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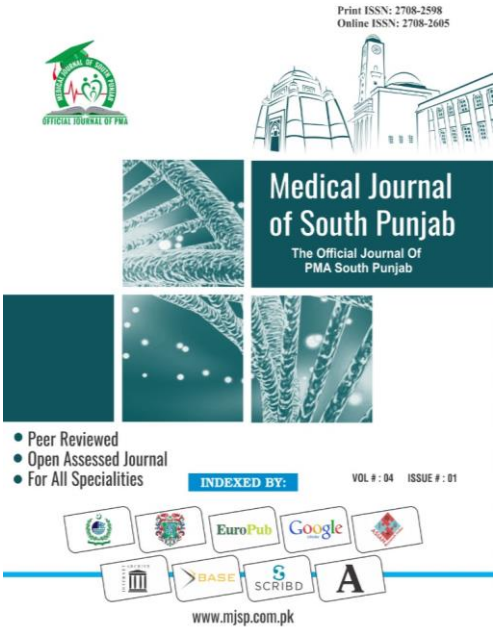


# Neurological complications in children with acute lymphoblastic leukemia

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**Original Article**

# Neurological Complications in Children with Acute Lymphoblastic Leukemia

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## ABSTRACT

***Objective:*** *To describe the frequency, clinical profile and outcome of neurological complications in children with Acute Lymphoblastic Leukemia (ALL)*

***Methods:*** *This retrospective observational study was conducted at Agha Khan University Hospital, Karachi, Pakistan. Study included clinical record of diagnosed acute lymphoblastic leukemia children (1 year to 18 years), admitted at pediatric oncology department between October 2009 and November 2019 to identify neurological complications during chemotherapy.*

***Results:*** *Out of 387 children with ALL, neurological events were reported in 72 (18.60%). Out of the affected patients, majority were males (n=49, 68.05%) with 44 (61%) children in between 1-10 years of age. Among these, 43 (60%) had Precursor B cell and 18 (25%) had T-cell ALL. The number of patients who developed neurological complications during induction were 29 (40%), during consolidation phase were 16 (22%) and 6 (8%) during maintenance phase of chemotherapy. Altered level of consciousness was found in 13 (18%), convulsions in 31 (43%), and motor weakness in 14 (19%). Systemic chemotherapy with high dose methotrexate 43 (60%), and L-Asparaginase 22 (31%) along with intrathecal methotrexate 41 (57%) was the most common predisposing factor. Neuropathy was found in 1 patient only. Most of the patients had gross and full recovery by hospital discharge, 7 (10%) expired and 8 (11%) had neurological deficit on hospital discharge.*

**Conclusion:** *Although most patients had full recovery, neurological complications are frequent during ALL therapy, and require early detection and prompt treatment to prevent permanent sequelae.*

***Keywords:*** *B Cell, Children, Complications, Lymphoblastic Leukemia, Neurology*

## 1. INTRODUCTION

Intensive chemotherapy in the treatment of children with acute lymphoblastic leukemia (ALL) has dramatically improved the outcome. These treatment modalities usually include vincristine, corticosteroids, methotrexate (MTX) and radiotherapy in both systemic and central nervous system (CNS) directed therapy. [1] In recent years, the 5 year event-free survival of children with acute lymphoblastic leukemia (ALL) has reached 80% with the application of intensive chemotherapy protocols.[1,2] Despite the improved outcome in ALL, antineoplastic therapy affects both malignant cells and normal cells from mild to debilitating range and all organ systems in the acute and long-term period. The frequency of side effects has also increased. Of these side effects, acute neurological events are important, occurring in between 3% and 18.4% of children with ALL.[3-6] In the acute term, reported neurologic complications have included mostly peripheral neuropathy, cerebrovascular accidents, and convulsions. Common neurologic complications developing after completion of ALL treatment include leukoencephalopathy and neurocognitive defects.[7-10] With the increase in survival detection of these complications would be more and important. (As survival rates increase, detection of these complications grows in importance).

