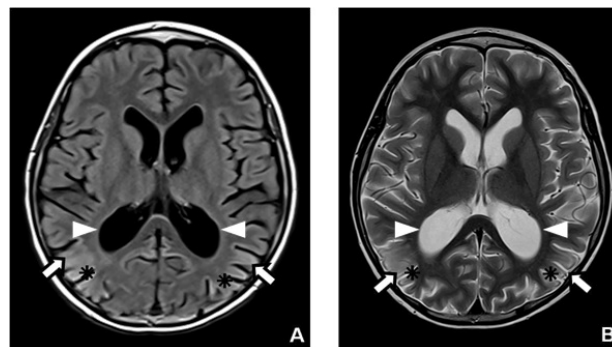


Figure 4: (A, B) Five months later, MRI underlines the persistence of a discrete corticosubcortical high signal on Flair (stars, A) and T2-weighted imaging (star, B), enlargement of the lateral ventricles (arrowheads A, B) with global cortical atrophy and enlargement of subarachnoid spaces, more pronounced in the posterior parietal cortex (arrows A, B).

Other causes could be post transplantation conditions, immunosuppression status, autoimmune diseases like systemic lupus erythematosus, infection, sepsis, shock, metabolic disorders, tumor lysis syndrome and cancer chemotherapy such as cytotoxic agents (cytarabine, vincristine, L-asparaginase and methotrexate), anti-angiogenic agents and immunomodulatory cytokines [2,4,8]. Pathogenesis of PRES is until now not well understood. In children as in adults, neurotoxicity of chemotherapy cytotoxic agents could be related to endothelial damage with release of endothelin, prostacyclin, and thromboxane A [9,10]. The cytokine release results in a sudden increase in systemic blood pressure, which is counterbalanced by sympathetic autoregulatory vasoconstriction. Owing to physiologically lower sympathetic innervation, this process is less efficient in the vertebrobasilar circulation than in the carotid arterial tree, which could explain the posterior brain involvement [9]. Autoregulation breakdown in cerebral circulation leads to cerebral hyperperfusion resulting in disruption of the blood-brain barrier, fluid extravasation into the interstitium and eventually, vasogenic edema [9]. Upon imaging, PRES usually reveals itself as a vasogenic edema involving subcortical white matter of the parieto-occipital lobes bilaterally [2,10].

According to a study of McKinney about 76 patients, the incidence of regions of involvement was parieto-occipital, 98.7%; posterior frontal, 78.9%; temporal, 68.4%; thalamus, 30.3%; cerebellum, 34.2%; brainstem, 18.4%; and basal ganglia, 11.8%. The incidence of atypical manifestations was enhancement, 37.7%; restricted diffusion, 17.3%; hemorrhage, 17.1%; and unilateral variant, 2.6% [11]. In case of chemotherapy including methotrexate administration, areas of restricted diffusion and decreased apparent diffusion coefficient diffusion can be detected indicating cytotoxic edema due to direct cellular derangement. Cytotoxic edema could be explained by the hyperperfusion with vasogenic edema causing mass effect with compression of local microcirculation [12]. Another theory suggests that the cytotoxic edema results in vasoconstriction leading to cytotoxicity [12].

Treatment of leukemia with a combination of chemotherapy cytotoxic agents is reported in the literature as a rare condition at risk of PRES due to neurotoxicity [2,6]. Several conditions may be similar to PRES in children; the ambiguous clinical manifestations and an atypical radiological appearance can confuse PRES with other diagnosis such as myelinolysis, encephalitis and acute disseminated encephalomyelitis (ADEM). In these cases, clinical history and imaging follow-up are used if necessary. However, the final diagnosis in our case was atypical PRES due to treatment by intrathecal and intravenous chemotherapy agents. In our patient, cytotoxic edema with restricted diffusion could be explained by the direct toxic effect on brain parenchyma due to metabolic derangement [13,14]. In PRES, just as in other conditions of brain parenchyma edema, areas with normal or increased diffusion (vasogenic edema) completely reverse, while areas with reduced diffusion (cytotoxic edema) are usually associated with permanent injury such as in our case and may result in cortical atrophy [5,15].

Conclusion

PRES following combination chemotherapy during the treatment of acute lymphoblastic leukemia has previously been reported in few cases. In our case an atypical involvement of thalamic nuclei and cortex with restricted diffusion due to a cytotoxic edema was observed. This case highlights that PRES should be considered in children in cases of extensive and very acute encephalopathy due to neurotoxicity clearly related to chemotherapy arising in children during chemotherapy treatment even when MRI presentation is atypical.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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