

# Incidence of Methotrexate induced Posterior Reversible Encephalopathy Syndrome in Pediatric Cancer Patients; A Case Series from a Tertiary Care Hospital, Pakistan

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## Abstract

**Background:** Posterior reversible encephalopathy syndrome has been attributed to be a major neurological manifestation of intrathecal methotrexate. Here, we present three cases of this syndrome after intrathecal methotrexate, one was male and two were females. All the patients were undergoing treatment for active acute lymphoblastic leukemia.

**Case reports:** Case-1, a five-year-old male, with isolated CNS relapse of pre-B ALL, was administered IT-MTX as part of chemotherapy protocol. Symptoms appeared for which magnetic resonance imaging was done, which was suggestive of PRES. Patient was found hypocalcemic and was managed conservatively. Case-2, an eight-year-old female with pre-B-ALL, developed symptoms after IT-MTX. All the labs were within normal limits so she was also managed conservatively. Case-3, a five-year-old female developed PRES 14 days after administration of IT-MTX. Only hypokalemia was found in laboratory investigations, and was also managed conservatively.

**Discussion:** Although MTX-induced PRES is well documented and may hinder the standard chemotherapy plan, but in all of our patients recovery was uneventful and they were continued with recommended therapeutic plans.

**Conclusions:** Pediatric patients with ALL after IT-MTX are at risk of developing PRES. Symptoms may get resolve by conservative management without discontinuation or delay in chemotherapeutic treatment.

**Keywords:** Methotrexate; Posterior reversible encephalopathy syndrome; Central nervous system; Acute lymphoblastic leukemia; Intrathecal

## Introduction

Central nervous system (CNS) is often recognized as a sanctuary for tumor cells in patients with lymph reticular malignancies. The addition of Methotrexate (MTX) to the leukemia treatment protocols has been found to be associated with an increased survival rate in children with acute lymphoblastic leukemia (ALL). Among the most frequent neurological manifestations of MTX toxicity, posterior reversible encephalopathy syndrome (PRES) is an acute neurological deterioration characterized by transient focal neurologic deficits beginning within 2 weeks of MTX administration [1]. This neurotoxicity makes the treatment options with chemotherapy for such lymphoma patients challenging. Evaluation of these patients usually reveals normal head computerized tomography (CT) scans and cerebrospinal fluid, while on magnetic resonance imaging (MRI), the hallmark of leukoencephalopathy (LEP) is hyper-intensities on T2-weighted imaging, and electroencephalogram (EEG) shows generalized slowing [2]. Although PRES is usually reversible and most patients recover fully with resolution of the imaging findings, but some suffer recurrences during subsequent courses of MTX or it may result in permanent damage [3,4]. We describe here the incidence and management of intrathecal (IT)-MTX induced PRES in three pediatric patients with cancer.

## Case Series

### Case 1

The patient, five-year-old male with the diagnosis of isolated CNS relapse of pre-B ALL, developed fits, floppiness and hypertonia, three days after receiving IT-MTX, 12 mg, as a part of O2P2 regimen. No such complaints were made during previous cycles. MRI was done and he was diagnosed with PRES after observing suggestive changes on MRI scan. Serum electrolytes were normal except hypocalcaemia. Renal and liver function tests were also within normal limits. Patient was

managed symptomatically with intravenous phenytoin, 30 mg three times a day (TID) and levetiracetam, 150 mg two times a day (BID) and his symptoms improved.

### Case 2

Eight-year-old female patient with isolated bone marrow relapse of pre-B ALL developed PRES, 10 days after receiving IT-MTX, 12.5 mg as a part of R2 regimen. She presented with history of fits. No previous cycles were reported with such complaints. PRES was confirmed on MRI. Serum electrolytes, renal function tests and liver function tests were within normal limits. Again, the patient was managed conservatively, and symptomatic treatment was done with intravenous phenytoin 30 mg TID and levetiracetam 200 mg BID.

### Case 3

This case refers to a five-year-old girl diagnosed with pre-B ALL. Her treatment was started and she developed PRES 14 days after administration of IT-MTX, 12 mg as part of Regimen A of United Kingdom Acute Lymphoblastic Leukemia (UKALL). She too presented with fits. Again, there was no history of any such complaints during previous cycles. PRES was confirmed after noticing suggestive changes on MRI. Serum electrolytes were normal except hypokalemia. Renal and liver function tests were also normal. This patient was also managed symptomatically and she started recovering.

