Childhood Acute Lymphoblastic Leukaemia; Epidemiology and Clinicopathological Features

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Abstract

Objective: To study epidemiology, clinical presentation and laboratory features of childhood Acute Lymphoblastic Leukaemia.

Method: This retrospective review included all newly diagnosed children with acute lymphoblastic Leukaemia less than 15 years of age registered from April 1999 to December 2004 at oncology unit of National Institute of Child Health and Children Cancer Hospital, Karachi. The objective was to look for epidemiological data, the clinical features and laboratory findings at presentation and compare it with reported literature.

Results: Acute lymphoblastic Leukaemia constituted 32 %(611 / 1890) of all cancers in this study. Majority of patients hailed from Karachi (59%) and interior Sindh (27%) while rest from other parts of country. Patient`s referral increased over the years, from 42 in 1999 to 127 in 2004.The age ranged between 3 months to15 years with a median age of 6.5 years. Male to female ratio was 1.7:1 Family history of cancer was present in 5% of patients. Fever and pallor were the commonest presenting features. Anaemia (86%), lymphadenopathy (75%) hepatomegaly (67%) and splenomegly (58%) were common findings on physical examination. Initial high white cell count (>50,000) was observed in 34% patients. Haemoglobin <7gm/dl was seen in 54% and Platelet counts less than 20,000 was observed in 33% cases. CNS disease was present in 5% and HBsAg was positive in 14% patients at diagnosis.

Conclusion: Acute Lymphoblastic Leukaemia accounts for one third of total registered cases. Age distribution in this series shows less prominemt early peak and more significant late peak and a median age of 6 years. Consangunity was found in 47% cases. The fraction with a WBC count above 50,000 mm3 (30%), a higher proportion with lymphadenopathy (75%) and haemoglobin less than 7 gm/dl (54%) suggest that Pakistani children have significantly higher burdens of Leukaemia cells at presentation. These may have prognostic implication resulting in poor outcome of Leukaemia in this part of the world (JPMA 59:150; 2009).

Introduction

First case of Leukaemia was reported by John Hughes Bennett in 1845 in an adult patient.[1] Leukaemia in a child was first reported by Dr Henry Fuller in 1846.[2] The disease remained universaly fatal till discovery of effective chemotherapy. Over last 50 years many new modalities of diagnosis and treatment of Leukaemia have evolved leading to improved survival.[3-7] The epidemiology, clinical and laboratory presentation of Acute Lymphoblastic Leukaemia (ALL) in children has been well described from western countries.[8,9] Unfortunately there is no large published data from Pakistan on childhood ALL epidemiology and clinoco-pathological features. This is important to know as our population differs markedly from western population with respect to the frequency of illiteracy, poverty, malnutrition and chronic infectious diseases. National Institute of Child Health (NICH) and Children Cancer Hospital, Karachi together caters almost 80% of all ALL seen in Karachi.

This study was undertaken to assess the clinical presenttion and laboratory features in childhood ALL.

Patients and Methods

This retrospective study was carried out at Oncology Unit of National Institute of Child Health (NICH) and Children Cancer Hospital, Karachi. The NICH is a government sector, 400 bedded children hospital. Children Cancer Hospital is a charitable tertiary care referral center for childhood cancer in Karachi treating every child suffering with cancer irrespective of paying ability.

Both oncology units have childhood cancer registry of all patients. The annual new patient referral currently in each center is 200-225 new cases of all cancers. All children under age of 15 years diagnosed with ALL from April 1999 to December 2004 were included in this study. Previously treated and relapsed patients were excluded.

A detailed performa was filled in for all patients stating age, sex, year of presentation, ethnicity, family history of cancer, consanguinity, presenting features, clinical and laboratory findings at presentation. The diagnosis of A.L.L was established on the basis of morphology and cytochemistry of bone marrow aspiration and trephine. Immunophenotyping was done only in difficult cases due to economic constraints and hence not included in the analysis. Other pretreatment work up included, Cerebrospinal Fluid (CSF) examination, urea creatinine, electrolytes, uric acid, calcium, phosphate, coagulation profile, liver function tests (LFT) including HBsAg, echocardiography, Chest X-ray and ultrasound abdomen in patients with bulky disease.

