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Original Article

Clinicopathological Analysis of Childhood Leukemia - A Study Conducted in a Tertiary Care Centre in South India

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Abstract

Background: *Leukemias constitute the most common diagnostic group of childhood cancers worldwide, and in India, accounting for about 31% of childhood cancers. More than 95% of childhood leukemias are acute leukemias. Symptoms and signs are a consequence of bone marrow failure or the involvement of medullary or extramedullary sites by leukemia.*

Aim: *To study the presenting clinical features and laboratory findings of children with leukemia and to study their relationship with different subtypes.*

Materials & Method: *This descriptive study was conducted in the department of Pathology, Govt. Medical College, Kozhikode, based on the details of all the newly diagnosed cases of leukemia in children aged between 0 - 12 years from 1st January 2013 to 30th June 2017.*

Results & Conclusion: *Out of 233 cases of childhood leukemia 232 were acute leukemia (99.6%) and one was chronic myeloid leukemia (CML). Male: Female ratio was 1.6:1. Most prevalent age group was 1to 4 years. Acute lymphoblastic leukemia (ALL) was the commonest type of leukemia, B- ALL being the predominant immunophenotype. The most common subtype of AML was AML with maturation. B-ALL was more frequent in younger children while T-ALL and AML in older children. Most common features at presentation were fever, bleeding manifestations, hepatomegaly, splenomegaly, pallor and lymphadenopathy. T-ALL presented with higher leucocyte count and hemoglobin concentration compared to other types. Most of the results were comparable with the available data from literature.*

Keywords: *Childhood leukemia, Acutelymphoblastic leukemia, Acute myeloblastic leukemia, B-ALL, T-ALL.*

Introduction

Leukemias constitute the most common diagnostic group of childhood cancers worldwide, and in India, accounting for about 31% of childhood cancers. More than 95% of childhood leukemias are acute leukemias. Acute lymphoblastic leukemia (ALL) accounts for about 77% of childhood leukemias. Acute myeloid leukemia (AML) for about 11%, Chronic myeloid leukemia (CML) for 2-3% and Juvenile myelomonocytic leukemia (JMML) for 1-2%. The remaining cases are a variety of acute and chronic leukemias that do not have classic features of ALL, AML, CML or JMML.[1,2]

AML and ALL differ substantially in response to therapy and course, and accurate differentiation of the two is fundamental to therapeutic decisions. Sub classification of each group is also of

increasing importance, as treatment continues to evolve for specific genetic and pathogenetic subgroups of disease.[3]. Immunophenotyping by flowcytometry is now standard for acute leukemias and required for the accurate diagnosis of ALL and some AMLs.[4]

Despite affecting children of all ages, the peak incidence of ALL is between two and five years of age, with a slight predominance among boys. [5] The incidence of AML in children remains stable during childhood, except for a slight increase during adolescence and a peak during the neonatal period.[4] Symptoms and signs are a consequence of bone marrow failure or the involvement of medullary or extramedullary sites by leukemia. Onset may be insidious and slowly progressive over weeks to months, or acute and explosive. In general, the more indolent the onset of symptoms, the better will be the outcome.[3]

The purpose of this study is to analyze the presenting clinical features and laboratory findings of children with leukemia and to study their relationship with different subtypes of leukemia.

Materials & Method

This was a descriptive study performed in the department of Pathology, Government Medical College, Kozhikode. All the newly diagnosed cases of leukemia in children aged between 0 - 12 years from 1st January 2013 to 30th June 2017 were collected from records. The diagnosis of different types of leukemia was based on the morphology in peripheral smear or bone marrow, cytochemistry and flowcytometry. The data collected and recorded were age at presentation, gender, presenting symptoms, signs, hemoglobin concentration (Hb), total leucocyte count (TLC) and platelet count at presentation, type of leukemia including immunophenotype.

