

Methotrexate-associated neurotoxicity in children with cancer: case series and literature review

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ABSTRACT

Methotrexate (MTX)-associated neurotoxicity is a reported adverse event in pediatric oncology. We report 4 cases of neurological damage during MTX treatment (1 patient with lymphoma, 3 patients with acute leukemia) who were successfully treated with aminophylline. The time to onset of neurological symptoms after intrathecal MTX injection ranged from 7 to 124 days (mean 60 days). The initial symptoms in all patients were focal seizures, which progressed to status epilepticus and neurological deficits (impaired consciousness, motor paralysis). All patients had normal cerebrospinal fluid results; 3 patients had cortical and subcortical lesions on brain magnetic resonance imaging. All patients were treated with aminophylline combined with dextromethorphan, and all four had a reduction in seizures or became seizure-free within 24 hours of drug use, and neurological deficits (motor paralysis, decreased consciousness, vision) were restored. No adverse events were recorded during treatment. Neurotoxicity associated with MTX is a diagnosis that should be considered in children treated with MTX with new-onset neurological symptoms. Treatment with aminophylline and dextromethorphan is effective, especially when used early before brain lesions are detected on magnetic resonance imaging.

Keywords: Methotrexate, neurotoxicity syndromes, seizure, pediatric.

1. INTRODUCTION

Methotrexate (MTX) is an antimetabolite and folic acid antagonist that is widely used as a chemotherapeutic agent and as an immunosuppressive drug for autoimmune diseases. However, MTX administration may cause a range of adverse effects, even at low doses. The incidence of these adverse effects increases with high-dose MTX ($\geq 500 \text{ mg/m}^2$), which is commonly administered to patients with acute lymphoblastic leukemia, central nervous system lymphoma, leptomeningeal metastases, and malignant bone tumors.¹

Acute/subacute MTX-induced neurotoxicity is defined as the occurrence of neurological symptoms (seizures, motor deficits, language impairment, visual disturbances, altered consciousness, and behavioral changes) within 2 weeks after MTX administration (intrathecal or intravenous), after other potential causes have been excluded.² The incidence is reported to be as high as 3 - 7% among children with acute lymphoblastic leukemia treated with MTX.³ MTX can cause acute, subacute, and chronic neurotoxicity.⁴ Acute and subacute encephalopathy associated with high-dose intravenous MTX is generally transient and resolves within 1 - 7 days after symptom onset. Transient acute encephalopathy occurs in approximately 3 - 15% of patients with cancer receiving high-dose intravenous MTX.⁴ In contrast, chronic encephalopathy has a more insidious course and often results in permanent neurological deficits. The mechanisms underlying MTX-induced neurotoxicity may involve disruption of central nervous system folate homeostasis and/or direct neuronal injury.⁵ The optimal management of MTX-associated encephalopathy remains controversial. Based on its proposed pathophysiological mechanisms, potential antidotal therapies include leucovorin, aminophylline, and dextromethorphan.⁶ Although several reports have demonstrated that MTX can be safely reintroduced in many patients, recurrent neurotoxicity has nevertheless been reported in 10 - 56% of patients following MTX rechallenge.⁴

Recently, the Neurology Center at the Vietnam National Children's Hospital has encountered a series of pediatric patients presenting with seizures following MTX treatment. We report

a case series of four patients diagnosed with MTX-associated brain injury, all of whom were successfully treated with aminophylline and dextromethorphan.

II. CASE PRESENTATIONS

From December 2024 to July 2025, we identified four pediatric patients with malignancies who developed seizures while receiving chemotherapy. One patient had Burkitt lymphoma, while three had acute leukemia (two patients with B-cell acute lymphoblastic leukemia [B-ALL], L2 subtype, and one with T-cell acute lymphoblastic leukemia [T-ALL]). All patients had a history of protocol-based intrathecal methotrexate (MTX) administration. The interval between intrathecal MTX administration and the onset of neurological symptoms ranged from 7 to 124 days (mean, 60 days). The initial neurological manifestation in all patients was focal myoclonic seizures, with episodes lasting from several seconds to one minute and occurring during both wakefulness and sleep. The seizures were less intense during sleep, and consciousness was preserved throughout the episodes. On admission, all patients were alert with a Glasgow Coma Scale score of 15 and had frequent, difficult-to-control seizures. None had focal neurological deficits, signs of raised intracranial pressure, or meningeal signs. Three of the four patients were afebrile, whereas one patient had febrile neutropenia. Subsequently, all patients progressed to focal status epilepticus, accompanied by deterioration in neurological function, including impaired consciousness, motor deficits, and language impairment. The clinical manifestations are described in detail in Table 1.

