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Original Article

Neurological Complications of Intrathecal Methotrexate in Children: A Prospective Study

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Abstract

Objective: To determine the neurological complications of Intrathecal Methotrexate (MTX) in pediatric patients receiving treatment for childhood malignancy in a tertiary care hospital of Islamabad, Pakistan.

Methodology: This prospective observational study was conducted at the Pediatric Oncology Department of the Children's Hospital, Pakistan Institute of Medical Sciences (PIMS) Islamabad from January to December 2024. During the study period, 96 patients aged 1–13 years received 796 intrathecal (IT) MTX administrations under aseptic conditions. We recorded both minor and major neurological complications occurring within 3 days following administration of IT MTX. The minor complications were defined as headaches, dizziness, or mild sensory disturbances, while major complications comprised serious neurological effects such as seizures, paralysis, or profound cognitive impairments.

Results: The mean age of patient was 5.37 years, with 56.3% aged 3–5 years and 68.8% being male. Acute Lymphoblastic Lymphoma (ALL) was the primary diagnosis in 91.7% of patients, with 61.5% receiving a 12 mg dose of IT MTX. Neurological side effects were reported in 28.9% (n=231) of IT MTX administrations. No major neurological complications such as seizures or paralysis were observed. Minor side effects included fever (5.0%), nausea (4.5%), vomiting (4.1%), and dizziness (3.8%). Most symptoms manifested within 24 hours and were treated within 7 days.

Conclusion: While our study reported no major toxic neurological events but only minor neurological effects developed after administration of chemotherapy. IT MTX plays an important role in pediatric oncology, but its neurotoxic potential requires close monitoring and management especially in children receiving IT chemotherapy for therapeutic or prophylactic purposes.

Keywords: Methotrexate, Intrathecal, pediatric oncology, drug-related side effects and adverse reactions, Islamabad, Pakistan.

Introduction

Methotrexate (MTX) is a critical antimetabolite drug in treating various pediatric diseases, including acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), brain tumors, osteosarcoma, inflammatory myofibroblastic tumor (IMT), juvenile scleroderma (JS), and juvenile idiopathic arthritis (JIA). MTX acts as a folate antagonist by inhibiting dihydrofolate reductase (DHFR), an enzyme essential for the synthesis of tetrahydrofolate. This disruption impairs DNA synthesis, repair, and cellular replication, particularly affecting rapidly dividing cells. Despite its efficacy, MTX resistance poses significant challenges, particularly in pediatric oncology, where it undermines the ability to achieve sustained therapeutic effects, resulting in reduced therapeutic efficacy and poor prognosis.[1]

MTX is used as a chemotherapeutic agent via different routes whether intravenous, oral or Intrathecal. It is commonly used via Intrathecal route for Central Nervous System (CNS) prophylaxis in ALL and Non-Hodgkin's Lymphoma (NHL). Initially, cranial irradiation was done for prophylaxis and treatment of CNS leukemia. However, radiation was associated with secondary cancers, growth retardation, and developmental delay. [2] Presently, MTX alone, as well as with other drugs like hydrocortisone and cytarabine is used to prevent and treat CNS leukemia and lymphoma. However, MTX can cause significant acute and long-term neurotoxicity in children undergoing chemotherapy.[3]

The clinical presentation of MTX-induced neurotoxicity includes altered mental status, seizures, and stroke-like symptoms. But patients may also present with mild symptoms like headache, backache, sleep disturbances etc.[4] MTX related neurotoxicity occurs in approximately in 3-7% of patients treated for ALL. Sub-acute neurotoxicity that occurs after 5-14 days of IT or intravenous (IV) MTX administration has been reported in 3−15% of cases.[5] The pathophysiology MTX-induced neurotoxicity is multifactorial. Long term deficits occur through induction of oxidative stress, immune system modulation, inhibition of neurogenesis and altered neurotransmission through the N-methyl-D-aspartate (NMDA) receptor.[6] Some studies also indicated that the neurotoxicity is due to increased adenosine concentration in the

cerebrospinal fluid. This further leads to cerebral vasodilatation that slows neurotransmitter release at presynaptic junction and thus alters the neuronal discharge.[7,8]