The objective of this study is to describe the frequency, clinical profile and neurological complications in children with acute leukemia, admitted in a tertiary care hospital of Karachi, Pakistan.

## 2. METHODOLOGY

This retrospective observational study included clinical record of diagnosed acute lymphoblastic leukemia children (1 year to 18 years) confirmed on bone marrow and peripheral blood or flow-cytometry, admitted at pediatric oncology department between October 2009 and November 2019 to identify neurological complications during chemotherapy. Ethical exemption has been obtained from the Ethics and Review Committee (ERC) of the Aga Khan University Hospital (IRB #.3429-one-ERC-14.).

Neurological complications like convulsions, headache, altered loss of consciousness, vision disturbances and ataxia were observed. This information along with baseline characteristics like age, gender, ALL phenotype, relapse cases, risk stratification, sign and symptoms at the time of presentation, phase of chemotherapy at the time of presentation and the drugs received before the presentation of neurological complications were also noted. Furthermore, laboratory investigations like complete blood counts (CBC), serum electrolytes, Prothrombin time (PT), partial prothrombin time (AP), and cerebrospinal fluid examination were recorded. The findings of electroencephalogram (EEF), magnetic resonance imaging (MRI) and computed tomography (CT) imaging were also observed where available.

Risk stratification was categorized as standard risk, high risk and very high risk. These categories are based on the NCI's Children's Oncology Groups' criteria for risk-based treatment. These are further elaborated in Table 1. The outcome of neurological complications were measured in terms of death, discharge without residual neurological complication, and discharge with residual neurological complication.

SPSS version 24 was used for the purpose of statistical analysis. Mean ±SD was computed for quantitative variables like age and weight of the patients. Frequency and percentages were calculated for gender, immunophenotyping, risk group, relapse of disease, and neurological complications.

Inferential statistics were explored using chi-square test and independent t-test. p-value <0.05 was considered significant. Multivariable logistic regression analysis was also applied among variables found significant in univariate analysis and adjusted odds ratio was computed. Backward logistic regression method was applied to develop the final model. P-value < 0.05 was considered significant.

## 3. RESULTS

Seventy two of 387 ALL children (18.6%), mean age diagnosis 8.9±4. years developed neurological complication. Of 72 patients who develop neurological complications 3 were CNS positive at the time of diagnosis. Patient's characteristics are shown in Table 1.

Neurological complications were significantly higher in patients with T-cell ALL phenotype (n=22, 30.1%) than that of patients with pre-B cells (n=50, 15.9%) (p-value 0.005). Similarly, neurological complications were significantly higher in high risk group (n=41, 23.6%) as compared to very high risk (n=8, 22.9%) and standard risk group (n=23, 12.9%) (p-value 0.030). Moreover, neurological complications were also significantly higher in patients with relapse as compared to patients with no relapse (p-value 0.005). (Table 1) Neurological complications were higher in males as compared to females, i.e. 49 (18.8%) and 23 (18.1%) respectively (p-value 0.861). A detailed analysis of patient demographics can be visualized in Table 2.

Among 72 patients with neurological complications, majority of events occurred during induction and consolidation phase of chemotherapy, i.e. 27 (37.5%) and 15 (20.8%) respectively. (Figure 1). Frequency of neurological symptoms among children with ALL showed convulsion 31 (43.1%), headache 28 (38.9%), vomiting 21 (29.2%), and fever 20 (27.8%) in majority of the patients. (Figure 2).

The findings of univariate showed that the odds of neurological complications were 2.27 times significantly higher in patients with T-cells Immunophenotyping (OR: 2.27, 95% CI: 1.27-4.09) patients with high risk group (OR: 2.07, 95% CI: 1.18-3.64) and very high-risk groups (OR: 1.99, 95% CI: 0.81-4.92) and in in patients with relapse (OR: 2.97, 95% CI: 1.34-6.61) . However, in multivariate analysis, relapse was the only variable found significantly higher After adjusting for all other covariates, neurological complication was found 3.11 times higher among patients who had relapse as compared to patients without relapse (aOR 3.11, 95% CI 1.33-7.23). (Table 3).