Table 1. Clinical characteristics

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age (years), sex	17, male	15, male	16, female	8, female

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Diagnosis	ALL-L2	BL	R/R T-ALL	ALL-L2
Treatment phase	Maintenance FRALLE 2000 T2	FAB LMB 96	FRALL	CCG1991
Interval from the last IT-MTX to neurological symptom onset (days)	7	124 Finish treatment for 1 month	62	50, oral MTX 6 tablets/ week
Clinical manifestations	Myoclonus left hand, left hemiparesis	Myoclonus right eye and right hand, difficulty speaking; altered consciousness.	Numbness, weakness in right hand, difficulty speaking, twitching right eye, headache, nausea, blurred vision	Myoclonus right hand and left leg, weakness in right hand, febrile neutropenia

R/R T-ALL: Relapsed/refractory T-cell acute lymphoblastic leukemia; ALL-L2: Acute Lymphoblastic Leukemia, B cell type, precursor cell, L2; BL: Burkitt lymphoma; IT-MTX: intrathecal MTX.

All patients underwent brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and video electroencephalography (EEG), as well as routine laboratory investigations, including a complete blood count, serum electrolytes, and liver and renal function tests, to exclude other potential causes of seizures (Table 2). Brain MRI revealed abnormalities in three of the four patients, predominantly consisting of bilateral symmetric cortical-subcortical lesions, most commonly involving the parietal and occipital lobes; one patient had a normal brain MRI. The lesions were hyperintense on T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) sequences, hypointense on T1-weighted images, and showed no contrast enhancement, findings suggestive of an inflammatory process and arguing against metastatic lesions (Figure 1). CSF analysis was normal in all patients, with normal cell counts, protein, and glucose levels. At admission, video EEG performed during seizures showed a normal background activity without ictal epileptiform discharges. Subsequently, as the patients progressed

to status epilepticus, EEG demonstrated epileptiform discharges, including sharp waves and sharp-and-slow-wave complexes, corresponding to the clinical seizures in one of the four patients.

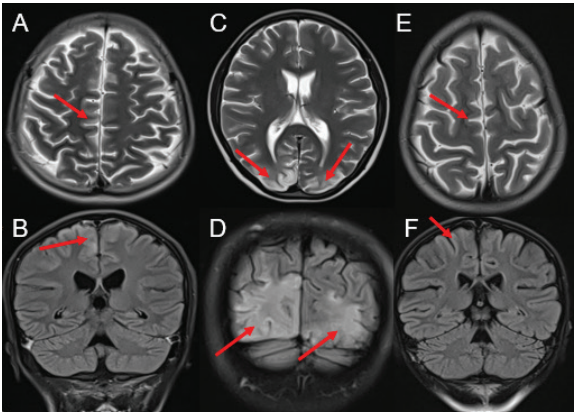


Figure 1. Magnetic resonance imaging (MRI) characteristics of the brain on T2W-Flair sequences

Figure A,B - Patient 1: Bilateral parietal cortical lesions, right-predominant; Figure C,D - Patient 3: Bilateral occipital cortical and subcortical lesions; Figure E,F - Patient 4: Bilateral parietal cortical lesions, diffuse cerebral atrophy.

All patients received oral antiseizure medications and continued intravenous therapy for seizure control; however, seizures remained refractory to treatment and progressed to status epilepticus. After excluding other potential

causes of seizures, including metastatic disease and central nervous system infections, MTX-associated neurotoxicity was considered the most likely diagnosis. All four patients were treated with aminophylline at a dose of 2 mg/kg administered intravenously over 30 minutes, followed by a continuous intravenous infusion at 0.5 mg/kg/h for 24 hours, in combination with dextromethorphan at 1 - 3 mg/kg/day. Treatment outcomes were assessed within 48 hours after drug

administration. All four patients showed a reduction in seizure frequency or complete seizure cessation within 24 hours of treatment, followed by gradual recovery of neurological deficits, including motor impairment, impaired consciousness, and visual impairment. Throughout treatment, patients were continuously monitored for level of consciousness, respiratory rate, pulse, blood pressure, and heart rate; no adverse effects were observed.

