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Original Article

Etiological Profile and Clinical Outcomes Of Acute Neurotoxicity During Pediatric ALL Treatment in a Developing Country

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ABSTRACT

Objective: To determine the causes, clinical manifestations, and consequences of acute neurotoxicity in pediatric patients undergoing therapy for acute lymphoblastic leukemia (ALL).

Study Design: A prospective longitudinal study.

Place and Duration of Study: Pediatric Oncology Department, Indus Hospital and Health Network, Karachi, Pakistan, from May to Oct 2021.

Methodology: Patients presenting within 48 hours of developing neurological changes were labeled to have acute neurotoxicity. Cerebrospinal fluid (CSF) analysis, neuroimaging, metabolic profile, and an electroencephalogram (EEG) were performed as needed. Neurotoxicity types, causes, and outcomes were analyzed.

Results: Among the 511 children studied, 36 (7.0%) developed neurotoxicity, while the remaining 475 showed no signs of neurotoxicity at six months of follow-up and were censored from the analysis. Methotrexate leukoencephalopathy (MLE) was the most common type of neurotoxicity, affecting 16 children during intensive and maintenance treatment. Meningoencephalitis and posterior reversible encephalopathy syndrome (PRES) were identified in seven and four children, respectively. Of the 36 children with neurotoxicity, 29 (80.5%) achieved full recovery. However, seven children (19.5%) died; one due to disease recurrence and six from various complications.

Conclusion: Most patients with neurotoxicity had complete recovery. The major causes of morbidity and mortality were MTX toxicity and CNS infections. More severe methotrexate neurotoxicity in our cohort is an important finding and needs further studies to understand the underlying cause.

Keywords: Acute lymphoblastic leukemia, Leukoencephalopathy, Meningoencephalitis, Neurotoxicity.

How to Cite This Article: *Hashmani S, Feroze AM, Rafique Z, Hamid SA, Raza MR, Ashraf MS. Etiological Profile and Clinical Outcomes Of Acute Neurotoxicity During Pediatric ALL Treatment in a Developing Country. Pak Armed Forces Med J 2026; 76(Suppl-5): S772-S777.*
DOI: https://doi.org/10.51253/pafmj.v76iSUPPL-5.12747

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common hematological malignancy, constituting 25% of cancer diagnoses among children younger than 15 years of age.[1] The mainstay of treatment of ALL is systemic and intrathecal chemotherapy. This intensive chemotherapy has improved the survival rate in ALL dramatically in the high-income countries (HIC), where >90% overall survival is being achieved.[2] Owing to different reasons, including late diagnosis and inferior supportive care, the overall survival in low and middle-income countries (LMIC) is generally around 50-60%.[3] This improved survival has occurred at the cost of some adverse events, including treatment-related neurotoxicity.[4] One study from Pakistan reveals that among the reasons for death, treatment-associated toxicity accounted for 64.8% of total mortality.[5]

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Received: 01 Oct 2024; revision received: 20 Dec 2024; accepted: 21 Dec 2024

Acute neurotoxicity causes significant morbidity in children with ALL. These neurological complications can arise either from disease-induced CNS infiltration or from therapeutic complications.[6] The latter group may encompass posterior reversible encephalopathy (PRES), cerebrovascular complications, infections, drug toxicity, and long-term neurocognitive effects.[7] The frequency of neurological complications encountered during ALL ranges from 3.6% to 17% in different studies.[8]

The goal of this study is to identify the causes, clinical signs, and outcomes of acute neurotoxicity in children receiving treatment for ALL. The consequences of neurotoxicity, particularly associated with chemotherapeutic agents, can be significant and may affect both short-term and long-term neurological health and development.[9] Late diagnosis, poor access to supportive care, and socio-economic constraints can exacerbate the situation in a developing country like Pakistan, hindering the timely recognition and management of neurotoxic events.[10] Moreover, nutritional factors in our population may alter drug

metabolism, potentially increasing the risk of neurotoxicity. Identifying the patterns of acute neurotoxicity in this context is crucial for optimizing treatment protocols, formulating preventative strategies, and improving the quality of life and long-term results for these children.