MTX is an effective mode of treatment in children for different cancers but it also carries potential side effects. The side effects may include headache, vomiting, nausea, back pain, allergic reaction, fever, fits, decrease in appetite and sleep disturbance. Some major adverse effects that may occur are weakness or paralysis of limbs, spinal fluid leakage, paresthesia, numbness and intra cranial hemorrhage.[9] There are certain long-term manifestations of the treatment as well, comprising of difficulty in neuro-cognitive function and working memory. Cases of cancer survivors developing leukoencephalopathy, transient ischemic attacks and altered mental status have also been reported.[10]

Despite the clear global evidence of MTX-related neurotoxicity, there is a critical gap in localized data, especially from Pakistan, where variations in patient genetics, treatment practices, nutritional status, and access to healthcare services may influence the occurrence and severity of neurological adverse effects. The scarcity of data on the neurological complications following IT MTX use in pediatric patients limits the ability of healthcare providers to anticipate, monitor, and manage these effects efficiently. Conducting a study on the neurological adverse effects of IT MTX is crucial to determine the severity, magnitude, and impact of these complications on pediatric cancer survivors, ultimately informing strategies for early detection, prevention, and management to improve treatment outcomes. This study aims to determine the adverse neurological effects of IT MTX in the pediatric population at a tertiary care hospital in Islamabad, Pakistan.

Methodology

This prospective observational study was conducted at the Pediatric Oncology Department of the Children's Hospital, Pakistan Institute of Medical Sciences (PIMS), a renowned tertiary care hospital in Islamabad, Pakistan, from January to December 2024. This study was approved by the Institutional Ethical Review Board of PIMS prior to its initiation (Ref: F.1-1/2025/ERB/SZAMBU/826), and included all children aged 1-13 years who received IT MTX for therapeutic or prophylactic purposes under standardized treatment guidelines such as the Pakistan Society of Pediatric Oncology (PSPO)-2018 and Children Cancer Leukemia Group (CCLG) protocols, depending on the diagnosis and disease risk stratification. Inclusion and exclusion criteria were not fundamental to this observational study, as the objective was to document neurological outcomes in a real-world clinical setting. Therefore, all children aged 1 to 13 years who received IT MTX during the study period—regardless of diagnosis, treatment intent (therapeutic or prophylactic), or other clinical characteristics were included, provided that informed consent was obtained from their parents or guardians.

During the study period, a total of 796 IT MTX administrations were performed in 96 patients. Written informed consent was obtained from parents or guardians, who were informed about the procedure, potential side effects, benefits, and post-treatment care. The procedures for Intrathecal therapy at the Operating Theatre (OT) of the Children's Hospital are performed under strict aseptic conditions by a skilled and trained pediatric hemato-oncologist, assisted by an experienced medical house officer and nurse. IT MTX is typically administered via lumbar puncture (LP) using a 25G spinal needle at the L2-L3 or L3-L4 interspace, with patients in the lateral decubitus position and under general anesthesia. Following the procedure, patients are monitored in the recovery room for one hour and advised to rest without a pillow for 24 hours.

Neurological adverse effects were monitored and recorded during follow-up visits 3 days post-administration using a standardized proforma. Parents were also instructed to report

Table 1: Neurological Complications Categorized by Severity in Pediatric Patients Receiving IT MTX[11-13]

Type of Complication	Category	Clinical Manifestations
Headache	Minor	Mild to moderate pain in the head, often transient
Backache	Minor	Localized lumbar pain post-procedure
Nausea/Vomiting	Minor	Gastrointestinal upset, often self-limiting
Fever	Minor	Low-grade fever post-lumbar puncture or due to aseptic reaction
Dizziness	Minor	Lightheadedness or unsteadiness
Paresthesia	Major	Tingling, burning sensations, or numbness in limbs
Nuchal rigidity	Major	Stiffness in the neck, possible sign of chemical meningitis
Seizures	Major	Convulsions, altered consciousness
Paralysis	Major	Partial or complete loss of motor function
Cranial nerve palsy	Major	Impaired eye movement, facial droop, or hearing loss
Chemical arachnoiditis	Major	Severe meningeal irritation, headache, photophobia, neck pain
Hypertension	Major	Elevated blood pressure potentially related to neurotoxic or systemic stress response
Posterior reversible encephalopathy syndrome (PRES)	Major	Seizures, headache, visual disturbances, altered mental status

