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Molecular Cytogenetics and Immunophenotypic Characterization of Childhood Acute Leukaemia Patients in Tertiary Care Center of Bangladesh – An observative study

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Abstract

Background: Childhood leukemia is genetically a heterogeneous disease. Various types of cytogenetic abnormalities and immunophenotypic character are present in leukaemia which are important for risk stratification, treatment and play as significant prognostic factor. Pediatric acute leukaemia presents with varying clinical, morphological, immunological and molecular characteristics. It is very highly curable if diagnosed and treated properly. For detail typing and subtyping of acute leukemia immunophenotyping and cytogenetics are crucial. The aim of this study was to find out the genetic abnormalities and immunophenotypic characterization of childhood acute leukaemia patients in Bangladesh. **Material & Methods:** This was a retrospective observational study and was conducted in the Department of pediatric hemato-oncology of Combined Military Hospital, Dhaka and Ahsania Mission Cancer Hospital, Mirpur, Dhaka, Bangladesh during the period from February,2014 to March, 2022. There was total 98 cases of acute leukaemia. **Results:** In total 98 patients completed the study. We found that 79.59% patients were ALL and 20.41% patients were AML. Among ALL 80.64% were B cell type, 6.40% were T cell Type ; 12.82 % had TEL/AML1 or ETV6/RUNX1 t(12;21)(p13;q22), 5.13% patient had TCF3/PBX1 or E2A/PBX1 t(1;19)(q23;p13). In AML30.00% patient had PML/RARAt(15;17)(q22;q21), 10.00% patient had AML1/ETO or RUNX1/CBFA2T1 t(8;21) (q22;q22), 5.00% patient had FLT3/ ITD. In case of B-ALL highest expression of antigen was CD19 (91.64%) followed by CD10 (80.58%), HLADR (67.94%), CD22 (72.68%), CD79a (72.68%), TdT (52.14%) and CD34 (48.98%). In 44.24% cases there was co-expression of CD10 and CD19 and there was 11.6% expression of myeloid marker CD13 and 1.58% expression of T cell marker CD5. In case of T-ALL there was 100% expression of CD3. Expression of other antigen CD4, CD5, CD7, CD8, CD4/8 co-expression, TdT was 60%. There was 40% expression of CD1a and CD2. There was 20% expression of CD10, CD34 and TCRab also. In case of AML highest expression was MPO (93.75%) followed by CD33 (87.50%), CD13 (81.25%), CD117 (75%), HLADR (43.75%) and CD64 (50%). There was 6.25% aberrant expression of B-ALL marker CD19 and T-ALL marker CD3, CD4, CD5, CD7 also. **Conclusion:** Depending on this study we can say that except few variations distribution of immunophenotypical subtypes and genetic abnormalities of childhood acute leukaemia are almost similar to other literature published from neighboring countries.This study will serve as a guideline for future study in our country in this aspect.

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Keywords:- Childhood acute leukaemia, Molecular Cytogenetics, Immunophenotyping.

