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Original Research Article

CLINICAL PROFILE OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN-PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Background: Leukemia is one of the most commonly seen malignancies in children. Leukemia is characterized by the neoplastic proliferation of hematopoietic stem cells and the accumulation of blasts and immature cells in the bone marrow. **Aim:** The study aims to determine the clinical profile of acute lymphoblastic leukemia in children between 1 month -12years of age at a tertiary care centre. **Materials and Methods:** The study included all children aged one month to 12 years diagnosed with acute lymphoblastic leukemia in the Institute of Child Health & Hospital for Children, Chennai, Tamilnadu, South India. Children with acute lymphoblastic leukemia who have started treatment outside, children with relapse of acute lymphoblastic leukemia, children with other haematological malignancies and children with other malignancies were excluded. **Result:** The majority (73.45%) of the children were from rural areas. B cell ALL was more common (91 cases) than T cell ALL (22 cases). 84.1% of the children had a fever as the initial symptom, followed by abdominal distension (33.6%). Pallor and hepatosplenomegaly were seen in more than 50% of the population. 77% of children had platelet values of < 100000 cells/mm3 at diagnosis. 89.38% of children had elevated LDH levels at diagnosis. 89% (101) of children aged 1 to 10 years belonged to the good prognostic group. Male sex and age group (<1 year and >10 years) were major prognostic indicators of treatment outcome. **Conclusion:** Early diagnosis and treatment play a pivotal role in predicting long-term disease survival, thereby reducing mortality and morbidity in ALL.

INTRODUCTION

Leukemia is one of the most commonly seen malignancies in children. The neoplastic proliferation of hematopoietic stem cells and accumulation of blasts and immature cells in the bone marrow characterizes leukemia. More than 80% of childhood cancer occur in low- and middle-income countries. Cancer is the 9th most common cause of death among children between 5 to 14 years in India.[1] Leukemia contributes to 40-50% of childhood cancer. Indian data shows ALL accounting for 75-80% of paediatric leukemia. The second highest incidence of childhood cancer in India occurs in Tamilnadu, after Delhi.[2]

ALL is one of the most common childhood malignancies. It accounts for approximately 25% of all childhood cancers and 75% of all leukemia worldwide. 80% overall, ALL occurs in children. Paediatric ALL is the first disseminated cancer shown to be curable contrary to adults. Worldwide, the curative rate of childhood ALL is 90% compared to adults' curative rate of 40%. In India, the 5-year survival rate is approximately 80%.[3,4] The cure rate in India is inferior to that of western countries. The reasons are a higher number of high-risk populations, limited data on cytogenetics, unfavourable cytogenetics to the drugs, increased incidence of relapse, febrile neutropenia, toxicity and lower report of incidence and delay. Of the various environmental risk factors, only one environmental risk factor, ionizing radiation, has been significantly linked to ALL. Genetic syndromes which have an increased risk of developing ALL (e.g.) Down syndrome, Fanconi anaemia, Shwachman-diamond syndrome, Bloom syndrome etc.[5]

Bone marrow aspiration study provides cells for morphological, histochemical, immunophenotypic, cytogenetic and molecular analysis to diagnose medullary leukemic spread. The key to cure and the overall outcome is early diagnosis and treatment. Since most childhood ALL occur in developing countries, the initial symptoms are encountered by

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the general physician and not by hemato-oncologists. Inadequate therapy and poor treatment outcome are sometimes due to delayed referral. This varied presentation of ALL presents a diagnostic challenge to the front-line physician.[6,7] Knowing the incidence and early presentation of the disease in the local population is essential for early referral and initiation of early treatment in children. Hence this study was aimed mainly to concentrate on varied clinical presentations of ALL in children to aid in early suspicion of disease, thus enabling prompt diagnosis and treatment.

Aim

The study aims to determine the clinical profile of acute lymphoblastic leukemia in children between 1 month-12 years of age at a tertiary care centre - Institute of child health and hospital for children, Chennai, Tamilnadu, South India.

MATERIALS AND METHODS

This prospective observational study was done after obtaining approval from Institutional Ethics Committee (IEC) meeting held on 07/07/2017 at Madras Medical College, Tamilnadu, India (IEC number 06072017) in children who got admitted to the Department of Haematology and Paediatric medical ward in Institute of Child Health & Hospital for Children, Chennai Tamilnadu, South India from August 2017 to September 2018.