any symptoms observed after therapy. Both minor and major complications were tracked, with minor complications including symptoms such as dizziness and headache, and major complications including more severe symptoms such as seizures and paralysis. This study adopted broader diagnostic criteria which allowed for the inclusion of a wider range of neurotoxic symptoms. Specifically, minor neurological complications were defined as headache, backache, fever, nausea, or vomiting. In contrast major neurological complications were defined as more severe symptoms, including nuchal rigidity, paresthesia, cranial nerve palsy, paralysis, or chemical arachnoiditis[11-13] (Table 1).

Statistical analysis was performed using SPSS. Results were presented as frequencies and percentages for categorical variables, and means with standard deviations for continuous variables. The onset and duration of symptoms were analyzed using chi-square tests to assess associations, with p-values less than 0.05 considered statistically significant.

Results

The patients' mean age was 5.37 years (SD = 2.502), the median age was 5.1 years, with 56.3% aged 3–5 years. Males comprised 68.8% of the cohort. The primary diagnosis was ALL, affecting 91.7% of patients, who predominantly received a 12 mg dose of IT MTX (61.5%). At the time of

Table 2: Demographic and Clinical Characteristics of Patients who Received IT MTX

Variables	Categories	Frequency (n)	Percent (%)
Age	< 3 years	5	5.2
	3-5 years	54	56.3
	6-12 years	37	38.5
Gender	Male	66	68.8
	Female	30	31.3
Diagnosis	ALL	88	91.7
	NHL	8	8.3
Dose of IT MTX	8 mg	3	3.1
	10 mg	17	17.7
	12 mg	59	61.5
	15 mg	17	17.7
Phases of chemotherapy	Prophase	3	3.1
	Induction	5	5.2
	Consolidation	19	19.8
	Interim Maintenance	16	16.7
	Delayed Intensification	18	18.8
	Maintenance	24	25.0
	COP	4	4.2
	COPADM	2	2.1
	CYM	5	5.1
Neurological side effects	Yes	230	28.9
	No	566	71.1

IT MTX administration, 25.0% of patients were in the Maintenance phase, 19.8% in the Consolidation phase, and 18.8% in the Delayed Intensification phase of chemotherapy. Out of 796 IT MTX administrations, neurological side effects were reported on 230 occasions (28.9%), while 566 administrations (71.1%) were without reported neurological side effects as shown in the Table 2.

COP: Cyclophosphamide, Oncovin (Vincristine), and Prednisone, COPADM: Cyclophosphamide, Oncovin (Vincristine), Prednisone, Adriamycin (Doxorubicin), and Methotrexate. CYM: Cyclophosphamide, Cytarabine, and Methotrexate

We found that none of the patients developed major neurological side effects, such as seizures, allergic reactions, neck rigidity, paresthesia, paralysis, hypertension, spinal fluid leakage, or anaphylaxis. Additionally, no patient underwent MRI brain imaging to assess neurological toxicity. However, minor neurological side effects were observed. The most common side effects were fever (40 occasions, 5.0%), nausea (36 occasions, 4.5%), vomiting (33 occasions, 4.1%), and dizziness (30 occasions, 3.8%). Other symptoms reported included headache (22 occasions, 2.8%), sleep disturbance (18 occasions, 2.3%), decreased appetite (19 occasions, 2.4%), back pain (17 occasions, 2.1%), and numbness (7 occasions, 0.9%).

The onset and duration of symptoms following IT MTX administration showed significant patterns (p-value < 0.05). Most side effects, including fever, dizziness, nausea, and vomiting, presented acutely within the first 24 hours. Additionally, sleep disturbances and headache also developed within this timeframe. The duration of symptoms was generally short, with the majority managed within 7 days. The symptoms developed after administration of IT MTX are presented in Table 3.