INTRODUCTION

Childhood leukemia is genetically a heterogeneous disease, highly associated with a wide spectrum of factors that play a role in the epidemiology, risk stratification, and therapeutic intervention. Pediatric acute leukaemia being a heterogenous disease presents with varying clinical, morphological, immunological and molecular characteristics.[1,2] It is very highly curable if diagnosed and treated properly. For detail typing and subtyping of acute leukemia immunophenotyping is crucial.[3,4] To do precise classification and identification of aberrant antigen expression among neoplastic population immunophenotyping is the only way.[5] Cytogenetic analysis of genes involved in disease-specific translocations is considered one of the most powerful tools leading to better understanding of chromosomal rearrangements and the mechanisms underlying leukemic transformation. More specifically, cytogenetic analysis has provided remarkable insights of a cell population and can detect several chromosomal and genetic abnormalities in various types of hematologic malignancies, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The presence or absence of chromosomal aberrations is a significant prognostic factor for both ALL and AML It is also important for selection of treatment, to predict prognosis and to see minimal residual disease (MRD). Acute lymphoblastic leukemia (ALL) is a neoplastic disease characterized by the abnormal proliferation of immature lymphoid cells. It is the most frequent hematologic malignancy diagnosed in children, and it represents ~25% of cancer diagnoses among children younger than 15 years of age.[6] Acute leukaemia is the most common childhood malignancy worldwide.[7] It is the most common childhood malignancy in Bangladesh also.[8] The relative survival rate is also very high in case of childhood acute leukaemia. From 2009 to 2015, the 5-year relative survival rates overall were 91.9 % in ALL and 68.7% in AML for children younger than 15 years of age.[9] Incidence of childhood leukemia occur in 1-10 year age group.[10] ALL is more common in 2-5 years of age and AML in <2 years and teenage age group.[11] The diagnosis of ALL is based on medical examination, flow cytometric immunophenotyping, cytochemical characteristics, and cytogenetic and molecular findings. ALL is classified as B-cell precursor acute lymphoblastic leukemia (BCP-ALL) and T-cell acute lymphoblastic leukemia (T-ALL), representing ~85 and 15% of the pediatric ALL cases, respectively. In addition, less than 5% of acute leukemias are classified as ambiguous lineage acute leukemia (ALAL). Several conventions have been used to define mixed phenotype leukemias, the most recent of which is the WHO classification of tumor of hematopoietic and lymphoid tissues, which takes into account the expression of the most specific markers for lineage assignment.[2] Nonrandom chromosomal abnormalities (CAs) have been reported in BCP-ALL and T-ALL. The Third International Workshop on Chromosomes in Leukemia [1983] was the first major study that demonstrated the independent prognostic significance of

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cytogenetic findings at diagnosis in ALL. Subsequently, several studies have been reported on CAs in childhood ALL, which support those first results and revealed important data of further recurrent structural and numerical CAs with a prognostic impact mainly in BCP-ALL. The most relevant examples of the prognostic impact of CAs are t(9;22) (q34;q11.2), t(4;11)(q21;q23) and near haploidy/low hypodiploidy, associated with poor prognosis, while high hyperdiploidy and t(12;21)(p13;q22) are associated with good prognosis. Conversely, in T-ALL, although recurrent CAs have been reported, they are mostly not associated with prognostic significance. G-banding is the method commonly carried out to detect CAs. It is relatively inexpensive and covers the complete spectrum of karyotypic abnormalities; however, it is not always successful, and sometimes the chromosomes have a poor quality and indistinct banding for an accurate analysis. The use of FISH and molecular techniques, such as RT-PCR, have led to the detection of cryptic chromosomal rearrangements such as t(12;21) (p13;q22)/ ETV6- RUNX1 (former TEL-AML1), which is the most common chromosomal rearrangement in BCP-ALL. Furthermore, some studies have applied spectral karyotyping or multi-FISH complemented by FISH with locus-specific probes, which are techniques that have proved very useful to clarify complex rearrangements. However, these methods are not routinely applied, since they are costly and labor-intensive procedures.[12] Bangladesh is a developing country. Most of the children affected by leukaemia are from poor socioeconomic background in the developing countries. It is very difficult for them to bear the cost of treatment as such many of them left treatment on the way.[13,14] Most of them can't afford the costly investigations and at the same time cytogenetic testing is not available in Bangladesh. There is very limited study on immunophenotyping of childhood acute leukaemia in Bangladesh because of many limitations. We are dependent on neighboring country to do the investigation which makes it more costly. For this reason there is very limited data are available on cytogenetics of acute leukaemia in Bangladesh. This study was undertaken to find out the molecular cytogenetic and immunophenotypic characterization of childhood acute leukaemia among bangladeshi children.

Objective

The objective of this study was to find out the genetic abnormalities and immunophenotypic characterization of childhood acute leukaemia patients in Bangladesh.