CT and MRI findings showed that of 15 patients, in whom CT scan was performed, abnormality was found in 5 (33.3%) patients whereas of 44 patients in whom MRI was performed, abnormality was observed in 26 (59.1%) patients. An insignificant association of mortality was observed with CT scan and MRI findings. Radiological findings seen were, acute ischemic infarcts in 10 (38.5%) and findings of PRES and periventricular leukomalacia in 5 (11.4%) patients each. (Figure 3)

Majority has received methotrexate 43 (60%) and vincristine 47 (65%), followed by asparaginase 22 (31%), doxorubicin and prednisolone 16 (22%) each. Intrathecal Methotrexate 41 (57%) seems to be the most common predisposing factor.

The blood pressure reading for 54 patients were found, out of which 3 (5%) were hypertensive. The electrolyte panel showed hyponatremia in 15 (24%) out of 63 patients with recorded sodium levels, and 30 (57%) out of 52 patients with recorded calcium levels had hypocalcemia.

During the inpatient stay, 15 (21%) patients had to be admitted to the intensive care unit

for careful monitoring. Most (57, 79%) of the patients recovered from the complication and were discharged in a stable condition. Those needing PICU admission 7 (12%) required ventilator support. Eight (11%) patients were alive with residual symptoms. Loss of vision occurred in 2 patients, lower limb paraplegia and abducens nerve weakness was seen in one patient each. A small portion of the patients couldn't recover from the neurological complications 8 (11%) and about 7 (10%) of the patients expired during the inpatient treatment course.

Of 7 patients expired, 3 (42.8%) patients suffered massive intra cranial bleeding as showed by their scans, 1 (14.3%) patient had severe thrombocytopenia, while 2 (28.6%) patients were found to have cerebral sinus thrombosis at the time of death.

**Table1:**

**Risk-categorization of ALL Patients**

| Risk Category | Description |
|---|---|
| Standard | • The WBC count is less than 50,000 cells/mm3 (50.0 x 109 cells/L).<br>• The child is 1to 10 years old.<br>• There are favorable genetics (the child has chromosome and gene abnormalities linked with a favorable prognosis).<br>• There are no unfavorable genetics (the child has no chromosome or gene abnormalities linked with an unfavorable prognosis).<br>• There are no blasts in the brain or spinal cord (called the central nervous system, or CNS) and the leukemia hasn't spread to the testicles.<br>• The day 29 bone marrow minimal residual disease (MRD) is less than 0.01%. |
| High | • The WBC count is greater than 50,000 cells/mm3 (50.0 x 109 cells/L).<br>• child is 10 years or older but younger than 13 years.<br>• The day 29 bone marrow MRD is greater than or equal to 0.01%.<br>• The leukemia has spread to the testicles. |
| Very High The | • The child is older than 13 years.<br>• There are unfavorable genetics.<br>• The day 29 bone marrow MRD is greater than or equal to 0.01% and one of the following:<br>o There are no favorable genetics.<br>o The WBC count is greater than 50,000 cells/mm3 (50.0 x 109 cells/L).<br>o The child is older than 9 years. |

**Table 2: Patient's characteristics**

| | Standard Risk | High Risk | Very High |
|---|---|---|---|
| No. of patients, n (%) | 178 (46) | 174(45) | 35 (9) |
| **Diagnosis on Immunophenotyping, n (%)** | | | |
| Pre-B ALL | 175 (98.3) | 117 (67.2) | 22 (62.9) |
| B-ALL | - | - | - |
| Pre-T ALL | - | 5 (2.9) | 1 (2.9) |
| T-ALL | 3 (1.7) | 52 (29.9) | 12 (34.3) |
| Mean age at diagnosis, Years | 5.74±2.1 | 11.15±3.5 | 13.16±2.9 |
| **Gender** | | | |
| Male, n (%) | 113 (63.5) | 123 (70.7) | 24 (68.6) |
| Female, n (%) | 65 (36.5) | 51 (29.3) | 11 (31.4) |
| Disease Relapse, n (%) | 11 (6.2) | 10 (5.7) | 8 (22.9) |
| No. of patients observed neurological complication, n (%) | 23 (12.9) | 41 (23.6) | 8 (22.9) |