Data was entered according to the variables onto spreadsheets of Microsoft Office Excel 97 - 03 and the variables were analyzed using standard analytical techniques with SPSS version 16.0 for Windows. Quantitative variables were expressed as mean while the qualitative variables were expressed as percentage. The difference and association between qualitative variables were analyzed using Chi-square test and quantitave variables using anova. p values <0.05 were considered significant.

Results

There were 233 new cases of childhood leukemia in our institution during the study period. The data showed a significant male preponderance (61.8% males and 38.2% females), M: F = 1.6:1. Majority of the children (173) were between 1and 9 years (74.3%), of them 109 (46.8 %) were in the age group 1 to 4 years. 15 (6.4%) were below 1 year and 45 (19.3%) were above 10 years. The youngest was a new born baby. (Fig 1)

Out of 233 children, 232 had acute leukemia (99.6%) and one had chronic myeloid leukemia (CML). Of the 232 acute leukemia cases, 199 children (85.8%) had acute lymphoblastic leukemia (ALL), 32 (13.8%) had acute myeloid leukemia (AML) and one was reported as ALL/AML M0. Immuno phenotyping using flowcytometry was done in 148 cases of ALL. 118/148 cases (79.7%) were ALL- B cell type (B-ALL) and 30/148 cases (20.3%) were ALL- T cell type (T-ALL). The most common subtype of AML was AML with maturation (10 out of 32 cases -31.3%). There were 5 cases of AML without maturation and 4 cases each of acute promyelocytic leukemia and acute monoblastic leukemia. 3 cases of acute myelomonocytic leukemia, 1 case of erythroleukemia and 2 cases of acute megakaryoblastic leukemia were also reported. Flowcytometry was performed in 10 cases of AML.

The most frequent presenting complaint of childhood leukemia was fever (66.1%) followed by bleeding manifestations (28.8%), joint pain (14.2%), tiredness (13.3%), respiratory tract infections (10.7%), abdominal pain (5.6%), bone pain (4.3%), and weight loss (3.4%). Rare complaints were edema, vomiting, body ache and abdominal distension.

172 (73.8%) children had hepatomegaly, 159 (68.2%) had splenomegaly, 140 (60.1%) had pallor and 132 (56.7%) had lymphadenopathy at the time of presentation. Mediastinal mass was detected in 7 children (3%) and out of this 6 had Acute lymphoblastic leukemia- T cell type (T-ALL). (Table 1)

5 (2.1%) children were with Down syndrome - Two were 12 years old and others were aged between 1 and 5 years. The youngest one had AML (Acute megakayoblastic leukemia) and others had ALL (Two had B-ALL , two had ALL which were not immunophenotyped). One child with thalassemia minor (4 year, male) had B-ALL. Mean hemoglobin of the study population was 7.4 g/dl ranging from 1.9 to 13.9 g/dl. Mean total leucocyte count (TLC) was 59,225 cells/mm^3 ranging from 810 to 5,48,000 cells / mm^3. Mean platelet count was 79993/mm^3, ranging from 4000 to 660000/mm^3.

Sub group analysis of acute leukemia

Male preponderance was seen in both ALL and AML. M:F ratio for ALL and AML were 1.6:1 and 1.7:1 respectively. T- ALL showed a higher degree of male preponderance, the ratio being 2.6:1 in this study. (p value 0.05)

Out of the 15 cases of acute leukemia in children below 1 year, 8 were ALL and 7 were AML. 21.9% of AML cases were seen below 1 year whereas only 4% of ALL were seen in this age group. Out of the 8 ALL cases, 4 were B-ALL and 4 were not immunophenotyped. No cases of T-ALL were reported below 1 year in this study. Major proportion of B-ALL (70 out of 118-59.3%) was in the age group 1-4 years. Majority of T- ALL cases (73.3%) were seen in children above 5 years. 12 out of 30 (40%) cases were between 5 and 9 years and 10 out of 30 (33.3%) were between 10 and 12 years. In case of AML also slight increase in number above 5 years (59.4%). (Fig 2).

