

Frequency and Risk Factors of Seizures in Children During Induction Remission Chemotherapy for Acute Lymphoblastic Leukemia (ALL)

SHAHINOOR AKTER SOMA¹, CHOWDHURY YAKUB JAMAL², INDIRA CHOWDHURY³, FARAH DIBA⁴, MOUSUMI SAHA⁵

Abstract:

Background: Seizure is one of the most common CNS complications among patients receiving chemotherapy for acute lymphoblastic leukemia (ALL). Seizures are seen in 8-13% of patients with ALL. Most seizure occurs during the induction and consolidation phases of treatment. However, not much is known about the risk factors of these seizure.

Materials & Method: This prospective observational study was conducted in the department of Pediatric Hematology and Oncology, BSMMU. One hundred and five newly diagnosed admitted children with ALL aged >1 year to <18 years, from May 2017 to March 2018 for induction remission chemotherapy and who fulfilled the criteria of case definition were enrolled into this study.

Results: This study showed that seizure frequency was 14.3% in children with ALL getting induction remission chemotherapy. Female patients developed seizures more than males which was statistically significant by univariate analysis ($p = 0.029$) but was not found to be a risk factor by multivariate analysis ($p = 0.059$). All the seizures developed in B-lineage ALL but there was no statistically significant association between lineage of ALL with development of seizures.

Conclusions: In this study slightly higher frequency of seizure in ALL patients on induction remission chemotherapy was found than previous studies (14.3% vs. 13%). Females developed seizures more than males.

Key words: Seizure, Acute lymphoblastic leukemia (ALL), risk factors, induction remission chemotherapy.

Introduction

Acute lymphoblastic leukemia (ALL) is the commonest pediatric malignancy. From January 2012 to December 2012, 58% of the 455 newly diagnosed children with malignancy in the Department of Pediatric Hematology and Oncology of BSMMU were ALL patients.¹ Long-term outcomes for children with ALL have greatly improved, with reported overall survival

rates >90% compared with <10% in the 1960s.² This dramatic improvement of the survival outcome is due to intensive and risk directed chemotherapy in the treatment of children with ALL. But intensive chemotherapy leads to significant morbidity including adverse neurological events. Typically ALL chemotherapy protocols includes four phases -(1) Induction phase (2) Consolidation phase/ CNS preventive therapy (3) Delayed intensification phase and (4) Maintenance phase.³

Neurological complications are among the most serious problems in children receiving chemotherapy, and may cause permanent disability or death. The most frequent neurologic complications are neuropathy, convulsions and meningitis.⁴ Seizures are seen in 8-13% of patients with ALL.⁵⁻⁹ Most of the seizures occur during the induction and CNS

1. Junior Consultant (Paediatrics), UHC, Nawabganj, Dhaka.
2. Professor, Department of Paediatric Hematology and Oncology, BSMMU, Dhaka.
3. Ex Resident, Department of Paediatric Hematology and Oncology, BSMMU, Dhaka.
4. Junior Consultant (Paediatrics), UHC keraniganj, Dhaka.
5. Assistant registrar, Department of Paediatrics, Faridpur Medical College Hospital, Faridpur.

Correspondence: Dr. Shahinoor Akter Soma, Junior Consultant (Paediatrics), UHC, Nawabganj, Dhaka. Cell phone: 01816384495, E mail: somabd79@yahoo.com

Received: 11/11/2020

Accepted: 9/8/2021

system consolidation phases.^{6,9-11} A seizure is defined as a transient occurrence of signs and/or symptoms arising from abnormal excessive or synchronous neuronal activity in the brain.¹² Seizures may be triggered by chemotherapeutic neurotoxicity, metabolic complications (hyponatremia, hypocalcaemia), Posterior reversible encephalopathy syndrome (PRES), cerebral hemorrhage, CNS infection, cerebral vascular disorders, and leukemic infiltration.^{6-8,13-15}

Not much is known about the risk factors of these seizure. A data regarding the same from Bangladeshi population is lacking. The knowledge of seizure in ALL in these patients is essential to improve overall survival rate by designing precise follow up plan and formulating management plan.

Thus, the purpose of this study was to see the frequency and risk factors of seizures in our children undergoing induction remission chemotherapy for ALL.