### Discussion

MTX is a part of many chemotherapy protocols purposive to treat malignancies in pediatric patients and is beneficial for preventing CNS relapse. In our setting, patients with ALL in early and late stage relapse are treated with a set of chemotherapy protocols containing different doses of MTX as shown in Table 1.

However, the drug also has a significant toxic effect on the CNS, when given in IT or high IV doses and can potentially lead to severe neurologic morbidity. This toxic effect can either

appear acutely, or as a late complication in the form of long-lasting, progressive neurological and cognitive deterioration. The overall incidence of acute MTX neurotoxicity may vary, depending on the dose of MTX in the treatment protocol [5]. PRES, being the commonest acute neurotoxicity, is characterized by headache, vomiting, seizures, confusion, visual disturbances, ataxia, encephalopathy and other neurological abnormalities.

Causes of PRES other than MTX, include malignant hypertension (including pre-eclampsia or eclampsia), intense uremia, drugs involved in immunosuppression and cancer chemotherapies such as cyclosporine, L-asparaginase, gemcitabine, vincristine, cytarabine, cisplatin and tacrolimus, usually used in cases of hematopoietic malignancies [6-8]. There are multiple risk factors for MTX-induced neurotoxicity, including intrathecal route, high dosages, young age, multiple neurotoxic agents and concomitant cranial radiotherapy [9].

Several mechanisms have been proposed for MTX induced neurotoxicity. These include increased accumulation of adenosine, elevated homocysteine levels with its excitatory effects on the N-methyl-D-aspartate (NMDA) receptors, and alterations of biopterin metabolism [7,10].

Differential for MTX toxicity is made on the basis of brain imaging and is associated with damage to the CNS white matter, called LEP. The hallmark of LEP is hyper-intensities on T2-weighted MRI. In MTX induced LEP, these T2 hyper-intensities are primarily located in peri-ventricular white matter, particularly in the centrum semiovale [11]. On diffusion-weighted magnetic resonance imaging (DWI), there is increased signal intensity along with hypo intensity on apparent diffusion coefficient (ADC) map, indicative of cytotoxic edema [12]. Despite such changes, patients often recover spontaneously from MTX induced encephalopathy indicating that this event is not necessarily irreversible.

In all of our cases, IT-MTX was administered to the patients and each case developed PRES on different days. Every patient experienced seizures as a clinical indication for PRES and a definitive diagnosis was made after getting MRIs. Although there is a limited data supporting the use of different treatment regimens for MTX induced neurotoxicity like aminophylline [13,14], adenosine antagonist, leucovorin, NMDA receptors antagonists, anti-inflammatory agents and dextromethorphan [15], but in all of our patients symptoms were managed conservatively. For the treatment of seizures like activity, anti-epileptic drugs were recommended. Hypocalcemia in the first case and hypokalemia in the third case were treated with the electrolyte replacement. All the patients had complete resolution of the symptoms and were continued with their treatment plans.

To the best of our knowledge, this case series will serve as the first source of local data to investigate further and to adopt suitable measures accordingly, in the best of patients' interest.

**Table 1:** Types of ALL and regimens containing MTX.

| Diagnosis                | Regimen  | Phase / Cycle   |
|--------------------------|--|---|
| ALL                      | <ul style="list-style-type: none"> <li>UKALL 2011 Regimen A</li> <li>UKALL 2011 Regimen B</li> <li>UKALL 2011 Regimen C</li> </ul> | <ul style="list-style-type: none"> <li>Induction</li> <li>Consolidation</li> <li>Delayed Intensification</li> <li>Interim Maintenance</li> <li>Maintenance</li> </ul> |
| ALL Isolated CNS Relapse | <ul style="list-style-type: none"> <li>AALL02P2- COG</li> </ul>  | <ul style="list-style-type: none"> <li>Induction</li> <li>Intensification I</li> <li>Intensification II</li> <li>Maintenance</li> </ul>                               |
| ALL Relapse              | <ul style="list-style-type: none"> <li>R-II protocol</li> </ul>  | <ul style="list-style-type: none"> <li>Induction</li> <li>Consolidation</li> <li>Continuation Cycle</li> </ul>  |

## Conclusions

IT-MTX may cause PRES in pediatric patients undergoing treatment for ALL, which impedes the progress towards scheduled chemotherapeutic plan. But patients may get improved clinical status with conservative treatment, without the need for discontinuation of chemotherapy.

## Disclaimer

The abstract or any part of this manuscript has not been published or presented previously in any conference. Written informed consents have been taken from the patients' guardians.

## Conflict of Interest

There are no financial, professional or personal interests linked with this manuscript.

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