MATERIAL AND METHODS

This was a retrospective observational study and was conducted in the Department of pediatric hemato-oncology of Combined Military Hospital, Dhaka and Ahsania Mission Cancer Hospital, Mirpur, Dhaka, Bangladesh during the period from February,2014 to March, 2022. There was total 98 cases of acute leukaemia. These are the following criteria to be eligible for the enrollment as our study participants: a) Patients who were aged up to 15 years old; b) Patients clinically suspected of acute leukaemia; c) Patients diagnosed by the WHO classification based on medical examination, flow cytometric

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immunophenotyping, cytochemical characteristics, and cytogenetic and molecular findings; And a) Patients not willing to participate in the study ; b) Patients who had neither immunophenotyping nor cytogenetic study were excluded from the study.

All cases were included in the study, their types and subtypes were evaluated. Variables that have been collected were age, sex, types and subtypes of leukaemia and their cytogenetic abnormalities. Immunophenotyping was done by flowcytometry of bone marrow aspiration and in few cases by immunohistochemistry of bone marrow trephine biopsy. As this test is not widely available in Bangladesh immunophenotyping and molecular cytogenetics were done from India. Immunohistochemistry was done from this institute. All data were collected from patient registry, scrutinized and then analyzed.

RESULTS

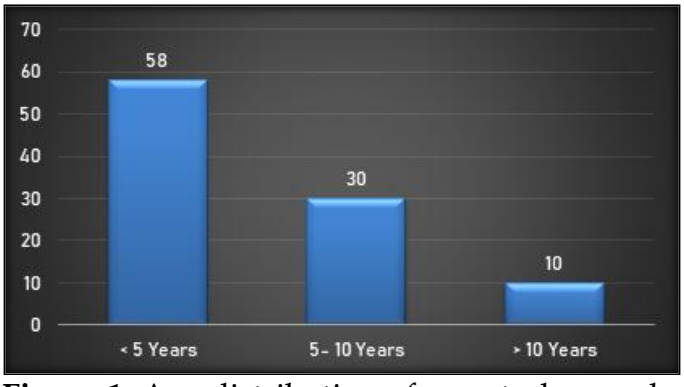

Figure 1: Age distribution of our study people (n=98).

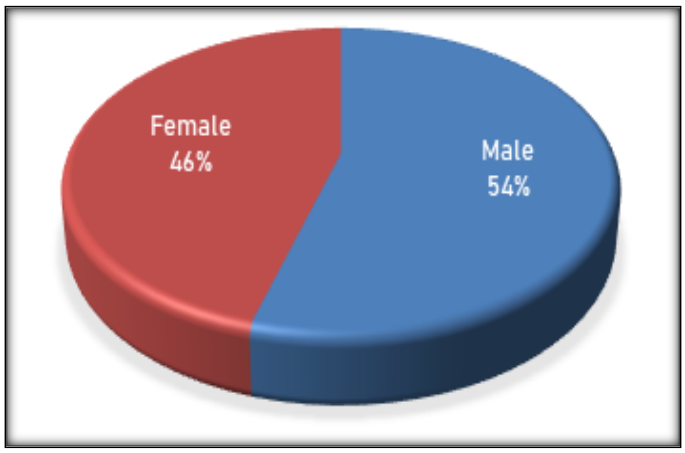

Figure 2: Distribution of patients as per gender (n= 98)

In [Figure 1] we showed the age distribution among our study people. We found that maximum 58 (59.18%) patients were <5 years age group followed by 30 (30.61%) patients from 5- 10 years age group and 10(10.20%) patients were from >10 years age group. In figure 2 we showed the distribution of patients as per gender. We found that majority (54%) of our patients were male compared to female (46%). Male female ratio was (1.17:1). In [Table 1] we showed the distribution of patients as per types and subtypes of Leukaemia. We found that 79.59% patients were ALL and 20.41% patients were AML. Among ALL 80.64% were B cell type, 6.40% were T cell Type and 62.82% were morphologically L1 variety and 37.18% were L2 variety and IPT not done in 12.8% cases. Among AML maximum 30.00% were M0, 25.00% were M3 type followed by 20.00% M1, 10.00% M4 and 15.00% were undifferentiated type and IPT not done in 20% cases. In [Table 2] we showed the cytogenetic findings of acute leukaemia among our study participants. In case of ALL 64.10% patients were negative for all cytogenetic abnormality, 12.82 % had TEL/AML1 or ETV6/RUNX1 t(12;21)(p13;q22), 5.13% patient had