Table 2. Investigation findings and treatment

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
MRI at the peak of the disease course	Bilateral parietal cortical lesions	Normal	Bilateral occipital cortical and subcortical lesions	Bilateral parietal cortical lesions, diffuse cerebral atrophy.
Video EEG at admission	Background activity was slower than expected for age, with left hemispheric epileptiform discharges then generalized to both hemispheres in ictal EEG	No ictal epileptiform discharges	No ictal epileptiform discharges	No ictal epileptiform discharges
CSF	Normal	Normal	Normal	Normal
Treatment	ADEs (VPA, LEV, CZP, LTG) IVMP Aminophylline	ADEs (LEV, OXC, CZP, PB) Aminophylline	ADEs (LEV) IVMP Aminophylline	ADEs (TPM, CZP) Aminophylline
Time from onset to use Aminophylline (day)	Day 31	Day 25	Day 13	Day 14
Response to treatment	Seizure-free after 9 hours of treatment with Aminophylline	Seizure-free after 24 hours of treatment with Aminophylline	Seizure-free after 24 hours of treatment with Aminophylline	Decreased seizure, myoclonus in right hand persists

MRI: Magnetic resonance imaging;
CSF: cerebrospinal fluid; EEG: video electroencephalography; ADEs: Antiepileptic Drugs; VPA: Valproic acid; LEV: Levetiracetam; OXC: oxcarbazepine; TPM: Topiramate; PB: Phenobarbital; CZP: clonazepam; LTG: lamotrigine; IVMP: Intravenous methylprednisolone; IVIG: Intravenous immunoglobulin.

III. DISCUSSION

Seizures are a neurological complication that may occur in patients with cancer, with a reported incidence of approximately 13%, accounting for 5% of all neurological complications. They are more frequently observed in children with acute leukemia, lymphoma, neuroblastoma, and sarcomas.⁷ Several conditions may cause

seizures in patients undergoing cancer treatment, including brain or leptomeningeal metastases, central nervous system infections, adverse effects of chemotherapy, paraneoplastic neurological syndromes, cerebrovascular lesions, and electrolyte disturbances. Although chemotherapy-induced brain injury is uncommon, it should be considered because early, targeted treatment can result in favorable outcomes. Chemotherapeutic and immunomodulatory agents associated with neurotoxicity include methotrexate (MTX), cisplatin, busulfan, chlorambucil, 5-fluorouracil, interferon-alpha, and cyclosporine A. All patients in our series developed new-onset seizures following treatment for their underlying malignancy. After excluding metastatic lesions and central nervous system infections, and following a detailed review of the treatment history and clinical course of the refractory seizures, we noted that all patients had received MTX as part of their treatment protocols, strongly suggesting MTX-associated neurotoxicity as the underlying cause.

MTX is a competitive inhibitor of the enzyme dihydrofolate reductase and is widely used in the treatment of lymphomas, acute leukemias, and medulloblastoma. MTX-induced toxicity is thought to involve multiple mechanisms, including: (1) direct toxicity to astrocytes, axonal loss, and demyelination; and (2) alterations in central nervous system biochemistry that disrupt neurotransmission. Inhibition of dihydrofolate reductase activity interferes with DNA and RNA synthesis, alters methionine and homocysteine concentrations, increases excitatory sulfur-containing amino acids, increases adenosine levels, and decreases tetrahydrobiopterin concentrations. MTX can be administered intrathecally, orally, intramuscularly, or