Fever was the most frequent presenting symptom in all types of acute leukemia followed by bleeding manifestations. 65.9% of children with acute leukemia had fever and 28.9% had bleeding manifestations. The most frequent sign elicited in children with acute leukemia on presentation was hepatomegaly (73.7%), the rate was higher in ALL (76.1%) compared to that in AML (59.4%) which is statistically significant (p value 0.009). T-ALL had highest rate of hepatomegaly (90%). Splenomegaly was noted in 71.4% cases of ALL and 50% cases of AML (p value 0.043). T- ALL had higher rate of splenomegaly compared to B-ALL, 83.3% and 71.2% respectively (p value 0.043). Pallor was noted in 68.8% cases of AML and 58.3% cases of ALL. The rate was higher in B-ALL (64.4%) compared to T-ALL (43.3%) (p value 0.165). 59.7% of children with ALL and 34.4% of children with AML had significant lymphadenopathy and the rate was higher in T-ALL (83.3%) than in B-ALL (55.9%)(p value 0.005). Mediastinal mass was detected in 20% cases of T-ALL , 0.8% cases of B-ALL and none in AML (p value 0.000). 6 out of 7 children (85.7%) with mediastinal mass were having T-ALL. (Table 1)

Mean hemoglobin concentration was lowest in B-ALL and highest in T-ALL (p value 0.003). Mean total leucocyte count (TLC) was highest in T-ALL and in B-ALL (p value 0.034). Percentage of cases with Hb >10g/dl and TLC >50,000/ mm^3 and > 1,00,000/ mm3 were very high in T- ALL compared to other types. Mean platelet count was lowest in B- ALL (p value .000). Percentage of cases with thrombocytopenia at presentation was less in T-ALL compared to other types, but it was statistically not significant. (Table 2)

Chronic leukemia

Only one child had chronic myeloid leukemia in this study (0.4%) who was a six year old female child. Her presenting complaints were fever and body ache. She had pallor, lymphadenopathy and hepatosplenomegaly at the time of presentation. She had marked leucocytosis (TLC- 95000/mm^3), thrombocytopenia (platelet count- 51,700/mm^3) and mild anemia (Hb- 10.7g/dl).