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TCF3/PBX1 or E2A/PBX1 t(1;19)(q23;p13) and 17.94% cases cytogenetics were not performed. In AML 30.00% patients were negative for all cytogenetic abnormality, 30.00% patient had PML/RARA t(15;17) (q22;q21), 10.00% patient had AML1/ETO or RUNX1/CBFA2T1 t(8;21) (q22;q22), 5.00% patient had FLT3/ ITD and 25.00% cases cytogenetics were not performed. In table 3 we showed the antigen expression of B-ALL, T-ALL and AML among our study subjects. In case of B-ALL highest expression of antigen was CD19 (91.64%) followed by CD10 (80.58%), HLADR (67.94%), CD22 (72.68%), CD79a (72.68%), TdT (52.14%) and CD34 (48.98%). In 44.24% cases there was co-expression of CD10 and CD19. In case of B-ALL there was 11.6% expression of myeloid marker CD13 and 1.58% expression of T cell marker CD5. In case of T-ALL there was 100% expression of CD3. Expression of other antigen CD4, CD5, CD7, CD8, CD4/8 co-expression, TdT was 60%. There was 40% expression of CD1a and CD2. There was 20% expression of CD10, CD34 and TCRab also. In case of AML heighst expression was MPO (93.75%) followed by CD33 (87.50%), CD13 (81.25%), CD117 (75%), HLADR (43.75%) and CD64 (50%). There was 6.25% aberrant expression of B-ALL marker CD19 and T-ALL marker CD3, CD4, CD5, CD7 also.

Table 1: Distribution of patients as per types and subtypes of Leukaemia (n=98)

Types of Leukaemia	**Number**	**Subtype of ALL**	**Number (n= 78)**	**%**
ALL	78 (79.59%)	L_1	49	62.82
		L_2	29	37.18
		L_3	-	-
		B – ALL	63	80.64
		T – ALL	5	6.40
		IPT not Done	10	12.8
AML	20 (20.41%)	Subtype of AML	Number (n=20)	%
		M_0	6	30.00
		M_1	4	20.00
		M_2	-	-
		M_3	5	25.00
		M_4	2	10.00
		Undifferentiated	3	15.00
		IPT not Done	4	20.00

Table 2: Cytogenetic findings of acute leukaemia among our study people (n=98)

Types of leukaemia	**Genetic Findings**	**Number**	**%**
ALL (n=78)	Negative	50	64.10
	Not done	14	17.94
	TEL/AML1or ETV6/RUNX1 t(12;21)(p13;q22)	10	12.82
	TCF3/PBX1 or E2A/PBX1 t(1;19)(q23;p13)	4	5.13
AML (n=20)	Negative	6	30.00

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	Not done	5	25.00
	PML/RARA t(15;17)(q22;q21)	6	30.00
	AML1/ETO or RUNX1/CBFA2T1 t(8;21) (q22;q22)	2	10.00
	FLT3/ ITD	1	5.00