Results

Acute lymphoblastic Leukaemia constituted 32 %(611 / 1890) of all cancers in this study. The yearly numbers of patient registered with diagnosis of Acute Lynphoblastic Leukaemia is shown in Fig-1. Males were 389 (64%) and females 222 (36%); male to female ratio was 1.7:1. Age

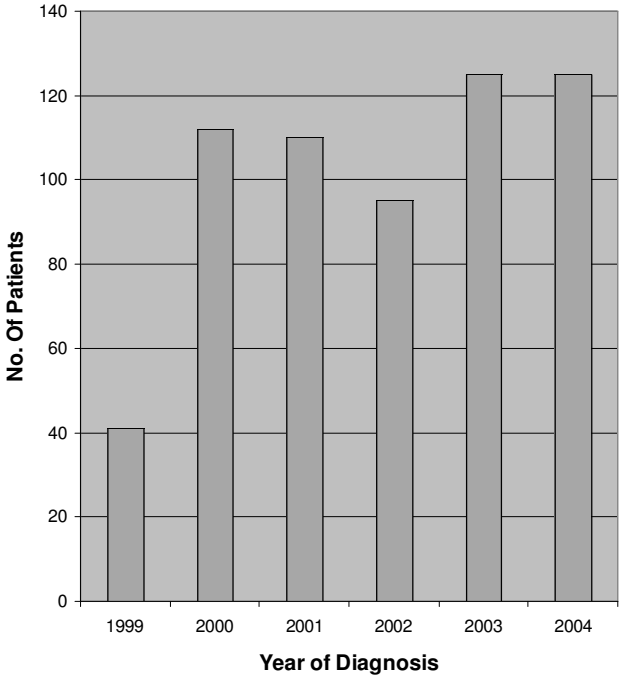

Figure 1: Year of Diagnosis.

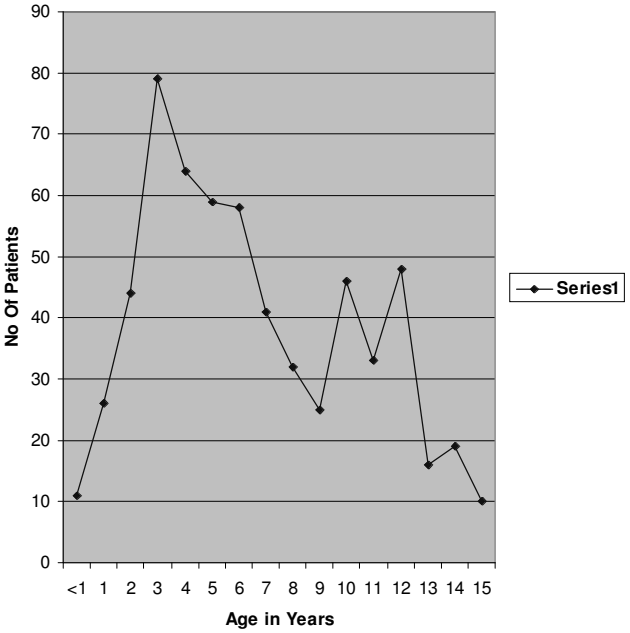

Figure 2: Age at presentation.

ranged from 3 months to 15 years with a median age of 6 years. Age distribution showed: less than 2 years 37(6%), 2-9 years 402 (66%) and 10-15 years 172 (28%). Two peaks of ages were observed between 2-5 years and another between 10-12 years (Fig-2).

The patients hailed from mixed ethnicity. Majority were urdu speaking (35%), Pushto speaking (19%), Sindhis (18%). Others included, Punjabi (13%) Balochi (8%), and 7%were others including refugees (Afghan, Burmese, Bengali etc.). Family history of cancer was present in 25 (4%). Consanguinity was observed in 287 (47%) patients.

Congenital anomalies were seen in 5 patients. Three patients had Trisomy 21, one patient had congenital heart disease, where as another had Hirshsprung disease.

The patients were brought in with wide spectrum of symptoms and duration. Fever was the most common presenting complaint seen in 95% patients followed by pallor (65%). Bleeding from mucous membrane or into skin was present in 26%. Bone or joint pains were experienced by 35% of patients.

On physical examination, 86% had anaemia of varying degree, followed by lymphadenopathy (75%) hepatomegaly (67%) and splenomegaly (58%) isolated or in combination with liver enlargement. Isolated testicular involvement was present in 2% of patients at presentation.