The study included all children aged one month to 12 years diagnosed with acute lymphoblastic leukemia in the Institute of Child Health & Hospital for Children, Chennai, Tamilnadu, South India.

Children with acute lymphoblastic leukemia who have started treatment outside, children with relapse of acute lymphoblastic leukemia, children with other haematological malignancies and children with other malignancies were excluded.

One hundred thirteen children were selected, and informed consent from the parent/guardian was obtained. Detailed information was collected regarding patient demographic characteristics, including a detailed history, clinical examination findings and laboratory parameters.

Detailed history in this study included fever and its duration irrespective of admission to the hospital, pallor, icterus, and lymphadenopathy, confirmed by clinical examination. The presence of rash and abdominal distension for hepatomegaly, splenomegaly, ascites and mass was asked. Abdominal pain, body aches, joint pain, difficulty walking, Bleeding in epistaxis, ecchymosis, gum bleeding, melena, hematochezia, and hematemesis were asked. A history of seizures and testicular swelling was asked for and confirmed by physical examination.

The child's nutritional status was determined by measuring height and weight. BMI was calculated for children more than five years of age. The anthropometric measurements were plotted in the growth chart to look for malnutrition. The history of initial symptoms was asked. Details were noted regarding the time, and referral details were taken for the initial hospital visit where ALL was suspected. The time taken for diagnosis from the appearance of initial symptoms was calculated in days.

Complete blood count, peripheral smear, blood sugar, renal function test (blood urea, serum creatinine), serum electrolytes (serum sodium, serum potassium), liver function tests (SGOT, SGPT), Serum uric acid, Serum Amylase, Serum LDH, Lipid profile (serum triglyceride, serum LDL, serum HDL) and urine routine. Imaging modalities, including X-ray chest, X-ray of long bones, USG abdomen, and echocardiography, were done. Blood and urine cultures were done to rule out infective causes and decide upon treatment.

Serum viral markers, mainly hepatitis panels, were done. Children who were suspected cases of ALL with classic symptoms and signs were confirmed by bone marrow aspiration examination and CSF analysis for malignant cells.

The bone marrow aspiration study and CSF tapping were done after obtaining informed consent from the parents. The diagnosis was confirmed by flow cytometric analysis of peripheral blood or bone marrow aspirate. Further, immunophenotyping was also done by using flow cytometry.

All Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) statistical package version 16.0. Descriptive statistics were calculated for each of the variables. All continuous data included mean ± standard deviation (±2 SD). Pearson Chi-square test was used to assess the significance. A power of 80% with a confidence interval of 95% with a p-value <0.5 was taken as significant.

RESULTS

One hundred thirteen children with ALL were included in the study. 73.45% of children were from rural areas, and 26.55% were from urban areas. 60.20% were boys, 39.80% were girls, and the male: female ratio was 1.58:1.

Age distribution: 3.53% below one year, 48.67% between 1-4 years, 35.40% between 5-8 years, and 12.40% between 9-12 years. The age range was between 1 month to 12 years, and the mean age was 4.92 years with a standard deviation of ± 2.96 years. The median age was four years, the youngest child was five months old, and the oldest was 12 [Table 1].

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Table 1: Demographic characters of the study

