Seasonal Variation in the Diagnosis of Acute Lymphoblastic Leukemia in Children

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ABSTRACT

Background: Acute lymphoblastic leukemia is the most common form of cancer and predominant subtype of leukemia in children. It is thought that the presence of seasonal variation in the diagnosis of acute lymphoblastic leukemia could link the disease to an infection as a cause for leukemia.

Objectives: To assess the seasonal variations in the diagnosis of ALL in pediatric patients.

Methods: This is a retrospective cross-sectional study; conducted in the period from August to December 2020 in the laboratory of hematology in Children Welfare Teaching Hospital in the Medical City in Baghdad. All the children who were diagnosed as acute lymphoblastic leukemia by morphological study on peripheral blood and bone marrow in the period from January 2015 to December 2019 were included in the study.

Results: Out of 577 patients diagnosed as leukemia, 441(76.4%) patients were diagnosed as acute lymphoblastic leukemia; their mean age was 5.7 ± 3.4 years with the range of 3 months to 13 years. The most frequent diagnosis of acute lymphoblastic leukemia occurs in spring while the least frequency was in winter; 122 (27%) patients were diagnosed in spring followed by 114 (25.9%) patients who were diagnosed in summer, followed by 110 (24.9%) patients diagnosed in autumn and the least number was in winter in which 95 (21.5%) patients were diagnosed as acute lymphoblastic leukemia. Regarding the diagnosis by months, the most frequent diagnosis occurs in March (12%) followed by June (10.5%); while the least frequency was in August and December (5.7%). This difference in the number of patients is not significant statistically.

Conclusion: There was no significant variation in the diagnosis of acute lymphoblastic leukemia in children, between the seasons, although there was difference in the frequency of diagnosis between seasons and months; the highest frequency was in spring and in March while the least frequency was in winter and in December and August.

Keywords: Acute lymphoblastic leukemia, Seasonal variation, Pediatric malignancy.

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Acute lymphoblastic leukemia (ALL) is the most common form of cancer (25-30%) and the predominant subtype of leukemia (75-80%) in children. The median age at diagnosis is 13 years; there is a sharp peak among 2-3 years old[1].

Acute lymphoblastic leukemia derives from the clonal proliferation of lymphoid progenitors cells in the bone marrow. The consequence of bone marrow infiltration is various cytopenias in the peripheral blood and is associated with the appearance of peripheral blast cells[2].

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Only small proportions (less than 5%) of patients have underlying hereditary genetic abnormalities. Ionizing radiation and chemical mutagens have been implicated in the induction of leukemia, but clear etiological factors for ALL cannot be identified in the majority of cases. Infection was the first suggested causal exposure for childhood ALL and remain the strongest candidate. Some hypothesis postulating that ALL results from an abnormal response to a common infection. There is no evidence to date of a unique or single transforming virus in ALL[1].

It is thought that the presence of seasonal variation in the diagnosis of ALL could link the disease to an infection as a cause for leukemia[3].

The first published studies on the seasonality of leukemia appear to be from Belgium, which reported a November - February peak in acute leukemia and this study includes adults and children patients[4].

Since then, several studies were carried out to explore seasonal variation or the presence of a peak incidence in the diagnosis of ALL, but with inconsistent results[5]; some of these studies have identified an obvious seasonal pattern, but other have not found a significant seasonal variation[6].

The aim of this study is to assess the seasonal variations in the diagnosis of ALL pediatric patients.

Methods

This is a retrospective cross sectional study; conducted for the period from August to December 2020 in the Laboratory of Hematology in Children Welfare Teaching Hospital in the Medical City, Baghdad.

All the children who attended Children Welfare Teaching Hospital and diagnosed as ALL by morphological study on peripheral blood and bone marrow in the period from January 2015 to December 2019 were included in the study.

The diagnosis of ALL was carried out by an experienced hematopathlogist and established according to the WHO classification of hematopoietic and lymphoid neoplasms[7].

The age, gender and date of diagnosis for each patient were recorded from the files of the patients.

Seasonal variation were observed as per the four seasons of Iraq; that is December to February was defined as winter, March to May as spring season, June to August as summer season and September to November as autumn season.

Analysis of data was carried out using the available statistical package of SPSS-27 (Statistical Packages for Social Sciences- version 27). Data were presented in measures of frequency, percentage, mean and standard deviation. The significance of difference (qualitative data) were tested using Pearson Chi-square test (X^2-test) with application of Yate's correction or Fishers exact test whenever applicable. Student t-test was applied for the quantitative data. Statistical significance was considered whenever the P value was equal or less than 0.05

Results

During the period from 1/1/2015 to 31/12/2019, 577 patients were diagnosed as acute leukemia, out of these patients, 441(76.4%) patients were diagnosed as acute lymphoblastic leukemia, their mean of age was 5.7 ± 3.4 (median 5) years with the range of 3 months to 13 years. The males were 254 (57.6%) patients with the mean of age was 6 ± 3.4 (median 5) years with range of 4 months to 13.6 years while the females were 187 (42.4%) patients with the mean of age was 5.4 ±3.3 (median 5) years with range of 3 months to 14 years and males to females ratio was 1.4:1. There was no significance difference in the age between males and females, (Table 1).