METHODOLOGY

It was a prospective longitudinal study conducted at the Pediatric Oncology Department, Indus Hospital and Health Network, Karachi Pakistan, from May to Oct 2021. Ethical approval was obtained from the Institutional Review Board (IRD_IRB_2021_05_019). The sample size for this study was calculated using OpenEpi software (version 3.01) based on an estimated incidence of acute neurological complications of 17%, a desired precision of 5%, and a confidence interval of 95%. The required sample size was determined to be 217 patients. However, a total of 511 children with ALL were enrolled, allowing for greater precision in estimating the incidence and outcomes of acute neurotoxicity and improving the representativeness of the study population. A non-probability consecutive sampling method was used for enrolling children, ensuring their caregivers gave informed consent.

Inclusion Criteria: Children of either gender, aged 1 to 18 years, diagnosed with acute lymphoblastic leukemia (ALL) were included in the study. Both newly diagnosed cases and patients undergoing various phases of treatment, including intensive and maintenance therapy, were taken to be a part of the project.

Exclusion Criteria: Children with similar clinical presentation but not diagnosed with ALL, associated psychological disorder, and/or metabolic syndromes, and with peripheral neuropathy were excluded.

All participants were followed prospectively for six months, during which patients presenting within 48 hours of developing neurological changes were labeled as having acute neurotoxicity. Those who did not develop acute neurotoxicity during the follow-up period were recalled at six months. CNS involvement was labelled in patients whose blast cells were present in the CSF of the child with acute neurotoxicity. A child presented with acute neurotoxicity with MRI showing hyperintense T2 and FLAIR signals in cortical and subcortical areas of cerebral hemispheres, especially in parietal and occipital lobes, was considered to have Posterior Reversible Encephalopathy Syndrome (PRES).

Methotrexate Leukoencephalopathy (MLE) is diagnosed in children who develop acute neurotoxicity within three weeks of Methotrexate administration, after other causes are excluded. MLE is classified into four subtypes: (i) Stroke-like Syndrome presents with neurological deficits and specific MRI findings; (ii) Disseminated necrotizing leukoencephalopathy shows necrosis in MRI scans; (iii) CNS demyelination subtype features abnormal signal areas on MRI without diffusion restriction or enhancement; (iv) Cases without MRI changes involve acute neurotoxicity but normal MRI results. A child was diagnosed with meningoencephalitis if they showed neurotoxicity and either abnormal CSF (high protein, increased WBC, low sugar), MRI findings, or EEG indicative of encephalitis. Cerebral venous sinus thrombosis (CVST) was diagnosed when neurological complications were present, and MRI or CT revealed a filling defect in the dural venous sinuses. Epilepsy was diagnosed after two or more unprovoked seizures plus seizure discharge on EEG; metabolic seizures were diagnosed if seizures occurred with low sugar, hypocalcemia, or hypomagnesemia. If neurological symptoms appeared but CSF, MRI/CT, metabolic workup, and EEG were normal, the cause was labeled as unidentified.

Data collection involved clinical evaluation and investigations for all patients who developed acute neurotoxicity, including cerebrospinal fluid (CSF) analysis, neuroimaging (CT scan and MRI), metabolic profile, and electroencephalogram (EEG) if indicated. The underlying causes of neurological complications were determined based on clinical findings and relevant workups, and outcomes were recorded as complete recovery, neurological deficits, or death due to neurological insult.

Data entry and analysis were performed using Statistical Package for Social Sciences version 21. Continuous variables were summarized as means and standard deviations, while categorical variables were presented as frequencies and percentages. The chi-square test was used to assess associations between clinical variables and acute neurotoxicity, with a p-value <0.05 considered statistically significant. The study utilized a structured data management system to ensure accuracy and consistency in data collection and analysis.

RESULTS

The study included a total of 511 children, among whom 36(7.0%) experienced acute neurotoxicity

during the six-month follow-up period. The remaining 475 children (93%) did not develop neurotoxicity and were censored at the six-month mark. This indicates an acute neurotoxicity incidence of 7.1% within this cohort. An isolated seizure was the most common symptom, followed by a seizure with altered mental status (Figure). Demographic variables and disease information, including phenotype, risk stratification, and CNS status, are shown in Table-I. The association of acute neurotoxicity was also determined with different clinical variables (Table-II). However, we found no significant association between any of the studied variables (p-value >0.05).