Study characteristics		N	Percentage
Study population	Rural area	83	73.45 %
	Urban area	30	26.55 %
Sex	Boys	68	60.2%
	Girls	45	39.8%
Age group	<1 year	4	3.53 %
	1-4 years	55	48.67 %
	5-8 years	40	35.40 %
	9-12 years	14	12.40 %
Immunophenotyping			
B cell ALL (N=91 children)	Males	50	54.94%
	Females	41	45.05%
T cell ALL (N=22 children)	Male	18	81.81%
	Female	4	18.18%
Marriage	Consanguineous marriage	20	17.7%
	Non-consanguineous marriage	93	82.3%
Mode of delivery	Normal vaginal delivery	97	85.8 %
	LSCS	16	14.2 %
Gestational age	Term	110	97.3 %
	Preterm	3	2.7 %
Birth weight	Normal birth weight	104	92 %
	Low birth weight	9	8 %
Development	Normal	111	98.2%
	Delay	2	1.8%
Nutritional status	Normal nutritional status	83	73.4 %
	Underweight	25	22.12 %
	Overweight	5	4.42%
Blood group	A	22	19.46%
	B	47	41.5%
	AB	7	6.20%
	O	37	32.75%
The interval between the onset of symptoms and diagnosis	13.13 (days) ± 12.15 (days).		
Symptoms	Fever	95	84.1%
	Fatigue	20	17.7%
	Rash	5	4.4%
	Paleness	14	12.4%
	Icterus	1	0.9%
	Anorexia	3	2.7%
	Bone pain	13	11.5%
	Joint pain	19	16.8%
	Difficulty in walking	4	3.5%
	Abdominal distension	38	33.6%
	Abdominal pain	11	9.7%
	Facial puffiness	5	4.4%
	Breathlessness	10	8.8%
	Seizure	2	1.8%
	Headache	4	3.5%
Signs	Pallor	59	52.2%
	Bleeding	24	21.23%
	Lymphadenopathy	34	30%
	Hepatomegaly	82	72.6%
	Splenomegaly	61	54%
	Hepatosplenomegaly	59	52.2%
	Parotid swelling	4	3.5%
	Tenderness	3	2.7%

Ninety-one children had B cells ALL, and 22 had T cells ALL. 54.94% were male, and 45.05% were female. 17.7% of children were born from consanguineous marriages. 98.2% of children attained age-appropriate milestones properly. 22.12% of children were underweight, and 4.42% were overweight for their age. Five children had severe acute malnutrition at the time of diagnosis. Blood group distribution: B group was the highest (41.60%), followed by the O group (32.74%), A group (19.46%), and AB group (6.20%).

The mean duration was 13.13 (days), with a standard deviation of 12.15 (days). The median was 10 (days). The minimum duration was seven days, and the maximum interval was 90 days.

84.1% (95) of the study population had a fever as the initial symptom, followed by abdominal distension (33.6%, 38). The frequency of other symptoms was seen in < 50% of the population.

1.8% (2) of children showed mediastinal widening, and 2.7% (3) showed pleural effusion. 2.7% (3) of children had pneumonitis changes in X-ray, and 92.8% (105) had normal chest X-ray findings.

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Two children presented with a case of hepatitis which occupies 1.8% of the study population. One (0.9%) child had tumour lysis syndrome at diagnosis. Among the many uncommon presentations of ALL seen in children, hepatitis and tumour lysis syndrome were observed.

Pallor (52.2%) and hepatosplenomegaly (52.2%) were seen in more than 50% of the population, and lymphadenopathy and bleeding in 30% and 20% of the study population. Two (1.76%) children had isolated splenomegaly, and four (3.5%) children had parotid swelling in their initial clinical examination [Table 1].

Table 2: Laboratory parameters

Lab Parameters	Mean ± SD	Range	N	Percentage
Hemoglobin	6.98 ± 2.86	<7 gm/dl	62	54.86%
		7 -11 gm/dl	40	35.59%
		>11 gm/dl	11	9.73%
WBC	55908.8±9107.4	<5000	20	17.7%
		5000 -50000	17	15.1%
		50000-100000	58	51.3%
		>100000	18	15.9%
Platelet	78518.6 ±13130.1	<20000	41	36.28%
		20000-50000	32	28.31%
		50000-100000	14	12.41%
		100000-150000	11	9.7%
		>150000	15	13.3%
Uric acid	5.46 ±2.67	Normal	32	28.3%
		Increased uric acid	81	71.7%
LDH	1003.01 ±123.38	Normal	12	10.61%
		Increased LDH	101	89.38%

90.26% (102) of children in this study group had a Hb value of < 11gm/dl, and 54.86% (62) children had a Hb value of < 7 gm/dl at diagnosis. 24.77% of children (28) had normal WBC count at diagnosis.

14.15% of children (16) had less than 5000/mm3, and 15.04% (17) had more than 100000/mm3. In the rest of the study group, 54.86% (62 children) of children had between 5000/mm3 to 50000/mm3, and 15.92% (18) had between 50000/mm3 to 100000/mm3.

3.5% (4) of children had pancytopenia at diagnosis. The mean platelet value of this study population was 78518.6 with an SD of ±131302.1. The median platelet value was 33000. 77% of the study population had platelet values of < 100000 cells/mm3 at diagnosis.