Table 3: Antigen Expression of B-ALL, T-ALL and AML among study subjects

Antigen	**Expression**					
	B- ALL(n=63)		**T- ALL(n=5)**		**AML(n=16)**	
	Number	**%**	**Number**	**%**	**Number**	**%**
CD19	58	91.64	-	-	1	6.25
CD20	20	31.60	-	-	-	-
CD22	46	72.68	-	-	-	-
CD79a	46	72.68	-	-	-	-
Tdt	33	52.14	3	60.00	-	-
CD34	31	48.98	1	20.00	6	37.5
CD38	11	17.38	-	-	2	12.5
CD117	1	1.58	-	-	12	75
CD10	51	80.58	1	20.00	1	6.25
CD 10/19 coexpression	28	44.24	-	-	-	-
CD3	-	-	5	100.00	1	6.25
CD4	-	-	3	60.00	1	6.25
CD5	1	1.58	3	60.00	1	6.25
CD7	-	-	3	60.00	1	6.25
CD8	-	-	3	60.00	-	-
CD4/8 co-expression	-	-	3	60.00		
CD36	-	-	-	-	2	12.5
MPO	-	-	-	-	15	93.75
CD13	7	11.06	-	-	13	81.25
CD14	-	-	-	-	3	18.75
CD15	1	1.58	-	-	6	37.5
CD33	3	4.74	-	-	14	87.5
HLADR	43	67.94	-	-	7	43.75
CD64	-	-	-	-	8	50
CD58	10	15.8	-	-	-	-
CD9	9	14.22	1	20.00	-	-
CD99	1	1.58	1	20.00	-	-
CD11b	-	-	-	-	3	18.75
IgM	3	4.74	-	-	-	-
CD1a	-	-	2	40.00	-	-

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CD2	-	-	2	40.00	-	
TCRab	-	-	1	20.00	-	-

DISCUSSION

In our study we found maximum 58 (59.18%) patients were <5 years age group followed by 30 (30.61%) patients from 5- 10 years age group and 10(10.20%) patients were from >10 years age group. [Figure 1] In other study (Coccé et al.) found the mean age of their study was 6.5 years with a median age of 5.5 years (range: 10 days–16 years); 85 were infants (< 1 year age).[12]

In this study we found majority (54%) of our patients were male compared to female (46%). Male female ratio was 1.17:1 [Figure 2] In other study (Coccé et al.) found in their study that the male to female ratio was 1.16 :1.[12] In our study we found 79.59% patients were ALL and 20.41% patients were AML. Among ALL 80.64% were B cell type, 6.40% were T cell Type and 62.82% were morphologically L1 variety and 37.18% were L2 variety and IPT not done in 12.8% cases. Among AML maximum 30.00% were M0, 25.00% were M3 type followed by 20.00% M1, 10.00% M4 and 15.00% were undifferentiated type and IPT not done in 20% cases. [Table 1] A study(Jawaid et al.) from Pakistan reported 14.7% AML and 83.3% ALL cases.[15] Two studies (Gujral et al. & Gupta et al.) from India reported 76.9 and 77.84% ALL cases respectively.[16,17] In a study of Bangladesh reported 58% cases of ALL.[18] Our study was similar to Pakistani studies (78.5-87%),[19,20] as well as an Indian study by (Madhumathi et al).[21] However studies from West reported between 72.9 and 91% frequency.[19,22] In our study we found that in case of ALL 64.10% patients were negative for all cytogenetic abnormality, 12.82 % had TEL/AML1 or ETV6/RUNX1 t(12;21) (p13;q22), 5.13% patient had TCF3/PBX1 or E2A/PBX1 t(1;19)(q23;p13) and 17.94% cases cytogenetics were not performed. In AML 30.00% patients were negative for all cytogenetic abnormality, 30.00% patient had PML/RARA t(15;17)(q22;q21), 10.00% patient had AML1/ETO or RUNX1/CBFA2T1 t(8;21) (q22;q22), 5.00% patient had FLT3/ ITD and 25.00% cases cytogenetics were not performed. [Table 2] In other study (de Thé et al.) found the t(15;17) (q22;q21) fuses the RARA gene on chromosome 17q21 to the PML gene on chromosome 15q22.[23] The vast majority of variant t(15;17) involves the PML and retinoic acid receptor-_ (RARA) genes and occur in acute promyelocytic leukemia (APL).[24] TEL/AML1, also known as ETV6/RUNX1, is considered the most common translocation in childhood ALL, with a prevalence of 20% to 25%.[25] The t(12;21) (p13;q22) translocation involves the ETS type variant 6 (ETV6) or translocated ETS leukemia (TEL) gene on 12p13 and the RUNX1 gene (AML1; acute myeloid leukemia 1) on 21q22.[24,26] The E2A gene is located within chromosome band 19p13 and 3 at the breakpoint of the t(1;19)(q23;p13) translocation.[27] This translocation characterizes pediatric precursor B–lineage ALL patients and can be either balanced t(1;19) or unbalanced der(19)t(1;19)(q23;p13) with 2 normal chromosomes.[28] In a study in 216 AML patient's incidence of FLT3-ITD mutation was 20.83%.[29] Cytogenetic abnormalities of the short arm of the chromosome 9 (9p) are observed in approximately 7% to 12% of