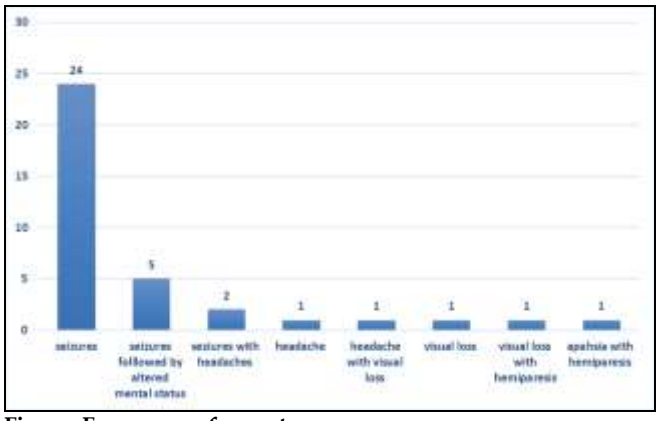

Figure: Frequency of symptoms

Table-I: Frequency Distribution of Demographic and Clinical Variables Among Study Participants (n=511)

Variables			Percentage (%)
Age	Mean (SD)	8.16±3.89	
Gender	Male	335	65.56%
	Female	176	34.44%
Phenotype	T-ALL	85	16.63%
	B-ALL	423	82.78%
	MPAL	3	0.59%
Risk stratification	SR	55	10.76%
	HR	456	89.24%
CNS status	1	453	88.65%
	2	23	4.50%
	3	35	6.85%
Acute neurological complications	Yes	36	7.1%
	No	475	92.9%

**T-ALL= T-cell Acute Lymphoblastic Leukemia, B-ALL=B-cell Acute Lymphoblastic Leukemia, MPAL=Mixed-Phenotype Acute Leukemia, SR=Standard Risk, HR=High Risk*

The outcome of patients concerning etiologies is shown in Table-III. Methotrexate leukoencephalopathy caused neurological insult in 16 children (44.4%), making it the most common cause of neurotoxicity. In three (18%) patients, the identified pathology was methotrexate stroke-like syndrome, from which one child had persistent ataxia on 6-month follow-up. In six (37.5%) children, methotrexate toxicity was identified with MRI showing chronic demyelination; among them, one child had refractory seizures, which were fatal. The other six (37.5%) were diagnosed as methotrexate leukoencephalopathy due to symptoms occurring within 3 weeks of methotrexate administration without any MRI changes. One of the children had disseminated necrotizing leukoencephalopathy and succumbed to refractory seizures. The children who had no MRI findings recovered completely to premorbid neurologic status.

Table-II: Analysis of the Association Between Acute Neurological Complications and Key Clinical and Demographic Factors (n=511)

Variables	Acute neurological complications		p-value
Gender	**Yes**	**No**	
Male	21	314	0.34
Female	15	161	
Diagnosis			
T-ALL	9	76	0.17
B-ALL	27	396	
MPAL	0	3	
Risk stratification			
SR	1	54	0.11
HR	35	421	
Total	36	475	

**T-ALL= T-cell Acute Lymphoblastic Leukemia, B-ALL=B-cell Acute Lymphoblastic Leukemia, MPAL=Mixed-Phenotype Acute Leukemia, SR=Standard Risk, HR=High Risk*

Table-III: Outcomes of Patients Experiencing Neurotoxicity Based on Underlying Etiologies (N=511)

Etiology	Total patients	Recovery	Neuro deficits	Expiry
MLE	16	13	1	2
Meningoencephalitis	7	4	0	3
PRES	4	4	0	0
Epilepsy	2	2	0	0
Metabolic seizures	1	1	0	0
CVST	1	1	0	0
IC bleed	1	1	0	0
CNS relapse	1	0	0	1
Cause not identified	3	3	0	0

MTX = Methotrexate, CNS = Central Nervous System, CVST = Cerebral Venous Sinus Thrombosis, PRES = Posterior Reversible Encephalopathy Syndrome, IC = Intracranial

The second most common cause was meningoencephalitis, which accounted for acute neurotoxicity in seven children (19.4%). All of them were diagnosed based on clinical findings, MRI, and/or EEG. CSF examination was not supportive in any child. Three of these children had persistent seizures with low Glasgow Coma Scale (GCS) and subsequently succumbed to their condition.