Materials & Methods:

The present single centered, prospective observational study was conducted over a period of one year from May 2017 to April 2018 in the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University. All patients admitted in the Department of Pediatric Hematology and Oncology, aged 1 to <18 years with both sexes diagnosed newly as ALL were the study population. Informed written consent from the parent or caregiver were obtained at the time of study enrollment. Data were collected using a preformed data collection sheet (questionnaire). Demographic data regarding age, sex, were collected from parents or caregiver. The diagnosis of ALL was based on history, clinical examination, and relevant investigations such as CBC with PBF examination, bone marrow study and immunophenotyping. Clinical information about pallor, temperature, pulse rate, blood pressure, respiratory rate and other general and systemic clinical parameters were taken. Prior to initiation of therapy baseline investigation were done. Chemotherapy was given to all patients with ALL according to UK ALL 2003 protocol after stratifying risk. Patients between the ages of 1 to 9.9 years with initial WBC of less than 50000 /cumm considered as standard risk. On the other hand, patients aged ≥ 10 years or initial WBC count ≥ 50000 /cumm were

considered as high risk. Regimen-A was given to standard risk group and regimen-B was specified for high risk group.

In case of regimen A, the chemotherapeutic agents used in induction phase included oral dexamethasone, vincristine, L-asparaginase, 6-mercaptopurine and IT/ TIT (intrathecal methotrexate, hydrocortisone and/or cytosine-arabioside). However, in regimen-B another drug daunorubicin was given additionally. All patients were monitored regularly from the start of chemotherapy up to 35 days of induction remission for the occurrence of seizure. Development of seizure and its type was confirmed by attending physician.

Statistical analyses were performed by using SPSS for Windows (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY: IBM Corp) software. Descriptive statistics (numbers and percentage) were calculated for all variables and statistical analyses were also applied to find associations between variable using Chi-square test. Risk estimation were calculated by using the Odds ratio through Cross tabulation and multivariate logistic regression analysis, with 95% confidence intervals. A p-value <0.05 was considered as significant.

Results:

Total 112 children with ALL were included in this study, among them 3 patients took discharge against medical advice and 4 patients died due to other cause. Finally data were analyzed among 105 patients. Among the 105 patients 86 (81.9%) were in the age group of <10 years, 19 (18.1%) patients were in the age group of ≥ 10 years. Mean age was 5.99 ± 3.89 years and range was between 1.20 to 16.0 years. Male were 63 (60%) and 42 (40%) were female patients. Male children were predominant in number. M: F ratio was 1.5:1. At diagnosis WBC count <50000/cumm was found in 69 (65.7%) patients, on the other hand at diagnosis WBC count ≥ 50000 /cumm was found in 36 (34.3%) patients. Among them, 94 (89.5%) patients were in B cell lineage and 11 (10.5%) patients were in T cell lineage. Fifty-six (53.3%) patients were treated with regimen A, whereas 49 (46.7%) were treated with regimen B.

Among the 105 patients in the study, 15 patients developed seizure. Seizure frequency was 14.3% in our study (Figure 1). Among the 15 patients who

developed seizure 10 were female and 5 were male. Female sex shows statistically significant risk for development of seizure by univariable analysis ($p = 0.029$). Age, WBC count at diagnosis, lineage of ALL and treatment regimen cannot be considered as risk factor, because those factors had no statistical significant relation with having seizure (Table-I). However all the seizure developed in B cell lineage ALL. None of these factors remained significant for the development of seizure by multivariable analysis (Table-II).

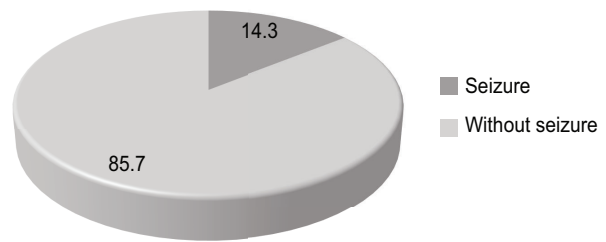


Fig.-1: Pie diagram showing frequency of seizure in ALL.

Table-I
Measurement of risk factors for seizure in children with ALL (n=105)

Variables	N	With seizure		Without seizure		OR 95% CI	P value
		No.	%	No.	%		
Age group (in years)							
1-10	86	13	15.1	73	84.9	1.510.31-7.35	0.605
>10	19	2	10.5	17	89.5		
Sex							
Female	43	10	23.3	33	76.7	3.451.09-10.9	0.029
Male	62	5	8.1	57	91.9		
Initial WBC count /mm³							
<50000	69	10	14.5	59	85.5	1.050.33-3.35	0.933
>50000	36	5	13.9	31	86.1		
Immunophenotype							
B-ALL	94	15	16.0	79	84.0	-	0.152
T-ALL	11	0	0.0	11	100.0		
Types of chemotherapy							
Regimen – A	56	7	12.5	49	87.5	0.7320.25-2.19	0.576
Regimen – B	49	8	16.3	41	83.7		

Table-II
Multivariate logistic regression analysis of risk factors for seizure in children with ALL (n=105)

Variables	B	S.E.	Wald	P value	OR	95% C.I. for OR	
						Lower	Upper
Age	.069	.109	.393	.530	1.071	.864	1.327
Sex	1.134	.600	3.569	.059	3.107	.958	10.069
Initial WBC count	-.513	1.048	.240	.624	.599	.077	4.667
Treatment regimen	.950	1.053	.813	.367	2.586	.328	20.384
Immunophenotype	-19.304	11976.73	.00	.999	.00	.00	.00

Discussion:

Several neurologic complications occur in children who receive chemotherapy for treatment of ALL and among the neurological complications, seizure is the most devastating one.