Out of a total of 796 IT MTX doses administered, hospital admission was required on 72 (9.1%) occasions due to neurological symptoms, and on 21 (2.6%) occasions, patients missed their next scheduled doses (Figure I).

Table 3: Neurological Side Effects that Developed after IT MTX Administration

Neurological side effects	Episodes		Onset of symptoms							
			0–24 hrs		24–48 hrs		48–72 hrs		>72 hrs	
	N	%	N	%	N	%	N	%	N	%
Dizziness	30	3.8	12	40.0	10	33.3	5	16.7	3	10.0
Fever	40	5.0	26	65.0	8	20.0	5	12.5	1	2.5
Sleep disturbance	18	2.3	14	77.8	3	16.7	1	5.6	0	0.0
Headache	22	2.8	10	45.5	7	31.8	3	13.6	2	9.1
Nausea	36	4.5	20	55.6	10	27.8	3	8.3	3	8.3
Numbness	7	0.9	3	42.9	2	28.6	2	28.6	0	0.0
Decreased appetite	19	2.4	4	21.1	3	15.8	5	26.3	7	36.8
Back pain	17	2.1	8	47.1	5	29.4	2	11.8	2	11.8
Vomiting	33	4.2	15	45.5	10	30.3	6	18.2	2	6.0

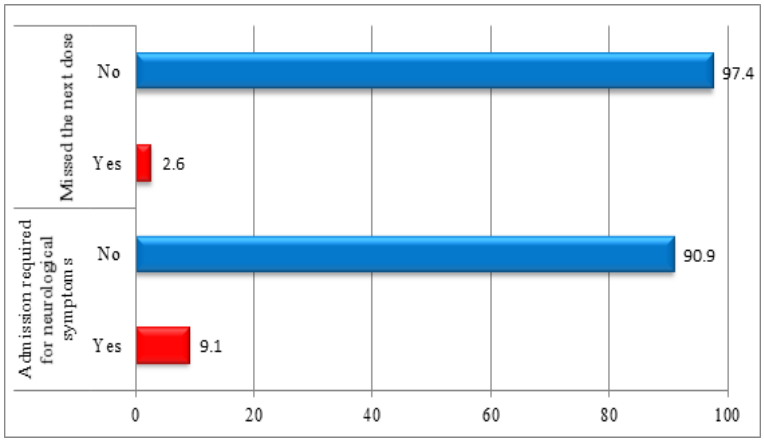

Figure I: Hospital Admissions and Missed Scheduled due to Neurological Symptoms

Discussion

IT MTX remains a cornerstone in pediatric cancer treatment, providing both therapeutic and prophylactic benefits, especially in the prevention and management of CNS involvement. We report our experience with adverse neurological events following IT MTX administration over a one-year period at our pediatric oncology center. No major neurotoxicity such as seizures, paralysis, or chemical arachnoiditis was observed in any patient. Minor neurological side effects were reported, with symptoms including fever, nausea, vomiting, and dizziness. These symptoms typically occurred within 24 hours of IT MTX administration and managed within 2 to 7 days.

In our study, neurological side effects were observed on 230 occasions (28.9%) out of 796 IT MTX administrations in 96 pediatric patients, as shown in Table 2. The majority of these events were classified as minor, yet clinically relevant. While several local studies have reported neurological complications associated with IT MTX, few have quantified their incidence in pediatric populations. For instance, Razi et al. (2021) described that children with ALL receiving IT MTX developed acute and sub-acute neurological dysfunction in approximately 3–15% of cases.[14] Similarly Hussain et al. (2022) presented a severe case of methotrexate-induced leukoencephalopathy in a 19-year-old patient with ALL, indicating the potential severity of such events.[15] Khan et al. (2020) reported three pediatric cases of posterior reversible encephalopathy syndrome (PRES) following IT MTX administration, highlighting rare but serious outcomes.[16]