The other causes included PRES [4(11.1%)], CVST [1(2.7%)], intracranial bleed [1(2.7%)], metabolic seizures [1(2.7%)], epilepsy [2(5.5%)], and CNS relapse [1(2.7%)]. No cause could be discerned in three (8.3%) children who presented with isolated seizures; they completely recovered with no repeat episodes on 6-month follow-up.

As shown in Table-IV, the highest number of neurological complications occurred during interim maintenance, followed by induction and maintenance phases. All four events of PRES occurred during prophase and induction. Methotrexate leukoencephalopathy mainly occurred during the late phases of intensive chemotherapy and during the maintenance phase of treatment. Meningoencephalitis did not show a predilection for any phase. CVST, intracranial hemorrhage, and metabolic seizures occurred during induction.

Table-IV: Distribution of Neurological Complications Across Different Phases of Leukemia Treatment (n=511)

Final Diagnosis	Prophase+ Induction	Consolidation	IM	DI	Maintenance
PRES	4	0	0	0	0
MTX toxicity	1	1	8	3	3
IC bleed	1	0	0	0	0
Meningoencephalitis	1	0	2	1	3
Metabolic fits	1	0	0	0	0
Epilepsy	0	1	1	0	0
CNS relapse	0	0	0	0	1
CVST	1	0	0	0	0
Cause not identified	1	0	1	0	1
Total	10	2	12	4	8

MTX = Methotrexate, CNS = Central Nervous System, CVST = Cerebral Venous Sinus Thrombosis, PRES = Posterior Reversible Encephalopathy Syndrome, IC = Intracranial

DISCUSSION

This study highlights the causes of acute neurotoxicity during treatment of ALL. The incidence of acute neurotoxicity in this cohort, 7.1%, is comparable to the 3.6–17% reported in high-income countries. The study reports that Methotrexate induced neurotoxicity had a predominant nature of toxicity. Though the subjects of this study reported complete recovery.

A previously published retrospective study reported neurological complications in 17% of participants. This difference may be attributed to multiple factors, including a shorter follow-up period and advancements in supportive patient care in the current study. Consistent with literature, our study also found seizures to be the most common presentation of acute neurotoxicity.[10] A recent study conducted by Sagi *et al.,* reported 20.6% mortality due to acute neurotoxicity; in comparison, our rate of 16.6% may represent an improvement in care over time; however, the study cohort had a 10-year study period, which could account for the difference.[11]

Methotrexate Leukoencephalopathy (MLE) was the most common cause of neurotoxicity in this cohort, which is in line with a study conducted by Ahmad *et al*.[3] The Methotrexate stroke-like syndrome was reported in only three children, which is a common manifestation in high-income countries. In most cases, methotrexate stroke-like syndrome shows complete recovery in high-income countries, as reported by Filbin *et al*.[12] In our cohort, one out of three children with methotrexate stroke-like syndrome developed persistent ataxia. The necrotizing methotrexate leukoencephalopathy, which was reported in one child and resulted in death despite early recognition and omission of subsequent methotrexate, aligns with the findings of a study conducted by Amatruda *et al*.[13] All children with white matter hyperintensities without contrast enhancement in Methotrexate leukoencephalopathy group recovered, except one child who died due to refractory seizures, which is in contrast to a study of Ramalingam *et al*.[14] The exaggerated toxicity of MTX in this cohort is responsible for dismal outcomes and it needs to be investigated. It is reported in one study that a minor acute CC genotype of rs2298383 (ADORA2A) is associated with a high risk of MTX-related neurotoxicity.[13] It was also reported that SLC19A1 was significantly associated with an increased risk of MTX toxicity.[14] ATXN1 rs68082256 is a single-nucleotide polymorphism (mutation) that was associated with an increased incidence of CNS toxicities.[6] Though it is beyond the capacity of our institution to detect single-nucleotide polymorphisms (SNPs), investigating this genetic polymorphism in future studies may provide insights into the heightened susceptibility to leukoencephalopathy.

