Pattern of Acute Lymphoblastic Leukemia Among Kurdish Children in Duhok City, Northern Iraq

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Abstract:
Although it is a common malignancy, there is a lack of information about leukemias in Kurdish people. To evaluate the pattern of acute lymphoblastic leukemia among Kurdish children in Duhok city/ North of Iraq, and to compare it with available data from other countries, 83 cases were studied of acute lymphoblastic leukemia diagnosed by bone marrow aspiration cytology, cytochemistry and immune-phenotyping between July 2006 and August 2010.

Data recorded included age, sex, area of residence whether rural or urban, socio-economic status, the presenting features and the initial peripheral blood and bone marrow findings. Ages ranged from 7 months to 14.5 years, the peak occurrence was between one and five years and the male to female ratio was 1.7:1. Most patients were low socio-economic class (86.7%), and 68% were living in rural areas.

The most frequent presenting features were pallor (88%) and bleeding tendency (65%), and 25.2% of patients had a leukocyte count above 50,000 per cubic millimetre. L1 and L2 morphology was approximately equal (51.6% and 46.9%, respectively). The percentage of T-cell ALL was higher than the range reported in other countries.

Conclusion: Acute lymphoblastic leukemia is an important health problem in Kurdistan region and its pattern differs in certain respects from that reported from different regions of the world though comparable in other aspects. The study recommends implementation of preventive, diagnostic and therapeutic strategies for leukemias in the Kurdistan region.

Keywords: Childhood acute lymphoblastic leukemia, epidemiology, Duhok

Introduction:
The occurrence of cancer during childhood remains one of the leading causes of childhood mortality even with the marked improvement in the treatment and cure of pediatric malignancies over the past three to four decades. Although the volume of epidemiologic research addressing the cause of childhood cancer is considerable, relatively little has been achieved regarding our understanding of the causes of childhood leukemia, which would have a direct impact on potential future prevention strategies. (1)

Leukemias are the most common cancers affecting children, accounting for 32% of all occurrences of cancer in children younger than 15 years and 27% of occurrences of cancer in children younger than 20 years. Acute Lymphoblastic Leukemia (ALL) accounts for 78%, Acute Myeloid Leukemia (AML) accounts for 18%, and Chronic Myeloid Leukemia (CML) is rarely seen, accounting for less than 4%. (2)

Leukemia is an important group of the malignancies reported in the Middle East. It was hypothesized that the Middle East countries have higher rates of leukemias, with respect to non-Hodgkin’s lymphoma, which were claimed to be three times more common than in Europe and the USA. (3) Physicians dealing with leukemias in developing countries face a great challenge with the diagnosis and management that demand advanced and very expensive facilities. Lack of information about leukemias in some developing countries may be a reason that health authorities do not include it seriously in their plans.

The purpose of this first study in Kurdistan Region (Northern Iraq) was to evaluate the pattern of ALL among Kurdish children and to compare it with available data from other countries as a study of the epidemiological pattern of leukemia is helpful in planning preventive and management strategies.

Patients and Methods:
Duhok is the third Governorate in the Kurdistan region in Northern Iraq, with a population of about 985,946 (according to the last census in 2010). Heevi Pediatric Teaching Hospital is the only hospital for children in Duhok City. The Oncology Unit was established in July 2006.
Between July 2006 and August 2010, eighty-three children were newly diagnosed with ALL and treated at Heevi Hospital; all were Kurdish from different regions of Duhok governorate.

The diagnosis of ALL was based on morphologic characteristics of bone marrow leukemic blast cells, classified according to the French-American-British (FAB) criteria and cytochemical studies.\(^{(4)}\) Immuno-phenotyping was performed in all patients but cytogenetics and molecular biology facilities were not available in Duhok City.

Data concerning age, sex, area of residence, socio-economic status, the presenting features, the initial peripheral blood and bone marrow findings were collected and analyzed.