White cell count (WCC) at presentation was less than 10,000 cells/cm in 37%, between10-50,000 in 33% and >50,000 in 30% patients (Fig-3). Haemoglobin at diagnosis

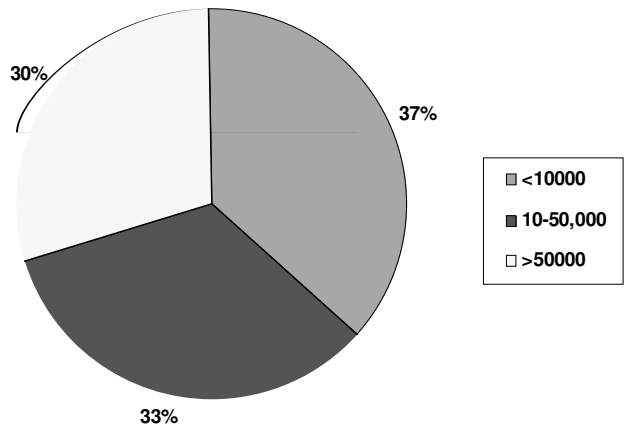

Figure 3: Initial white cell count (mm^3)

was <7gm/dl in 54%. Between 7-11gm/dl in 38% and > 11gm/dl in 8% patients. Platelet count was less than 20,000mm^3 in 33%, between 20-100 in 45% and >100 in 22%. Central Nervous System (CNS) disease as shown by positive CSF cytology was present in 5% of children. Chest X-ray showed involvement of lymph nodes or pleural effusion in 29% patients. Hepatitis B antigen (HBsAg) done at presentation was positive in 14% patients.

Discussion

Acute lymphoblastic Leukaemia (ALL) is the most common cancer seen in children accounting for 25% of all childhood cancers. Boys are affected more commonly with a sex ratio of 1.3 :1.[9-11] The relative frequency of Leukaemia is similar throughout the world.[12] In our study ALL constituted 611/1890 (32%) of all cancer. Higher prevalence of A.L.L in this study may be because in newly established Oncology units, haematological malignancies are more often referred than solid tumours. The age distribution of A.L.L in developed countries shows a very marked early peak between 2 and 5 years, followed by a small peak between 10 -12 years and the median age of 4 years.[9-11] In our study we also had a peak between 2 to 5 years which is not as prominent as the western population and a second peak between 10-12 years which is more pronounced than the western pouplation and the median age was 6.5 years. The reasons for these differences may be because of less number of common ALL in early peak and more T cells in the second peak. Since we have not done immunophenotyping in our patients we cannot validate this.

In this study family history for different cancers was positive in 5% of patients. In 0.9% it was positive for blood cancer e.g. Non-Hodgkins lymphoma and acute myeloid Leukaemia. A similar experience has been reported by Shami et al.[13] However, Mendelian inheritance was not analyzed in our study but other studies have reported recessive mode of inheritance.[13]

Certain genetic disorders e.g. Trisomy 21, Bloom's syndrome, and Fanconi's anaemia have more chances to develop lymphoreticular malignancies.[8] In our study three patients had Down's syndrome (Trisomy 21).

The prevalence of consangunity among parents of children with ALL in the study was 52%. This is not surprising and consistent with the findings of high rate (60%) of consangunity among Pakistani population shown by other groups.[14,15]

The fraction with a WBC count above 50,000 mm^3 (30%) was higher than reported from developed countries which is (17%).The prevalence of hepatomegaly (67%) and splenomegaly (58%) was similar to that reported from western countries. However lymphadenopathy was more common (75% vs 50%) in this study. Higher proportion of patients with a WBC count above 50,000 mm^3 and lymphadenopathy suggests that Pakistani children have significantly higher burden of leukaemic cells at presentation. In such patients tumour lysis syndrome and

hyperuricaemia was also observed (13% and 28%). Frank renal failure was not observed in any patient, however renal parenchymal changes of varying degree (grade I - III) in 34 (9.3%) patients were observed on ultrasound examination.

Haemoglobin less than 7 gm/dl was seen in 54% while only 8% had Hb > 11gm/dl. Higher haemoglobin has been reported to denote poor prognosis in western series,[16,17] however data from India has shown lower Hb associated with worse prognosis.[18] Central Nervous System disease at diagnosis, confirmed on initial CSF examination was found in 5% patients.

Signicant number of patients (14%) showed Hepatitis B surface antigen positivity at diagnosis. This finding is consistent with the observation of ALL series from India. The prognostic significance of this finding need to be investigated in other studies.[19]

Conclusion

From the results of our study, it can be concluded, that ALL is the commonest malignancy in children in this part of the world. However, certain differences have been noted from western data e.g. the age distribution is different; we see Leukaemia in each age group and the peaks at 2-5 and 10-12 are not very tall. Consanguinity being very common in our country has increased risk for development of Leukaemia in siblings /1st degree relations.

Apart from general poor prognostic factors like under nutrition and infection, it has uncertain unfavorable prognostic markers which are more pronounced like male predominance, high white cell count, higher haemoglobin and CNS disease at presentation. These may add to higher mortality observed in patients with ALL in our country.

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