intravenously. Intravenous doses of ≥ 500 mg/m² are considered high-dose MTX and are commonly used in the treatment of acute lymphoblastic leukemia and lymphoma.⁷ The reported incidence of MTX-induced neurotoxicity ranges from 3% to 15%, with acute, subacute, and chronic forms described.^{4,8} The incidence varies according to the route of administration, with rates of 4.73% following intrathecal administration, 21.43% following intravenous administration, and 10% following combined intrathecal and intravenous administration.⁹ MTX-induced neurotoxicity may manifest as seizures, neurological deficits, and diffuse brain injury and is often associated with cumulative MTX exposure, typically occurring 5 - 14 days after high-dose MTX administration. Most patients with acute-onset toxicity present with stroke-like episodes or posterior reversible encephalopathy syndrome and recover well within 1 week following treatment with leucovorin.⁴ Less common manifestations, including spinal cord injury and polyradiculopathy, have also been reported in association with MTX.⁹ Delayed-onset cases occurring several months to years after MTX exposure are often associated with severe and permanent neurological sequelae.⁶ In our case series, the interval between intrathecal MTX administration and the onset of neurological symptoms ranged from 7 to 124 days (mean, 60 days), which was longer than that reported by Natnasak et al., who observed an interval of 1-46 days (mean, 10 days).⁹

Brain MRI plays an important role in the diagnosis and prognostic assessment of patients with MTX-associated neurotoxicity. In a 2024 study by Natnasak et al., the most common sites of brain involvement were the subcortical and deep white matter (54.55%), centrum semiovale (40.91%), and periventricular white matter

(36.36%). The corpus callosum, cerebellum, and brainstem were involved in 13.64%, 13.64%, and 9.09% of patients, respectively. Cortical atrophy was detected in 55.56% (10/18) of children but was not observed in adults.⁹ In our case series, three patients had bilateral symmetric cortical-subcortical lesions, with more extensive abnormalities observed in patients who received treatment later in the disease course. This difference may be attributable to the timing of MRI acquisition, as patients imaged later may have more extensive lesions than those imaged during the early stages following symptom onset. Notably, patient 2 had no abnormalities on brain MRI and demonstrated a more favorable long-term neurological outcome than the other patients.

There is no established specific treatment for MTX-induced neurotoxicity. Several therapeutic options, including leucovorin, dextromethorphan, and aminophylline, have been investigated, but conclusive evidence supporting their efficacy remains lacking. Corticosteroids may be used to reduce vasogenic edema. Leucovorin is commonly administered in cases of acute neurotoxicity occurring during or within 24 - 48 hours after MTX administration. Based on the proposed pathophysiology of MTX-induced neurotoxicity, studies measuring adenosine concentrations in the cerebrospinal fluid have demonstrated elevated adenosine levels, which may induce cerebral vasodilation and consequently contribute to cerebral ischemia.¹⁰ Aminophylline is thought to exert its therapeutic effect through competitive antagonism of adenosine, whereas dextromethorphan acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, thereby inhibiting homocysteine-mediated excitotoxicity. Accordingly, several studies have reported the efficacy and safety of

aminophylline in the treatment of MTX-induced neurotoxicity.¹⁰ Given the subacute-to-chronic onset of neurological symptoms in our patients, we selected aminophylline in combination with dextromethorphan. All four patients demonstrated a therapeutic response, ranging from partial reduction to complete cessation of seizures within 48 hours of treatment, with no adverse effects observed.

The reported risk of recurrent neurotoxicity with continued MTX treatment ranges from 0% to 24%.¹¹ In some cases, MTX was successfully continued in combination with leucovorin administered 24-30 hours after intrathecal MTX and 30 or 36 hours after intravenous MTX, with no recurrence of neurotoxicity.^{2,12} The authors recommend that permanent discontinuation of MTX is not necessary after an episode of neurotoxicity has stabilized; however, subsequent MTX treatment should be deferred until complete neurological recovery.² In our case series, two patients completed their treatment according to protocol, while the other two patients died from severe measles-related complications. Therefore, the risk of recurrent neurotoxicity following MTX rechallenge could not be assessed.

IV. CONCLUSION

MTX-associated neurotoxicity should be considered in children receiving MTX who develop neurological symptoms after other potential causes have been excluded. Treatment with aminophylline and dextromethorphan appears to be effective, particularly when initiated early, before structural brain abnormalities become evident on neuroimaging.

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