**Results:**

The median age of patients was 4.9 years (range: 7 months-14.5 years); 73.5% were within the favorable prognostic age group (one to ten years); 20.5% were above 10 years and 6% were below one year of age. The male to female ratio was 1.7:1 (Table 1). Fifty-seven patients (68%) were living in rural areas, and 72 (86.7%) were of low socio-economic class. The presentation of patients was most frequent in spring and winter (Table 2). Pallor, bleeding tendency, splenomegaly, hepatomegaly and fever in descending order were the most frequent presenting features (Table 3). Thrombocytopenia and anemia were equally seen and 25.2% had a leukocyte count above 50,000 per cubic millimeter (Table 4).

According to the FAB classification, 42 (50.6%) patients had L1, 39 (46.9%) had L2, and two (2.5%) had L3 blast morphology. Immuno-phenotyping of all patients showed that 23 (27.7%) were T-cell, 57 (68.6%) precursor B-cell, and three (3.6%) mature B-cell ALL.

**Table 1: The age and sex distribution of patients**

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;1yr</th>
<th>1-5yr</th>
<th>&gt;5yr &lt;10yr</th>
<th>≥10 yr</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>2</td>
<td>29</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>3</td>
<td>15</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>44</td>
<td>17</td>
<td>17</td>
<td>83</td>
</tr>
<tr>
<td>Percent (%)</td>
<td>6</td>
<td>53</td>
<td>20.5</td>
<td>20.5</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2: Seasonal variation**

<table>
<thead>
<tr>
<th>Season</th>
<th>Winter</th>
<th>Spring</th>
<th>Summer</th>
<th>Autumn</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>27</td>
<td>29</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Percent (%)</td>
<td>32.5</td>
<td>35</td>
<td>14.5</td>
<td>18</td>
</tr>
</tbody>
</table>

All patients were treated with chemotherapy according to UK ALL 2003.

Early death during remission induction therapy occurred in three patients (3.6%) with sepsis. Forty-eight patients (57.8%) attained complete remission by the 15th day, and 27 (32.5%) by the 30th day of induction chemotherapy. Failure of induction remission was seen in eight (9.6%) patients.

**Discussion:**

There are no reports on the epidemiology of cancer in the Kurdistan region/North of Iraq and this is the first attempt to study the pattern of childhood ALL in this region. Eighty-three pediatric cases of ALL were diagnosed
between July 2006 and August 2010; 20.7 cases per year, but this is not necessarily representative of the real incidence of ALL in Duhok Governorate since there is no guarantee that all cases of ALL from this population were enrolled and a few cases might have been diagnosed and treated elsewhere. However, the above figure gives at least a crude incidence rate that can be used by the health authorities as a rough guideline in future health planning.

There is a wide variation in the incidence of childhood ALL by geographic location. The highest annual incidence rates are reported in Costa Rica, Ecuador, Hong Kong, Denmark, and Singapore (39.5 to 46.3/million population), whereas some of the lowest rates are found in Zimbabwe, India, Israel, and Algeria (11.6 to 14.3/million). (1)

The incidence rate for all leukemias is higher in children younger than five years of age and decreases with age. (5) In this study, the peak age incidence was between one and five years (53%) with a male preponderance in all age groups except in infants where there were three females and two males; these findings are almost universal. (6,7) In the developed countries there is a significant peak in the incidence of childhood ALL between the ages of 2–5 years, and one subtype, referred to as common ALL, is the most common type in this age group. (8) A study conducted in Saudi Arabia showed that the mean age of children with ALL was 5.27 years, the median age was 4.27 years, and the age range was 0.2–14.5 years. (9)

The age-adjusted incidence for boys exceeds that for girls, with a male-to-female ratio between 1.1:1 and 1.3:1. (10)

The percentage of adolescent patients in our study (≥10 years) was higher than that reported in Saudi Arabia (20.5% vs. 10.9%). (10) The age of patients with ALL significantly correlates with clinical outcome. Adolescents (10–21 years of age) with ALL have a less favorable outcome than children aged one to ten years although not as poor as infants. Adolescents with ALL more frequently present with adverse features at diagnosis, including T-cell ALL immune-phenotype, higher presenting leukocyte count, and a lower incidence of potentially favorable cytogenetic abnormalities. (11,12)

Most of our patients were of low socio-economic class. There are a number of descriptive studies that have investigated the relationship between leukemia and socio-economic status. In most of these studies a weak association was observed between leukemia and high socio-economic status. (13–16)