**Table 3:**

**Regression analysis of patients associated with neurological complication**

| Variables | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | AOR (95% CI) | p-value |
| **Immunophenotyping** | | | | |
| T Cell | 2.27 (1.27-4.09) | 0.006 | 1.61 (0.81-3.19) | 0.169 |
| Pre-B-Cell | Ref | | Ref | |
| **Risk Group** | | | | |
| High Risk | 2.07 (1.18-3.64) | 0.011 | 1.68 (0.91-3.13) | 0.097 |
| Very High Risk | 1.99 (0.81-4.92) | 0.036 | 1.26 (0.47-3.37) | 0.645 |
| Standard Risk | Ref | | Ref | |
| **Relapse of Disease** | | | | |
| Yes | 2.97 (1.34-6.61) | 0.007 | 3.11 (1.33-7.23) | 0.0 |

**Figure 1: Phase of chemotherapy at the time of neurological complications**

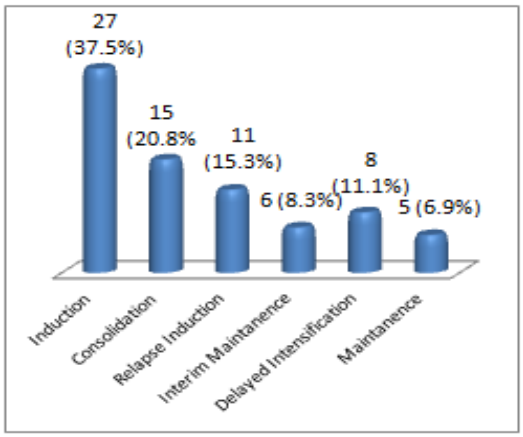



**Figure 2: Frequency of Neurological Symptoms among children with acute lymphoblastic leukemia**

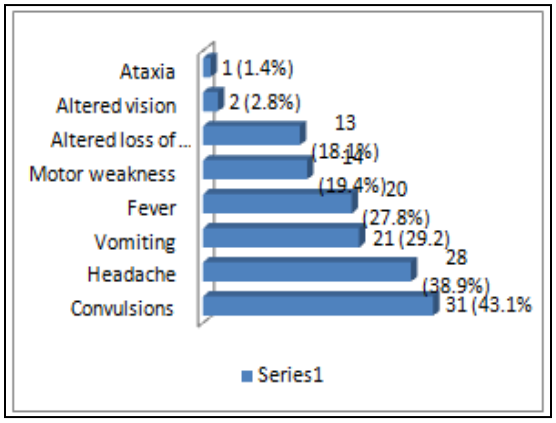
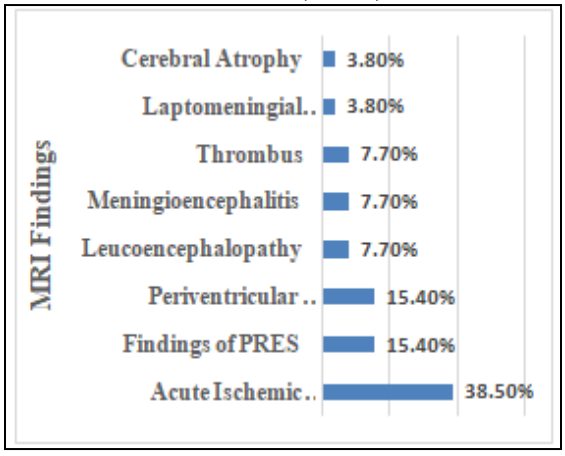



