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Epidemiological Features of Childhood Acute Leukemia at MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC), Tehran, Iran

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ABSTRACT

Aim: MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC) is one of the main national referral centers for childhood malignancies. Due to large number of referrals, data compiled at this center can consider as reference for any issues related to national health strategies and policies in order to facilitate and optimize medical services for pediatric malignancies. This report provides data regarding epidemiology of ALL and AML in children who referred to our center for diagnosis and treatment.

Methods: The enrolled patients were 216 eligible children suffering from ALL and AML who have been referred to MPTRC since 2007 to 2011. Basic epidemiological information recorded as a checklist for each individual patient.

Results: Out of patients, %79.62 had ALL and %20.38 had AML. In the ALL %57)98) and In the AML %63.6)28) were males. The mean age in the ALL group was 0.92±5.5 years and in the AML group 0.96±6 years. Familial incidences of malignancies recorded in 28 patients with ALL (%16.3) and in 5 patients with AML (11.6 %). In ALL group seven (%4) and in AML group three (%6.8) had underline disease. Parental consanguinity was evident in (n=19 ,41 %) of both groups.

Conclusion: According to our data both ALL and AML have the same frequency as compared with data from developing countries. Considering the cure rate of 80-60 % in patients with ALL and AML, these data may serve the health authorities for more effective environmental and preventive measurements, purposeful for facilitating up-to date diagnostic and treatment modalities, psychological support programs for respective family members and educational purposes.

Key words: ALL, AML, epidemiology, Iran, malignancy

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Introduction

Malignancies in general and particularly in children are considered worldwide as major public health issues in regard of facilitating specialized centers ,medical and nursing personnel and providing financial resource[1-2]. According to official reports, cancer ranks after car accidents and coronary heart disease as the third cause of death in Iran[3] and pediatric cancers rank as the sixth group of common malignancies in Iran[4].

Exposure to environmental and genetic alternations and familial history of cancer can be considered as causative factors in etiology and pathogenesis of Acute Leukemia[5].

Acute leukemia is the most frequent malignancy in most part of the world with a prevalence of over 30 % of all childhood malignancies[6-7]. Acute Lymphoblastic Leukemia (ALL) and Acute Myeloblastic Leukemia (AML) comprise 97 % of all acute leukemia[8-9]. AML is less frequent than ALL (20 versus 80%) and characterized by rapid progression[10-11]. ALL manifests in the majority of children between the age of 2-5 years and is more frequent in males than females[12-13], with mean age of 2.9 versus 2.2 years for males and females in developing countries and respectively 4.2 versus 3.52 years in developed countries[14-15].

Notably in children less than 15 years old, the incidence of ALL varies 20-35 cases per million worldwide and AML is 9.8 to 10.6 per million respectively[16-18]. Each year in the US approximately, 3250 children diagnosed with Acute Leukemia who 2400 had ALL[19-20]. MPCTRC is a NGO to support children suffering from cancer that has started since early 1991[1]. Nearly 12500 patients with childhood malignancies have been supported by MPCTRC since 1991 to 2011. At MPCTRC most referred and admitted patients have acute leukemia (n=451) in terms of urgency in concordance with reports from centers else where in Iran. Due to large number of non-specificand asymptomatic leukemic cases, the immediate prognosis and cure for decreasing early and late complications is inevitable.

The purpose of this study is to evaluate the epidemiological and clinical manifestations of Acute Leukemia in children admitted to MPTRC for accurate diagnosis and treatment.

Patients and Method

Since 2007 to 2011, 1640 children with malignancy referred and admitted to MPCTRC. The enrolled patients were acute leukemia cases, who registered for treatment or consultation. In this simple sampling study, 235 patients who treated at other centers and referred only for consultation excluded from the analysis. Thus, this cross sectional study comprised 216 eligible patients. Diagnosis and treatment of considered diseases based on clinical findings also morphological criteria based on FAB classification, flow cytometry and some cytogenetic aberrations. Treatment modalities were I-BFM 2002 and AML-BFM-83.