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childhood ALL cases.[24] In regard to 9q abnormalities, deletion of the long arm of chromosome 9 [del(9q)] occurs at a frequency of 0% to 4% to 6% in AML with an inferior clinical outcome.[24] In the current study we found that in case of B-ALL highest expression of antigen was CD19 (91.64%) followed by, CD10 (7680.58%), HLADR (67.94%), CD22 (72.68%), CD79a (72.68%), TdT (52.14%) and CD34 (48.98%). In 44.24% cases there was co-expression of CD10 and CD19. In case of B-ALL there was 11.6% expression of myeloid marker CD13 and 1.58% expression of T cell marker CD5. In case of T-ALL there was 100% expression of CD3. Expression of other antigen CD4, CD5, CD7, CD8, CD4/8 co-expression, TdT was 60%. There was 40% expression of CD1a and CD2. There was 20% expression of CD10, CD34 and TCRab also. In case of AML heighst expression was MPO (93.75%) followed by CD33 (87.50%), CD13 (81.25%), CD117 (75%), HLADR (43.75%) and CD64 (50%). There was 6.25% aberrant expression of B-ALL marker CD19 and T-ALL marker CD3, CD4, CD5, CD7 also. [Table 3] Studies reported CD19 as the most sensitive marker for diagnosis of B-ALL.[30,31] Some study reported CD79a as the most often expressed antigen.[22] A wide range of aberrant expression of myeloid antigens including CD13 and CD33 in B-ALL and T-ALL cases reported in different literature.[32,33] There is 14% aberrant expression of CD13 and 4% aberrant expression of CD33 in case of B-ALL in this study which is consistent with a study done in Srilanka.[34] Negativity for CD20, as B-cell specific marker was observed in 61.8% of B-ALL cases reported by (Tong et al.).[22] Absence of CD10 expression was observed in 5-18.8% reported in eastern and western studies. [21,33] In case of T-ALL all cases were positive for CD3. It is an established fact that CD3 is the best marker for T-ALL. It is also same in some other study.[34,35] CD5 and CD7 expression is lower in this study may be due to small sample size. In case of AML maximum positivity was MPO followed by CD33, CD13 and CD117 but study from Pakistan and India shows that maximum positivity is for CD33 and CD13.[35,36] In case of AML there is 6.66% aberrant expression of B cell marker CD19 and T cell marker CD3, CD5 and CD7. In a study it was published that in 7.5% cases B cell marker may be present with AML and 16.8% cases T cell marker may be present with AML.[37]

Limitations of the study

Our study was done in two Centre only. We could only study the patients who attended at the pediatric hemato-oncology department of our study places. In our study small sample size was also a limitation. In our study some cases immunophenotyping and in some cases cytogenetics were not performed. Correlation between morphologic subtype and immunophenotypical subtype was not done.

CONCLUSIONS

In our study we found that despite immunophenotyping and cytogenetic analysis are crucial for acute leukaemia these were not done in all center in our country due to limitations of facility. There is no large scale study also on immunophenotyping and molecular cytogenetics in childhood acute leukaemia. This study will serve as a guideline for future study in this aspect. Depending on this study we can say that except few variations distribution of immunophenotypical

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subtypes and genetic abnormalities of childhood acute leukaemia are almost similar to other literature published from neighboring countries.

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