**Figure 3: Radiological Findings of children with acute lymphoblastic leukemia (n=26)**




## 4. DISCUSSION

The neurological complications in ALL patients can either be an acute presentation or long term sequelae of the chemotherapy. In a previous study, Aytac et al recorded 40 out of 265 patients with neurological findings, out which 57.5% underwent cranial radiotherapy, 42.5% belonged to the higher risk group, and 17.5% had relapse.[5] However, in our findings, majority of the patients were not in relapse (61, 17%). Acutely presenting symptoms included walking disabilities, neurogenic bladder, dysarthric speech, jaw pain and meningitis. In the long term, generalized convulsions, hearing and speech disorders with mental and motor retardation were seen. Out of all the complications, the most commonly occurring during treatment were neuropathy, convulsions and meningitis.[11]

Parasole et al. analyzed ALL patients who were treated at their institute in a nine year period, and 27 out of 253 patients suffered neurological complications.[6] The presentations included eye deviation, tonic-clonic seizures, hallucinations, speech and motor disturbances. About 70.4% of the cases resolved quickly, both spontaneously and also with administrations of benzodiazepines or barbiturates, and 29.6% of the patients were admitted in the intensive care unit.[6] Similarly, in our patient cohort, 21% of patients were admitted in the Paediatric Intensive Care Unit (PICU), however, most of them recovered rapidly without medical intervention. In 18 (67%) of patients, the electroencephalography was abnormal, showing slow rhythm of cerebral activity and focal abnormal spikes in various brain lobes, with and without ischemic changes and pathological MRI scans were observed in 18 (52%) of our patients.

Acute ischemic infarct was the most frequent neurological complication found in our study, followed by Posterior Reversible

Encephalopathy Syndrome (PRES). This syndrome comprises of a combination of headache, seizures, altered mental status and visual disturbances.[12] On neuroimaging, predominantly transient posterior bilateral lesions in cerebral white matter are found. This condition has been linked to cancers, hypertension, eclampsia, renal disorders and autoimmune diseases. The cortical and subcortical regions of occipital and parietal lobes are more commonly involved. The exact mechanism of disease is unknown, but it has been hypothesized that high blood pressure causes endothelial damage in the blood brain barrier, leading to capillary hyper perfusion and consequent vasogenic edema.

Acute lymphoblastic leukemia in children is fundamentally managed with CNS directed therapy. Mainly white matter destruction, vascular damage leading to hemorrhage and calcification and enlargement of ventricles or sulci as a sign of cortical atrophy has been reported due to this kind of therapy.[5] The major chemotherapeutic agent found to be the cause of acute, sub-acute and chronic neurological complication is methotrexate, which is a folate-antagonist.

In order to prevent relapses in bone marrow, testicles and CNS, an intensive chemotherapy schedule is administered to ALL patients. Prior to this, a precise risk assessment is required for a successful treatment, which includes assessing the status of the CNS at the time of diagnosis. According to current protocols, a CNS directed therapy is adopted in which initial CNS assessment decides whether a single IT MTX should be given, or in case of the CNS being affected, lumbar puncture may be done and a triple IT MTX therapy is administered.[13]

Asparaginase has shown to be an integral part of ALL therapy, given that optimum dose of Asparaginase can significantly improve outcomes in the patients. Thus, clinicians managing children with ALL and a therapy - associated thrombosis are faced with a significant dilemma i.e. should they re-expose the patient to Asparaginase with the attendant risk of recurrent thrombosis or omit Asparaginase from therapy and thereby increase the risk of relapse. Qureshi et al. showed that optimal Asparagine depletion is central to the success of modern regimes for treatment of ALL, however predisposing to a significant risk of thrombosis. Nevertheless, their study demonstrates that re-exposure to Asparaginase is feasible and safe for the patient.[14]

## 5. CONCLUSION

Although most patients had full recovery, neurological complications are frequent during ALL therapy, and require early detection and prompt treatment to prevent permanent sequelae.

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