8.3% (32) of children had elevated uric acid levels according to their age-related value. 71.7% (81) of children had normal uric acid levels at diagnosis.

89.38% (101) of children had elevated LDH levels at diagnosis. 10.61% (12) of children had normal LDH levels [Table 2].

Table 3: Immunophenotyping

Symptoms	N	Percentage
B ALL	87	76.99%
Pro B ALL	4	3.5%
T ALL	21	18.6%
Early T Cell precursor ALL (ETP-ALL)	1	0.9%

Eighty-seven children (77%) had B ALL, and four (3.5%) had pro B ALL. Twenty-one children (18.6%) had T cell ALL, and one child (0.9%) had early T cell precursor ALL [Table 3].

Table 4: CALLA antigen (CALLA) distribution

Type	N (113)	CALLA result	(N)	Percentage	
B CELL ALL	91	CALLA POSITIVE	79	86.81%	P 0.23
		CALLA NEGATIVE	12	13.18%	
T CEL ALL	22	CALLA POSITIVE	8	36.36%	P 0.00008
		CALLA NEGATIVE	14	63.63%	

Among 113 children with ALL, 77% (87) had CALLA positivity in their immunophenotyping. The remaining 23% (26) of children showed CD10 negativity.

Among children with B cell ALL, 80.53% (91) and 86.81% (79) had CALLA positivity, and the remaining 13.18% (12) of children were CALLA negative B cell ALL. Among 19.5% (22) with T cell ALL, 36.36% (8) of children had CALLA positivity, and the remaining fourteen cases (63.63%) were CALLA negative T cell ALL.

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Table 5: Distribution of prognostic factors

Prognostic factor	ALL (113)	B CELL (91)	T CELL (22)	Pearson correlation coefficient
Age < 1 year, >10 years	11% (12)	7.69% (8)	18.18% (4)	R= 0.8205 Strong association
Male	60.17% (68)	54.98% (50)	81.81% (18)	
Hepatomegaly	72.6% (82)	72.52% (66)	72.72% (16)	
Splenomegaly	54% (61)	53.84% (49)	54.54% (12)	
Lymphadenopathy	30% (34)	29.67% (27)	31.81% (7)	
WBC >50000/mm3	30.97% (35)	26.37% (24)	50% (11)	
Platelet <100000/mm3	77% (87)	83.51% (76)	54.54% (12)	
Elevated LDH	89.38 % (101)	86.81% (79)	100% (22)	

According to the prognostic factor, the age group is divided into 1 to 10 yrs, <1 year and >10 years of age group. 89% (101) of children belonged to the good prognostic group (age group 1 year to 10 years). 11% (12) of children were <1 year and >10 years of age group belonging to the poor prognostic age group.

Male sex and age group (<1 year and >10 years) were the major prognostic indicators of treatment outcome. Those with Organ infiltration (hepatomegaly, splenomegaly and lymphadenopathy), WBC count more than 50000/mm3, platelet counts, and LDH level had poor prognosis [Table 5].

DISCUSSION

In our study, 113 children diagnosed to have ALL were included. Of 113 children, 60.17% were male, and 39.82% were female. The male: female ratio was 1.58: 1. Male predominance was noted in our study. The findings of our study were similar to the observations of studies done by Guru et al.[3] & Kulkarni et al.[8] In the study done by Guru et al., 78.1% were boys, and 21.9% were girls. The male: female ratio is 3.5:1. In a study by Kulkarni et al., male predominance was noted.

According to immunophenotypic distribution, 80.53% (91) had B-cell ALL, and 19.46% (22) had T-cell ALL. The same observation was noted in a study done by Sousa et al. [9]

The study was conducted on 76 patients under the age of 19 years. B cell ALL was found in 89.5%, and T cell ALL in 10.5%. B cell ALL was the commonest type in people who are less than 19 years. Guru et al. (3) study had 88.6% of B cell ALL

In our study, 73.4% (83) had normal nutritional status at diagnosis, and 22.12% (25) were underweight. 4.42% (5) were overweight at the time of diagnosis. A study by Kumar et al.[12] showed that 50% were undernourished, and no overweight children were observed.

In our study, the B blood group was commonly found in children affected, with ALL accounting for 41.5%. The study done by Tavasolian et al.[13] showed a higher number of ALL patients had AB blood group (p-value <0.001). Li SY et al. (14) Compared the clinical features of ALL in male and female patients. The most frequent blood group was the O blood group, but in our study B blood group was most commonly observed.