Epidemiological Evaluation

According to a checklist data collected for each patient that, included information about sex, age at diagnosis, type of leukemia, flow cytometry reports, clinical findings, underlying diseases, family history of cancer, consanguinity and countries. This checklist filled at the first admission for each patient. All Patients categorized according to their age at diagnosis into four groups: less than one year, 1-5, 5-10 and over 10 years old.

Data analyzed by SPSS version 19, with confidence intervals of 95%. Kolmogorov-Smirnov test had been used for consideration normal pattern of variables, Chi-square for parametric and Spearman method for non-parametric data respectively.

Results

Out of 216 enrolled patients, 172 had ALL (%79.62) and 44 AML (%20.38). In the ALL group, 98 were males (%57) and 74 females (%43). In the AML group, 28 were males (63.6%) and 16 females (36.4%). In ALL patients, M/F ratio was 1.32 and in AML patients, it was 1.75 respectively.

In ALL group, the mean age ± Std.D was 5.5 ± 0.92 years, range 6 months to 15 years. In the AML group, the mean age ± Std.D was 6 ± 0.96 years, range 6 months to 15 years. The Kolmogorov-Smirnov test has not demonstrated any comparable age distribution pattern in ALL and AML. The analysis by Spearman test has not revealed any significant relation between patient's age and sex at diagnosis in either study groups.

At the first admission out of enrolled patients, 19(11%) and seven (15.9%) were asymptomatic in ALL (n=172) and AML (n=44) groups respectively. According to table I, the most frequent clinical findings in ALL patients were fever (51.2%), organomegaly (31.4%), bone pain (22.1%), pallor (19.2%), bleeding (15.7%), nausea and anorexia (10.5%) respectively. In AML patients' fever (43.2%), organomegaly (27.3%), bleeding (22.7%), pallor (15.9%), bone pain (13.6%), nausea and anorexia (13.6%) were the most common clinical findings respectively (Table 1). Pearson and Spearman analysis showed in ALL group, significant relations between bone pain and organomegaly, bleeding, pallor (P-Value=0.015) also between nausea and anorexia with weight loss and pallor (P-Value=0.017). In addition, in AML group the significant relation between fever and pallor was disputable (P-Value=0.03). Analysis by chi-square test revealed the significant relationship between pallor and ALL patients range >one to <5 years.

Out of 172 patients with ALL 99 (57.6%) classified as L1 type and the others as L2 and L3. According to immunophenotyping, the majority of ALL group had pre- B ALL (n= 62, 36%) and early pre-B ALL (n=53. 30.8%). Only two patients had mixed lineage of T and B cells (1.2%). In AML patients the majority had M4 (n=12. 27.9%), M3 (n=9, 20.9%) and 51.2% (n=23) had other types. The immunophenotyping's results revealed that the majority of AML group had non-M3 phenotype (n= 12, 27.9%). Fifty patients (29%) and nine (20.5%) had WBC count more than 20,000 at the first admission in ALL and AML group respectively.

Relapse had been seen in 44 (25.6%) patients with ALL and 15 (34.1%) patients with AML respectively. The site of relapse in considered patients

Table 1: clinical manifestations in considered patients

	< 1 year		1-5 years		5-10 years		> 10 years	
	ALL	AML	ALL	AML	ALL	AML	ALL	AML
Male	5(71.4%)	1(50%)	36(52.9%)	7(50%)	26(59.1%)	8(80%)	31(58.5%)	12(66.7%)
Female	2(28.6%)	1(50%)	32(47.1%)	7(50%)	18(40.9%)	2(20%)	22(41.5%)	6(33.3%)
Fever	4(4.5%)	1(5.3%)	40(45.5%)	6(31.6%)	19(21.6%)	5(26.3%)	25(28.4%)	7(36.8%)
Organomegaly	4(7.4%)	0(0%)	24(44.4%)	3(25%)	13(24.1%)	5(41.7%)	13(24.1%)	4(33.3%)
Bleeding	0(0%)	0(0%)	11(40.7%)	5(50%)	8(29.6%)	3(30%)	8(29.6%)	2(20%)
Bone pain	0(0%)	0(0%)	10(26.3%)	3(50%)	11(28.9%)	2(33.3%)	17(44.7%)	1(16.7%)
Nausea& anorexia	2(11.1%)	0(0%)	10(55.6%)	2(33.3%)	2(11.1%)	2(33.3%)	4(22.2%)	2(33.3%)
pallor	1(3%)	0(0%)	21 (63.6%)	2(28.6%)	4(12.1%)	2(28.6%)	7(21.2%)	3(42.9%)