Fig. 1 Age group of children with leukemia

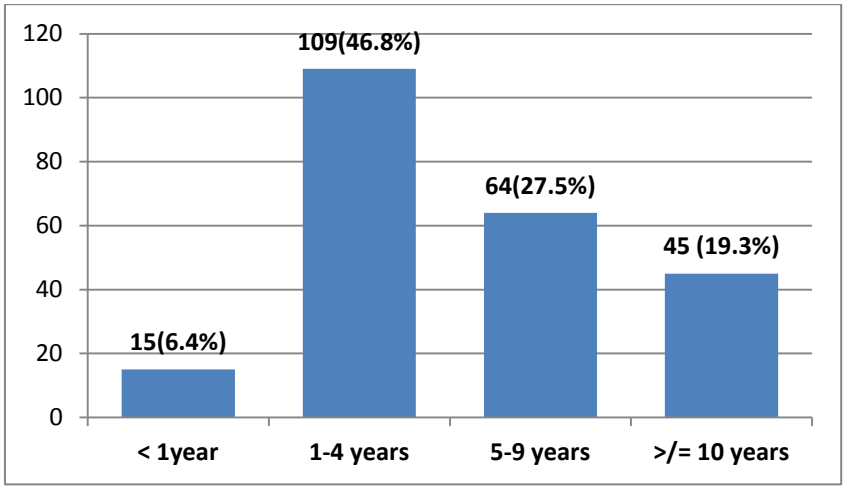
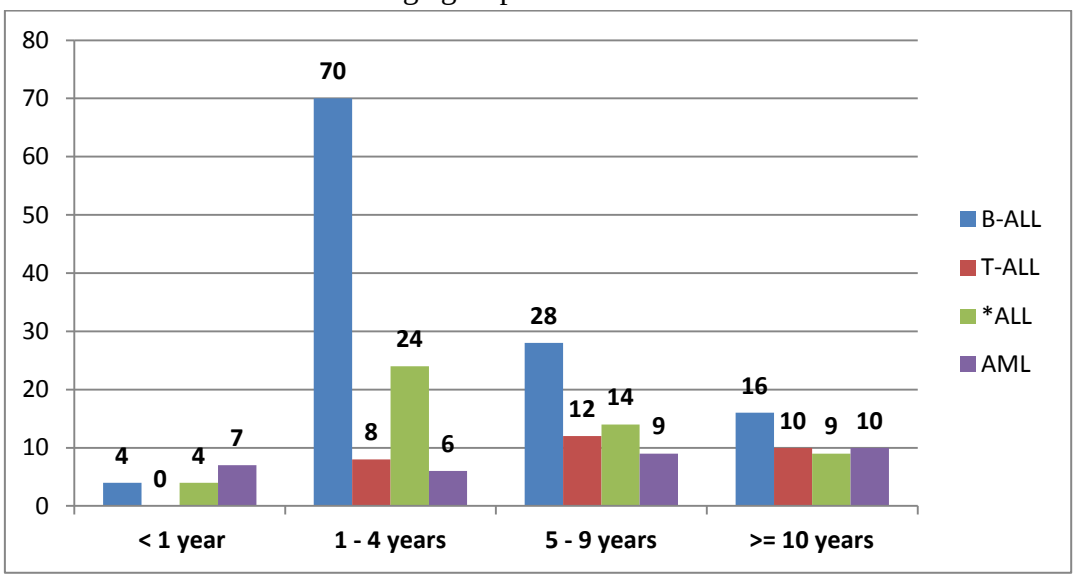


Fig 2 Types of acute leukemia in different age groups



*ALL not immunophenotyped

Table 1 Presenting symptoms and clinical signs in childhood leukemia

Symptoms	B-ALL(118) n, (%)	T-ALL(30) n, (%)	*ALL(51) n, (%)	AML(32) n, (%)	ALL/AML0(1) n, (%)	CML(1) n, (%)	Total(233) n, (%)	P value
Fever	81 (68.6)	18 (60)	29 (56.9)	24(75)	1(100)	1(100)	154 (66.1)	0.424
Bleeding manifestation	37 (31.4)	8 (26.7)	13 (25.5)	8 (25)	1(100)	1(100)	67 (28.8)	0.576
Joint pain	20(16.9)	2 (6.7)	5(9.8)	6(18.8)	Nil	Nil	33 (14.2)	0.575
Tiredness	12(10.2)	7 (23.3)	8 (15.7)	4 (12.5)	Nil	Nil	31(13.3)	0.521
Respiratory tract infections	7(5.9)	2 (6.7)	12 (23.5)	4 (12.5)	Nil	Nil	25 (10.7)	0.029
Abdominal pain	6 (5.1)	3 (10)	3 (5.9)	1(3.2)	Nil	Nil	13(5.6)	0.273
Bone pain	9 (7.6)	Nil	1 (2)	Nil	Nil	Nil	10 (4.3)	0.273
Weight loss	1 (0.8)	3 (10)	2 (3.9)	2 (6.3)	Nil	Nil	8 (3.4)	0.273
Signs								
Hepatomegaly	93 (78.8)	27 (90)	32 (62.7)	19 (59.4)	1 (100)	Nil	172 (73.8)	.009
Splenomegaly	84 (71.2)	25 (83.3)	33 (64.7)	16 (50)	1 (100)	Nil	159 (68.2)	.043
Pallor	76 (64.4)	13 (43.3)	27 (52.9)	22 (68.8)	1(100)	1(100)	140 (60.1)	.165
Lymphadenopathy	66 (55.9)	25 (83.3)	28 (54.9)	11 (34.4)	1(100)	1(100)	132 (56.7)	.005
Mediastinal mass	1 (0.8)	6 (20)	Nil	Nil	Nil	Nil	7(3)	.000