Another study by Akshay *et al.,* found that 3 out of 5 patients with MTX leukoencephalopathy had abnormal B12, folate, and homocysteine levels at pre-specified times.[15] This may suggest that the baseline poor nutritional status of children in low- and middle-income countries (LMIC) could be responsible for the increased sensitivity to methotrexate (MTX) observed in our cohort. However, this study was unable to assess pre-existing nutritional deficiencies in this study population.

Neuroinfectious diseases constitute an important cause of acute neurological complications in LMIC and are responsible for three deaths in this study. A study by Xiao *et al.,* also reported high mortality due to neuroinfections in children with ALL.[16] Managing serious infections in immunocompromised patients requires a comprehensive, multidisciplinary approach involving infectious disease specialists, intensivists, and microbiologists. However, this level of care may not be feasible in many centers within LMICs. It is important to suspect CNS infections in children with ALL who present neurological symptoms and start prompt treatment with antibiotics and antivirals to improve the outcomes. Antifungal therapy should also be given when imaging favors a fungal infection. The low prevalence of vaccination and poor hygienic conditions are also responsible for high mortality due to neuroinfections in developing countries.[16]

Four children in our study developed PRES, and all made a full recovery. Similarly, one patient had CVST and recovered completely. These outcomes are consistent with findings reported in studies like study of Lin *et al*.[17] Hyponatremia may develop in nearly 15% of patients during the induction phase, and vincristine is likely responsible for this by causing inappropriate ADH secretion. We had only one child who developed a hyponatremic seizure and recovered well. Intracranial bleed was cause of seizures in one patient during induction, which is in line with findings reported in the Indian population.[15] It was not possible to discern the cause of intracranial bleed in the child as his platelet counts were normal and he had no CVST. No cause of seizures could be found in three patients. This might be due to the epileptogenic properties of chemotherapy employed in ALL treatments. All these children responded well to anti-seizure medications, and there was no recurrence of seizure or neurologic deficit. One child had seizures as a presenting feature of CNS relapse. This highlights the importance of excluding CNS relapse in a patient with neurological symptoms.[18]

This study gives insight into the major causes of morbidity and mortality in patients presenting with acute neurotoxicity in LMIC. Herein, we report improved outcomes of acute neurotoxicity from LMIC as compared to findings of study reported by Gandy *et al*.[19] Meningoencephalitis and Methotrexate induced white matter injury are two most common acute neurologic issues in our population. However, our study only followed up for six months, and a longer follow-up period is required to reliably evaluate the sequelae and consequences of neurotoxicity.[20]

Furthermore, the role of inadequate nutritional status and genetic polymorphisms in our population needs to be explored systematically and prospectively. Future research should focus on specific genetic polymorphisms, such as ADORA2A, and nutritional deficiencies, like Vitamin B12, to assess their roles in acute neurologic toxicities within our population.

LIMITATION OF STUDY

This prospective longitudinal study was observational, so it cannot confirm causal links between methotrexate toxicity and other effects. External validity may be limited by differences in patient compliance, treatment protocols, and follow-up times. Additional confounders—diet, medications, and comorbidities—could have influenced biochemical and clinical outcomes.

CONCLUSION

Most patients with neurotoxicity had complete recovery. The major causes of morbidity and mortality were MTX toxicity and CNS infections. More severe methotrexate neurotoxicity in our cohort is an important finding and needs further studies to understand the underlying cause.

ACKNOWLEDGEMENTS

All the patients and faculty members of Pediatric Hematology and Oncology department of Indus Hospital and Health Network.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SH & AMF: Data acquisition, data analysis, critical review, approval of the final version to be published.

ZR & SAH: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MRR & MSA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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