Table 2: the relation between sites of relapse and sex in considered patients				
	ALL		AML	
	Male	Female	Male	Female
Bone Marrow	12(60%)	8(40%)	8(61.5%)	5(38.5%)
CNS	7(87.5%)	1(12.5%)	1(100%)	0
Testis	1(100%)	0	0	0
Multiple	11(73.3%)	4(26.7%)	1(100%)	0

Table 3: relapse time in considered patients after CR1		
	ALL	AML
Less than 1 year	6 (3.5%)	8 (18.2%)
1-2 years	10 (5.8%)	5 (11.4%)
2-5 years	25 (14.5 %)	2 (4.5%)
More than 5 years	3 (1.8%)	0
Without relapse	128 (74.4%)	29 (38.6%)
Total	172 (100%)	44 (100%)

were as table 2. There were significant relation between sexes and relapse in ALL group (P-Value =0.05). Analysis showed that relapse in males was more than in females in both ALL and AML patients. Table 3 shows the relapse time in ALL and AML patients after first complete remission (CR1). The mean of relapse time in ALL patients was 2.05±1.51 year and in AML patients was 1±0.79 year.

In the ALL group (n=172) 28 patients (16.3%) had positive familial cancer history and in the AML group (n=44) five patients (11.6%) reported respectively. The most common familial cancer histories in ALL group were as hematological malignancies, neoplasm of gastro-intestinal tract and hepato-cellular carcinoma and in AML group the majority of patients had hematological malignancy as a familial cancer history.

Underlying diseases and comorbidities were recorded in both groups as 7 (4%) in ALL patients and 3 (6.8%) in AML patients. Ewing sarcomas, Down Syndrome, NHL, AML and nephrotic syndrome with kidney transplant have been seen in ALL group whereas ALL and Retinoblastoma have been seen in AML group.

Parental consanguinity reported in 27patients with ALL (15.7%) and 14 patients with AML (32 %). Almost all patients have been Caucasians (Iranians n=198, Azerbaijani n=six, Afghans n=3) and minor fraction Iraqis n=two.

Discussion

Aim of this study has been evaluation the epidemiological features of ALL and AML patients, who referred and admitted to MPCTRC (MAHAK's Pediatric Cancer Treatment and Research Center) for diagnostic procedures, treatment and follow-up. MAHAK as a NGO to support children suffering from cancer has started since early 1991. It has social and supportive activities at pediatric hematology and oncology departments in academic centers in Tehran, Iran. In line of its activities, a registry for childhood cancers has been set up since then. MPCTRC has started its clinical activities since 2007 by realizing the necessity for a comprehensive center dedicated to pediatric cancer treatment and research for respective age groups. The estimated annual cancer incidence in Iran is 150 per 100.000in children aged 15-0 years, meaning 3.500-3.000 new cancers, which is higher than reported from developed countries, although some reports indicate an increasing cancer incidence in these countries4.

The prevalence of acute leukemia in most part of the world is over %30 of all childhood malignancies[7], whereas out of 1640 admitted patients at MPCTRC, %27.5) 451) had acute leukemia. This frequency has nearly conformity with worldwide reported prevalence of acute leukemia. The reason for this slightly difference (%2.5) is about admitted patients who referred to MPCTRC with other malignancies as Soft Tissue Sarcoma and Brain Tumors. According to MPCTRC data, ALL comprised 80% and AML 20% of acute leukemia, which is in concordance

with reported reports in the literature[1,3,6,7]. Smith et al. concluded that ALL represented 78% of leukemia cases in patients less than 15 years old while AML was 16% respectively.