The comparatively higher incidence observed in our cohort may reflect the broader diagnostic criteria adopted in this study (detailed in Table 1), which included a wide range of both minor and major neurological symptoms. This inclusive approach may include neurotoxic events that are typically underreported or unrecognized in previous studies, such as those reported by Hussain et al. (2022) and Khan et al. (2020) which mainly focused on major neurological complications.
Globally, the reported incidence of methotrexate-induced neurotoxicity varies significantly. Bhojwani et al. (2014) identified clinical neurotoxicity in 3.8% of children with ALL receiving high-dose MTX.[17] Mateos et al. (2021) reported a 7.6% incidence among 1,251 children across six pediatric oncology centers in Australia,[18] while Harris et al. (2023) found a 10% incidence in a cohort of 351 pediatric patients.[19] These discrepancies likely reflect differences in treatment protocols, genetic susceptibility, supportive care practices, and the diagnostic criteria used to define neurotoxicity. Collectively, these findings highlight the critical need for standardized definitions, uniform monitoring protocols, and early intervention strategies for neurotoxicity in pediatric oncology.

Despite the relatively high incidence of neurotoxic symptoms in our cohort, IT MTX was generally well tolerated. Notably, no major neurological complications were observed, such as seizures, allergic reactions, neck rigidity, paresthesia, paralysis, hypertension, spinal fluid leakage, or anaphylaxis. This aligns with the findings of Byrnes et al. (2016) and De la Riva et al. (2017), who also reported a low frequency of severe neurotoxic events in pediatric patients undergoing Intrathecal chemotherapy, reaffirming the general safety of the treatment in this population.[20, 21]

However, minor neurological complications were relatively common. As illustrated in Table 3, fever (5.0%), nausea (4.5%), vomiting (4.1%), and dizziness (3.8%) were the most frequently reported adverse neurological events. These findings are consistent with those of Sonia et al. (2021), who reported headaches, nausea, vomiting, back pain, and fever as the most prevalent minor side effects in their cohort.[22] Other symptoms observed in our patients included headache (2.8%), sleep disturbances (2.3%), decreased appetite (2.4%), back pain (2.1%), and numbness (0.9%), albeit at lower frequencies. Recognition and proactive management of these neurological symptoms are essential to minimize discomfort and ensure adherence to treatment regimens.

Importantly, our findings revealed a significant pattern in the onset and duration of these symptoms ($p < 0.05$), as detailed in Table 3. Most adverse effects, including fever, dizziness, nausea, vomiting, headache, and sleep disturbances, appeared acutely within the first 24 hours following IT MTX administration. These symptoms were largely transient, resolving within seven days in most cases. This observation aligns with findings by Rijmenams et al. (2021), who found that neurological symptoms typically manifested shortly after IT chemotherapy and resolved within a few days.[23] The acute and self-limiting nature of these symptoms reinforces their manageable profile in the clinical setting.

Nonetheless, the clinical implications of these neurological side effects should not be underestimated. In our cohort, 72 out of 796 (9.1%) IT MTX administrations required hospital admission due to neurological symptoms, and 21 administrations (2.6%) resulted in missed subsequent scheduled doses (Figure I). These findings highlight the potential for even minor neurological side effects to disrupt treatment adherence and impose a significant burden on healthcare resources. The 9.1% hospitalization rate underscores the need for close monitoring post-administration, particularly during the acute phase when symptoms are most likely to emerge. Byrnes et al. (2016) similarly noted that while severe neurotoxicity was rare, minor side effects occasionally required additional medical management and contributed to treatment delays.[20] Therefore, early recognition and management of neurotoxic symptoms are essential to maintaining the continuity and effectiveness of therapy.

Limitations

While this study has few limitations, including a single-cohort focus and lack of control group, but it informs policy implications for improving patient care and suggests avenues for further research, including multicenter trials to validate findings and assess preventive measures. Future multicenter studies are needed to validate these findings, optimize preventive strategies including pharmacologic prophylaxis, and explore long-term cognitive impacts of repeated IT MTX exposure.

Conclusion

This study found that IT MTX in pediatric cancer patients is generally well-tolerated, with mild and transient side effects such as fever, nausea, and headache. No major toxic events

were observed. However, oncologists should remain vigilant about the potential for mild complications and ensure that patients and caregivers are informed about the possible side effects. Furthermore, maintaining high standards of aseptic techniques during chemotherapy administration is crucial to prevent serious neurological complications. These practices are essential for minimizing the risk of severe adverse events and enhancing patient safety during treatment.

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