In our study, hepatomegaly (72.6%) was most commonly observed, followed by pallor (52.2%). Shalal et al.[7] did a retrospective study on 55 patients to show the initial presenting features of ALL. In their research, whiteness was the most common presenting sign coherent with our study.

In our study, 2.7% of children had Pleural effusion, whereas 1.8 % of the population had pleural effusion in the study by Shalal et al.[7] Our study observed most children (57.52%) had WBC counts in the 5000-10,000/mm range. Hyperleukocytosis was observed in 15% with a WBC count > 100000/mm. Similar findings were noted in the study by Shalal et al. (16.4%). [7]

Kong et al.[16] reported twenty (19.2%) of 104 children had an initial leukocyte count of more than 100x109, and 11 patients had a leukocyte count of more than 200x109/L. T cell phenotype, massive splenomegaly and male gender were strongly associated with hyperleukocytosis.

Among 113 children, 33.6% had severe thrombocytopenia with a platelet count < 20,000/mm. In the study by Shalal et al.[7] 25.5% and in Pahloosye et al.[17] 19% of cases had severe thrombocytopenia in their study population. In our study, 3.5% had pancytopenia at the time of diagnosis. In the study by Kulkarni et al.[8] 11.02% had pancytopenia with ALL, and all had better prognoses. The hyperuricemic children had a high tumour burden, adversely affecting the treatment outcome. In our study, hyperuricemia was observed in 28.3% of children at the time of diagnosis, similar to the study by Sevinir et al.[18]

89.38% of the study population had elevated LDH levels. Uncommon presentations noted were hepatitis (1.8%) and tumour lysis syndrome (0.9%), respectively. Tumour lysis syndrome 32.04% was observed in the study done by Siddaiahgari et al.[4]

Hyperleucocytosis with tumour lysis syndrome was noted in 0.9 % of the 15% study population, which was significantly less compared to the 22% indicated in a study done by Siddaiahgari et al.[4]

According to immunophenotypic distribution, 80.53% (91) had B-cell ALL, and 19.46% (22) had T-cell ALL. B-cell ALL was the commonest leukaemia observed in our study. This observation was similar to the other studies conducted in India. Siddaiahgari et al.[4] Observed that the common immunophenotype was B cell ALL. Guru et al. study had 88.6% of B cell ALL.

In our study, 77% were CALLA positive, and the remaining 23% were CALLA negative. This

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observation was similar to the Pandian et al.[15] study in which 91.7% of ALL showed CD10 positivity. In the Siddaiahgari et al. (4) study, 88.75% were CALLA positive, and 11.25% were CALLA negative. In the study by Khan et al. (19), 93.1% of B cells ALL expressed CD10, and 45.4% of T cells ALL expressed CD10. Based on CD10 distribution immunophenotyping, in B cell ALL, CD10 positivity was noted in 86.81%, and 36.36% had CD10 positivity in T cell ALL.

In our study, children in the age group < 1 year were 3.53%, and children over ten years were 7.07%, accounting for 11% of the study population with a poor prognosis. Important factors which determined the prognosis were male (60.17%), Hepatomegaly (60.17%), Splenomegaly (54%), Lymphadenopathy (30%), WBC more than 50000/mm was seen in 30.97%, platelet less than100000/mm was seen in 77%, and Elevated LDH was observed in 89.38%. Similar prognostic factors influenced the affected children in the study conducted by Arya et al.[10] and Pahloosye et al.[17]

CONCLUSION

ALL was found to be the most frequent childhood haematological neoplasm. ALL were commonly seen in the age group of 1 - 4 years (48.67%). Most children (89%) belong to the good prognostic age group of 1-10 years. B cell ALL (80.53%) was noted more commonly than T cell, and varied presentation of ALL was noted in our study. Early diagnosis and treatment play a pivotal role in predicting long-term disease survival, thereby reducing mortality and morbidity in ALL.

Limitations

Children aged between 1 month to 12 years were only included in this study. The sample size was limited due to the inclusion of eligible cases only during the study period. This study was a hospital-based study that does not represent the whole background population. Karyotyping and Cytogenetic abnormalities as prognostic factors of ALL could not be done in our study.

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