*ALL not immunophenotyped

Table 2 Baseline hematological parameters at presentation in different types of acute leukemia

Hematological parameters	B-ALL N =118	T-ALL N=30	AML N=32	P value
Mean Hb (g/dl) (Ranges)	6.9 (1.9-13.6)	8.9 (3.5-13.9)	7.6 (3.3-12.7)	0.003
Cases with Hb >/= 10 g/dl (no.& %)	18(15.3)	11 (36.7)	3 (9.4)	0.021
Mean TLC (cells/mm^3) (Ranges)	48725.4 (1500- 454000)	108483 (1070-388000)	69589 (2100-548000)	0.034
Cases with TLC >50,000 cells/mm^3 (no. & %)	29 (24.6)	13 (43.3)	11(34.4)	0.21
Cases with TLC >1,00,000 cells/mm^3 (no. & %)	15(12.7)	12 (40)	8 (15.7)	0.001
Mean platelet count (cells/mm^3) (Ranges)	66630.5 (4000- 358000)	105866.7 (4000-660000)	78875 (6000-338000)	.000
Cases with thrombocytopenia (Platelet count < 150000/ mm^3) (no & %)	104 (88.1)	23 (76.7)	28 (87.5)	0.43

Table 3 Comparison of signs & symptoms of childhood leukemia between previous two studies and the present study

Signs & symptoms (%)	Biswas S et al, West Bengal (2009) [6]	Clarke RT et al, U.K (2016) [10]	Present Study (2017)
NO. of cases	75	3084	233
Fever	85.3	53	66.1
Bleeding manifestations	38.7	52	28.8
Joint pain	9.3	15	14.2
Tiredness	-	46	13.3
Recurrent infections	7.4	49	10.7
Abdominal pain	9.3	12	5.6
Bone pain	8	26	4.3
Weight loss	-	29	3.4
Hepatomegaly	72	64	73.8
Splenomegaly	60	61	68.2
Pallor	64	54	60.1
Lymphadenopathy	50.7	41	56.7
Mediastinal mass	1.33	-	3

Discussion

The study was conducted in the department of Pathology, Government medical College, Kozhikode. 233 newly diagnosed cases of childhood leukemia were there during the study period.

99.6% (232/233)of cases were acute leukemia. 85.8% (199/232) of acute leukemia were acute lymphoblastic leukemia, 13.8% (32/232) were acute myeloid leukemia which is comparable to the literature data.[4]. One case of acute leukemia (0.4%) was unclassified. In a study by Biswas et al from West Bengal the incidence of ALL, AML and acute leukemia cytochemically unclassified were 72%, 18.7% and 9.3% respectively. [6]

Out of the 199 reported cases of ALL, flowcytometry for immunophenotyping was done from our institution in 148 cases. In the present study B-ALL were 79.7% and T-ALL were 20.3% comparable to the literature data.[4,7] Details of immunophenotyping were not available in 51 cases. Majority of them were taken to some other centers for further management and for others flowcytometry could not be performed due to inadequate sample. Out of 32 cases of AML, flowcytometric analysis was done in 10 casses.

Male predominance was seen in all subtypes of acute leukemia (M:F ratio=1.6:1) similar to the study by Sousa DW et al from Brazil (M:F = 1.9:1)[5] and it was highest in T-ALL (M: F ratio 2.6:1). In the study by Prajapathi Z et al from Ahmedabad, the M:F ratio was 3.8 :1 for acute leukemia.[8]

The most frequent presenting symptom in this study population was fever followed by bleeding manifestations similar to the three previous studies from West Bengal, Rawalpindi and UK. [6,9,10]