The most frequent diagnosis of ALL occurs in spring while the least frequent was in winter; 122 (27%) patients were diagnosed as ALL in spring, followed by 114 (25.9%) patients diagnosed in summer, followed by 110 (24.9%) patients diagnosed in autumn and the least number was seen in winter in which 95 (21.5%) patients-were diagnosed as ALL, (Table 2). There is no significant differences in the diagnosis of ALL between the seasons (p value = 0.617).

Regarding the diagnosis by months, the most frequent diagnosis of ALL was done in March (12%) followed by June (10.5%); while the least frequency was in August and December (5.7%), (Table 3). There is no significant differences in the diagnosis of ALL between the months (p value = 0.337).

Table 1: The age distribution of the patients.

Patients	*No. and % of patients*	*Age mean (median)*	*Range of the age*
Males	254(57.6)	6.0 (5.0)	*4 months-13.6 years*
Females	187(42.4)	5.4 (5.0)	*3 months-14 years*
Total	441(100)	5.7 (5.0)	*3 months-13 years*

Table 2: The total patients diagnosed with ALL (n=441) during the period 2015-2019 distributed by seasons of diagnosis.

SEASON	**MALE**		**FEMALE**		**TOTAL**	
	No.	%	No.	%	No.	%
Spring	68	26.8	54	28.9	122	27.6
Summer	65	25.6	49	26.2	114	25.9
Autumn	64	25.2	46	24.6	110	24.9
Winter	57	22.4	38	20.3	95	21.5
TOTAL	**254**	**57.6**	**187**	**42.4**	**441**	**100%**

Table 3: The total patients who were diagnosed with ALL (n=441) during the period of 2015-2019 distributed by months of diagnosis.

Month	**No.**	**%**
January	39	8.8
February	31	7.0
March	53	12.0
April	33	7.5
May	36	8.2
June	46	10.4
July	43	9.8
August	25	5.7
September	40	9.1
October	43	9.8
November	27	6.1
December	25	5.7
Total	**441**	**100%**

Discussion

The study showes that there is variation in the frequency of the diagnosis of ALL during the seasons of the years (The most frequent diagnosis of ALL occured at spring while the least frequent was in winter) but this variation is not significant statistically. These results were similar to the study of Mutlu and Erduran 2012 which was carried out in Turkey and showed that most of the patients (31%) were diagnosed with ALL during spring, whearase only 15% were diagnosed during winter season[8].

The highest frequency of diagnosis in the spring season and the least in winter can be explained by the weather; the spring season has a temperate weather which makes visiting the hospital or the clinic easy while in winter, there is raining and cold which makes visting hospital or clinic more difficult especially for people in the villages or in distant places.

Regarding the statistical insignificance in the seasonal variation in the present study, many studies showed the same result; the study of Gustafsson and Carstensen 2000, which was carried out in Sweeden and included more than thousand cases of childhood ALL (below 14 years age) stated that there was no statistially significant clustering found around time of diagnosis[9]. Also, the study of Gao et al 2005 shows no seasonal variation in the diagnosis of ALL in Singapore and Hawaii[6].

The study of Nyon et al 2008 analysed 121 cases of children aged under 5 years who were diagnosed with ALL in Hungary, they

found no seasonal effect related to the date of diagnosis[10].

Nurullah et al 2018 studied the seasonsl variation in the cancer diagnosis (including leukemias) for patients below 20 years age in three Canadian provinces; the study did not show a seasonal variation in the various cancer types (including leukemias) in the pediatric population in these provinces[11].

The study of Basta and James et al in 2010 showed seasonal variation around the month of birth for childhood ALL, but not on the months of diagnosis[12]. Other studies showed an excess in the diagnosis of ALL in seasons; Ross et al 1999 showed a summer season peak in the diagnosis of childhood ALL in the United States[5]. Kulkarni and Marwaha 2013 in India showed that the maximum number of children presented and diagnosed was in August to November[13].

Other few studies showed significant seasonal vriation; the study of Westerbeck et al 1998 which carried out in Manchester city showed that there was a significant excess in summer and this supports evidence for infectious aetiology for ALL[3].

A recent study (Hassan and Adil et al 2020) that was carried out in Pakistan on adults patients showed significant seasonal variation in the diagnosis of of ALL; the highest incidence was in summer season[14].

The present study showed that the most frequent diagnosis of ALL was made in March (15%) followed by June (10.4%); while the least frequent was in August and December (5.7%); Such variation may increase the burden of ALL treatment on the medical staff of the hospital in March. However, this result was similar to the study of Mutlu and Erduran 2012 which was carried out in Turkey and showed that most of the patients (16%) were diagnosed with ALL in March followed by July (13.9%)[8]. So several studies carried out to express seasonal variation in the diagnosis of childhood ALL with inconsistent results.

In conclusion; there was no significant variation in the diagnosis of ALL in children, between the seasons, although there was difference in the frequency of diagnosis between seasons and months; the highest frequency was in spring and in March while the least frequency was in winter and in December and August.

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