In this study fifteen patients (14.3%) developed seizures out of 105 patients with ALL getting induction remission chemotherapy. In the previous studies seizures were seen in 8-13% of patients with ALL.⁵⁻⁹ The present study has found a slightly higher frequency of seizure than some of the previous studies.

In our study statistically significant difference in risk for development of seizures in ALL patients between 1-10 years age group and >10 years age group was not found. In a retrospective study on 1464 ALL patients treated with (NOPHO) ALL2008 protocol showed that patients aged 10- 17.9 years had higher risk of development of seizures both in univariable and in multivariable analyses. Older age may act as a risk factor for seizures in ALL pediatric patients as they have poor overall outcome, more adverse effects to therapy including thrombosis.¹⁶ Rank et al. showed that ALL patients aged 10.0-17.9 years had an increased risk of cerebral venous sinus thrombosis ($p = .003$).¹⁷

The present study showed female patients developed seizures more than males which was statistically significant by univariate analysis (Odds Ratio - 3.45, $p = 0.029$). But female sex was not found to be a risk factor by multivariate analysis ($p = 0.059$).

Many previous study also found female preponderance to develop seizure in ALL. Maytal et al. in their study found that females are at a significantly higher risk to develop seizures ($p = 0.033$).⁶ Aytac et al. found that females develop more CNS complications including convulsions than males and the male: female ratio was 1:4 for development of these complications.⁴ Parasole et al. also found that females develops more CNS complications including convulsions than males and their male:female ratio was 1:2.⁸ Khan et al. showed that female patients with ALL had statistically significant poor seizure control than male.¹⁸

This increased frequency of seizure in female patients may be due to gender variation in drug pharmacokinetics and pharmacodynamics. Data regarding gender-related drug efficacy and safety profile are limited, but evidence suggests that girls are more vulnerable to the development of side effects

than boys. Gender is an crucial stratification factor and should be incorporated in all cancer trial for improving treatment.¹⁹

Females have different metabolic activities, so they are more vulnerable to most cytotoxic drugs. Different enzyme expression levels and enzyme activities which is regulated indirectly by sex hormones have been implicated for gender-associated differences in metabolism of drugs. In addition, differing body composition like muscle/fat ratios plays a role in treatment efficacy. During the menstrual cycle the sensitivity to a drug is changed. Half-life of drugs is often longer in females, which leads to increased toxicity to drugs but also associated with improved survival. Studies have shown that there are about 40% difference in pharmacokinetics between

men and women for most drugs. It has been found that a greater number of differentially expressed genes are present on the X chromosome. The clustering of genes on the sex chromosomes makes them prone to numerous epigenetic modification.²⁰ So, it can be postulated that increased toxicity to chemotherapeutic drugs in females may be the cause of more seizure in this group.

In the present study B-ALL was found in 94 (89.5%) of patients and T-ALL in 11(10.5%) of patients which is more or less consistent with known immunophenotypic presentation of ALL. According to Lankowsky et al. B precursor ALL accounts for about 80% and T-ALL accounts for 15-20%.²¹ Although in our study all the seizures developed in B-lineage ALL, no statically significant association between these subtypes of ALL with development of seizures was found. But Anastasopoulou et al. in their study showed that patients with T cell immunophenotype has increased risk of development of seizures in univariable analysis but not in multivariable analysis.¹⁶

Among the 15 patients who developed seizure 10 patients had initial WBC count $< 50000 /\text{mm}^3$ and 5 patients had initial WBC count $> 50000 /\text{mm}^3$. Initial WBC count and treatment regimen cannot be considered as risk factor for development of seizure in our study, because those factors had no statistical significant relation with having seizure.

Conclusion:

In this study a slightly higher frequency of seizure (14.3% vs 13%) in children during induction remission chemotherapy for ALL was found compared to previous

studies. Chance of development of seizure is more in female patients. Though statistically not significant all the seizures developed in B-ALL immunophenotype.

Acknowledgement:

We would like to thank our patients and their parents who participated in this study.