In the two previous studies by Prajapathi Z et al and Clarke RT et al, around 30% of the cases had weight loss and bone pain but in our study less than 5% of cases had these symptoms.[8,10] Frequent signs elicited at presentation were hepatomegaly, splenomegaly, pallor and lymphadenopathy in the present study and in the previous studies. [6,8,10] (Table 3) In the present study it is seen that hepatomegaly, splenomegaly and lymhadenopathy were more associated with ALL than AML and the association is more with T-ALL compared to B-ALL. 85.7% of cases with mediastinal mass were diagnosed as T-ALL .But it was detected in only 20% cases of T-ALL in the present study unlike the data in literature. [4]

Majority of the children were between 1 and 9 years (74.9%) similar to the study by Sousa et al and Siddhiqui et al [5,11] with major proportion (46.8%) in the age group 1 – 4 years. In case of B-ALL, 59.3% were between 1 and 4 years, whereas 73.3% of T-ALL cases were seen in children above 5 years. Acute leukemia in children below 1 year was only 6.5% of total cases with almost equal proportion of ALL and AML. 21.9% of AML cases were seen below 1 year whereas only 4% of ALL were seen in this age group. No cases of T-ALL were reported in children below 1 year in this study. 59.3% of AML were seen in children above 5 years. Thus the present study shows that AML is more frequent in older children and infants, T-ALL in older children and B-ALL in younger children.

Down syndrome (Trisomy 21) represents the most common inherited disorder that predisposes to the development of acute leukemia with about 14 fold risk above the general population. [3] In this study 2.2% of children with acute leukemia (5 out of 232 cases) were having Down syndrome.

Mean hemoglobin concentration at presentation was lowest in B-ALL (6.9g/dl) and highest in T-ALL (8.9g/dl), comparable to the findings of Sousa et al in their study.[5] At diagnosis children with T-ALL had significantly higher Hb levels than other subtypes. 36.7% children with T-ALL had Hb concentration > 10g/dl at presentation while in all the other subtypes it was < 16%. The hemoglobin level appears to be an indirect gauge of the biologic aggressiveness of leukemia. With explosive disease, symptoms evolve before anemia has time to develop. Normal hemoglobin levels are associated with bulky extramedullary involvement and a high percentage of blasts in the proliferative (S) phase of the cell cycle.[3] Severe anemia (Hb<7g/dl) was detected in 58.5% of B-ALL, 30% of T-ALL and 43.8% of AML cases. Mean TLC at presentation was very high in T-ALL patients compared to other subtypes which is comparable with the literature.[5,7] 29.7% of cases of acute leukemia had TLC >50.000/mm^3 similar to the study from Ahmedabad.[8] Percentage of cases with TLC > 50,000/mm^3 and > 1,00,000/ mm^3 were very high in T-ALL compared to other subtypes. Hb > 10g/dl and TLC > 50,000/ mm^3 at presentation are indicators of poor prognosis .[3] More than 75% of children had thrombocytopenia at presentation in all the subtypes.

In the present study only one case of Chronic myeloid leukemia (CML) was detected (0.4%). In the study from Ahmedabad, CML constituted 2.59% of hematological malignancies in childhood. In another study by D'Costa G G et al from Mumbai 9.4% of leukemias in children were CML. In both these studies CML was seen in late childhood, above 10 years.[8,12] In the present study a six year old child had CML.

Conclusion

The most prevalent age group for childhood leukemia is 1 to 4 years. Most common symptoms and signs at presentation are fever, bleeding manifestations, hepatomegaly, splenomegaly, pallor and lymphadenopathy. Acute lymphoblastic leukemia (ALL) especially B-ALL is the most common childhood leukemia. Male predominance is seen in all subtypes of acute leukemia. B-ALL

is more frequently seen in younger children and T-ALL in older children. AML is more frequent in older children and infants. At diagnosis children with T-ALL have significantly higher Hb levels and TLC compared to other subtypes. Most of the children with acute leukemia have thrombocytopenia at presentation.

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