The incidence of ALL in patients younger than 15 years old was significantly higher in males than in females (nearly 1.3 fold), which is resemblance as reported literatures[8,12,13]. Likewise, AML had the same incidence rate in males higher than females (nearly 1.7 fold) in patients more than five years old. According to analysis and comparing by other literature reviews, we can assume that our data is as similar as to other reports[10,11,14,15].

Literature reviews for considering the incidence of acute leukemia showed that the peak age being 1-5 years for ALL (the mean age=5.5±0.92) and more than 10 years for AML (the mean age=6±0.96). In this study, both groups had resembled mean age with other reported in the literatures[11,13].

Nearly 85-89% of ALL in children classified as FAB L1. Immunophenotyping distribution of ALL demonstrates that pre-B Cell ALL accounts for 80% of cases while T-Cell accounts for 15-20%[20]. In this study, L1 and pre-B ALL was the most common phenotype in ALL group. FAB classification revealed that M5 and M7 are more common in early childhood while older children are more likely to have M0, M1, M2 and M3[20]. According to the results of this report, in AML group, M4 and M3 were the most phenotypes. This difference is because of our utilize and instruments for classification.

Initial symptoms are not specific to ALL and AML[1]. Many of clinical features of AML are similar to ALL; these features can be fatigue, fever and infection, weight loss, bone pain, or ganomegaly, petechial6. In this study, fever and organomegaly were common in enrolled patients. The less common clinical manifestations were pallor and bleeding. The relation between bone pain and some clinical features (organomegaly, bleeding, pallor, nausea and anorexia, lose weight and pallor) was significant so it can be dispute by later prospective researches.

Gaynon and coworkers found that at least 30% of patients have an adverse event with current therapies making relapsed ALL (incidence 30.9 X 0.3= 9.3 cases / 10^6 children / year). Azarm and coworkers found that CNS relapse was more in female than male but Ching-Hon Pui concluded that there were no significant differences in CNS relapse between the two sexes[20]. There were significant differences of relapse between two sexes in ALL group. The relapse was more frequent in male than female. These data are in concordance with other literatures.

Incidence of childhood cancer in families suffering from cancer is well-established[17]. One example is associations of breast cancer in the family and occurrence of acute childhood leukemia. These examples points to specific genetic mechanisms predisposing for cancer in other family members. According to the present study, ALL and AML patients had high percentage of positive familial of cancer history, respectively 16.3% and 11.6 %. Whereas the positive familial cancer rate in most part of the world is 2-3%. According to reported reports, the effect of positive familial history of cancer on risk of childhood hood acute leukemia is still unclear and it needs more investigations around this subject[17-18].

In addition, the high rate of parental consanguinity in both ALL an AML groups (15.7% and 32% respectively) may be another genetically augmenting factor for cancer. The serious affair is that the frequency of consanguineous mating in the population of Iran is higher (24-64% in urban populations) than those reported (30%) for the Middle Eastern[3-4]. This data can probably reveal that there may be some impressions of consanguineous mating

on childhood malignancy's rate in Iran. The low socio-economic status of the study patients may account as another predisposing cancer factor. These results indicate the need for surveillance of family members afflicted with cancer[3]. Caucasians are more likely to develop acute leukemia than African-Americans, Asians or Hispanics. Nearly the most cases in this study were Caucasians.

In conclusion, the presented data demonstrate the same frequency of epidemiological and clinical features in acute leukemia. However, apart from higher male affliction in ALL and , high mean age at presentation in both groups there are significant differences in terms of high consanguinity rate and high incidence of familial cancer history as compared to reports from developed countries. A possible association between environmental factors and cancer genesis can deduct from cancer clustering in one report.

Health Authorities can utilize epidemiological data compiled at MPCTRC as basis for their medical care planning and various informative and educational programs. Furthermore, our data are accessible for academic research institutions.

Disclosure

The authors taking part in evaluation and writing the manuscript have not any conflict of interest for this report.

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