Seasonal variation in the onset of disease could provide supportive evidence of an infectious cause. Two-thirds of the patients in our study presented during the rainy seasons in Duhok (spring and winter), and this may be related to common infections, especially viral infections, during these two seasons. Westerbeek and associates have demonstrated significant seasonal variation in the date of the first symptom of childhood ALL, with peaks occurring in November. (17) However, a larger study of 15,855 patients with childhood leukemias has failed to reveal any evidence of seasonality. (18)

Pallor and bleeding tendency were the most frequent presenting features and they were found in 88% and 65%, respectively, followed by splenomegaly (61.4%) and hepatomegaly (56%). Similar results were found in Saudi Arabia, (9) while in Western countries only 30–50% of children with ALL have enlargement of the liver or spleen, with organs palpable more than 4 cm below the costal margin, (19) indicating that most of our patients presented rather late. We observed that many patients were mis-diagnosed as bacterial infections or anemia and were given treatment accordingly. This mis-diagnosis is due to improper evaluation of certain features of leukemia such as fever, anemia and splenomegaly, which are similar to those of common infectious diseases in our country. This causes delay in referral of such cases, affecting treatment outcome and prognosis.

One of the patients presented with obstructive jaundice, and contrast-enhanced computed tomography (CT) of the abdomen showed a diffusely enlarged pancreas. Pancreatic involvement in ALL is a very rare manifestation and only a few cases have been reported previously, and obstructive jaundice secondary to a pancreatic mass as a primary presentation of ALL has not been reported in the surgical literature. (20)

With the exception of WBC count at diagnosis, the pattern of hematological findings among our patients did not differ from the findings of other workers, where anemia in association with thrombocytopenia was a common presenting feature of childhood ALL. (21) The percentage of patients with a leukocyte count above 50,000 per cubic millimeter was higher than that observed in Saudi Arabia (25.2% vs. 16.6%), possibly due to an increased percentage of T-cell ALL among our patients. There is a wide range of leukocyte counts observed at the time of diagnosis, from extremely low to more than 1 million cells per cubic millimeter. Approximately 20% of children with ALL present with leukocyte counts of more than 50,000 cells per cubic millimeter. (22) The initial peripheral blood leukocyte count is a significant predictor of treatment outcome, with worsening outcomes as the leukocyte count increases. Since 1996 many investigators have considered a leukocyte count of 50,000 cells per cubic millimeter as the level separating patients with a higher risk of relapse from those with a more favorable prognosis. (23)

Using the FAB morphological criteria, L1 and L2 were approximately equal in our patients (51.6% and 46.9%, respectively), compared to Western countries and Saudi Arabia where L1 was the predominant type (84% and 67.9%, respectively). (9,24) Historically, results from some clinical trials have suggested that L2 morphology conveyed a worse prognosis than L1 morphology. (25) Although when patients are treated with more intensive regimens, the FAB classification no longer appears to be
an independent prognostic variable.\(^{(26)}\)

The distribution of T-cell ALL in this study (27.7%) was higher than the range reported in Western countries and Saudi Arabia (10-15% and 13%, respectively).\(^{(9,22,27,28)}\) The independent adverse effect of T-cell immune-phenotype is well known and patients with T-cell ALL had a significantly worse outcome than did those with precursor B-cell ALL.\(^{(29)}\) The higher percentage of patients above 10 years of age with initial WBC count greater than 50,000 cells per cubic millimeter, and T-cell phenotype in this study may explain, to some extent, the relatively higher percentage of patients with failure to achieve remission (9.6%) after one month of therapy. Failure to achieve remission after one month of therapy is uncommon, occurring in fewer than 5% of patients, and it is observed more commonly in patients with high presenting leukocyte counts, T-cell phenotype, and/or the Philadelphia chromosome.\(^{(30,31)}\)

**Conclusion:**

Leukemia is an important health problem in the Kurdistan region and we have limited diagnostic facilities and inadequate facilities for standard management. The pattern of childhood ALL among Kurdish children differs in certain aspects from that seen in other countries and is comparable in others. Awareness of the magnitude of the problem demands implementation of preventive, diagnostic and therapeutic strategies for leukemias in the Kurdistan region as well as planning epidemiologic studies and research programs.

**References:**