References:

1. Islam A, Eden T. Brief report on pediatric oncology in Bangladesh. *South Asian J of Cancer*. 2013;2:105-06.
2. Hunger SP, Loh ML, Whitlock JA, Winick NJ, Carroll WL, Devidas M et al. COG Acute Lymphoblastic Leukemia Committee. Children's Oncology Group's 2013 blueprint for research: acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2013;60:957-63.
3. Margolin JE, Rabin KR, Steuber CP, Poplack DG, Acute Lymphoblastic Leukemia. In: Pizzo PA, Poplack DG, editors. *Principles and practice of pediatric oncology*. 6th ed. Lippincott Williams & Wilkins; 2015. 518, 546.
4. Aytaç S, Yetgin S, Tavil B. Acute and long-term neurologic complications in children with acute lymphoblastic leukemia. *Turk J Pediatr*. 2006;48:1-7
5. Mainero G, Barisone E, Boffi P, Farinasso L, Landolfi C, Dalponte S et al. Convulsions during treatment of acute lymphoblastic leukemia in children. *Minerva Pediatr*. 2000;52:205-14.
6. Maytal J, Grossman R, Yusuf FH, Shende AC, Karayalycin G, Lankowsky P et al. Prognosis and Treatment of seizures in Children with Acute Lymphoblastic Leukemia. *Epilepsia*. 1995;36:831-36.
7. Lo Nigro L, Di Cataldo A, and Schiliro G. Acute neurotoxicity in children with B-lineage acute lymphoblastic leukemia (B-ALL) treated with intermediate risk protocols. *Med Pediatr Oncol*. 2000;35: 449-55.
8. Parasole R, Petruzzello F, Menna G, Mangione A, Cianciulli E, Buffardi S et al. Central nervous system complications during treatment of acute lymphoblastic leukemia in a single pediatric institution. *Leuk Lymphoma*. 2010;51:1063-71.
9. Baytan B, Evim MS, Güler S, Güne° AM, Okan M. Acute central nervous system complications in pediatric acute lymphoblastic leukemia. *Pediatr Neurol*. 2015;53:312-18.
10. Rahman AA, Mannan MA, Sadeque S. Acute and long-term neurological complications in children with acute lymphoblastic leukemia. *Bangladesh Med Res Counc Bull*. 2008;34:90-93.
11. Fasano RE, Bergen DC. Intractable epilepsy in patients treated for childhood acute lymphocytic leukemia. *Seizure*. 2009;18:298-302.
12. Mohamad A, Mikati. Seizure in Childhood, In: Robert M, Kliegmann S, Bonita F and Joseph W, editors. *Nelson Textbook of Pediatrics*. 19th ed. Elsevier India; 2015. 2013.
13. Qureshi A, Mitchell C, Richards S, Vora A, Goulden N. Asparaginase related venous thrombosis in UKALL 2003, reexposure to asparaginase is feasible and safe. *Br J Haematol*. 2010;149:410-3.
14. Kawanami T, Kurita K, Yamakawa M, Omoto E, Kato T. Cerebrovascular disease in acute leukemia: a clinicopathological study of 14 patients. *Intern Med*. 2002; 41:1130-34.
15. Chamberlain MC. Leukemia and the nervous system. *Current Oncology Reports*. 2005;7:66-73.
16. Anastasopoulou S, Heyman M, Eriksson MA, Niinimäki R, Taskinen M, Mikkil S et al. Seizures during treatment of childhood acute lymphoblastic leukemia: A population-based cohort study. *Eur J Paediatr Neurol*. 2020;27:72-77.
17. Rank CU, Toft N, Tuckuviene R, Grell K, Nielsen OJ, Frandsen TL et al. Thromboembolism in acute lymphoblastic leukemia: results of NOPHO ALL2008 protocol treatment in patients aged 1 to 45 years. *Blood*. 2018;131:2475-84.
18. Khan RB, Morris EB, Pui CH, Hudson MM, Zhou Y, Cheng C et al. Long-term outcome and risk factors for uncontrolled seizures after a first seizure in children with hematological malignancies. *J Child Neurol*. 2014;29:774-81.
19. Gabriele L, Buoncervello M, Ascione B, Bellenghi M, Matarrese P, Carè A. The gender perspective in cancer research and therapy: novel insights and on-going hypotheses. *Ann Ist Super Sanita*. 2016;52:213-22.
20. Schmetzer O, Flörcken A. Sex differences in the drug therapy for oncologic diseases. In: Barrett, James E , editors. *Handb Exp Pharmacol*. Springer, Berlin, Heidelberg. 2012;(214):411-42.
21. William L, Carroll and Bhatla, Acute Lymphoblastic Leukemia. In: Lankowsky P, Lipton JM, Fish JD, editors. *Lanzkowsky's Manual of Pediatric Hematology and Oncology*. 6th ed. Academic Press; 2016.367.