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Evaluation of risk factors in children with acute lymphoblastic leukemia

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The aim of the present study was to investigate the influence of some possible risk factors in development of ALL. A hundred and sixteen children diagnosed as ALL over a three year period in our institute were involved in the study. Their ages ranged between 1 and 14 years (7.35±3.8). Four hundred children without any malignant or chronic disorders served as the control group. Male sex, increased paternal age (over 40 years), presence of malignant disorders among close relatives, pesticide exposure and birthweight over 4 kg seemed to be the factors associated with increased risk of ALL in children. [Turk J Cancer 2002;32(1):5-11]

Key words: Acute lymphoblastic leukemia, risk factors, childhood, epidemiology

Childhood leukemia comprises 35% of all malignancies in children under 15 years of age. Acute lymphoblastic leukemia (ALL) accounts for approximately 75-80% of childhood leukemia with an incidence of 0.004%, that shows a peak between 3-5 years of age (1,2). However, geographic variation has been reported (1-4). Male preponderance has been described especially in the pubertal ages. Variable demographic, prenatal, perinatal, genetic and environmental factors have been suggested to contribute to the development of childhood ALL. Included, these are; increased paternal or maternal age, maternal use of oral contraceptives, in-utero viral infections, living in proximity to high voltage power lines or exposure to electromagnetic fields, parental occupational exposures, socioeconomic status, higher birthweight, male sex, in-utero ionizing radiation exposure, having a sibling, especially a monozygotic twin with leukemia, and history of maternal fetal loss (2,5-8). Definitive links between several of these risk factors such as exposure to ionizing radiation, male sex, having a sibling or twin with leukemia, and childhood ALL have been well established (9-15). However, the etiology remains undetermined in majority of patients; therefore, further case-control studies are warranted. Here, we investigated the association of some demographic, genetic, prenatal, perinatal and environmental factors with the development of childhood ALL in a case-control study.

Materials and Methods

One hundred and sixteen children diagnosed to have ALL, between December 1993 and December 1996, in the Department of Pediatric Oncology of Dr. Sami Ulus Childrens' Hospital were involved in the study. Sixty-six of them were male and the remaining were female with a mean age of 7.35±3.8 years (range: 1-14 years). The majority of the patients were of low socioeconomic status. Seventy-nine percent of the patients are still alive, whereas 37% either died or were lost to follow-up. The control group consisted of four hundred children between the ages of 1-14 years without any malignant, hematologic or chronic disorders, who were seen in the outpatient clinics for mild infectious diseases. Data including age, sex, birthweight, history of breast-feeding, intrauterine exposure to infectious agents, medications, ionizing radiation, maternal and paternal age, maternal smoking during pregnancy, paternal occupation, history of malignant disorders among the family members and close relatives of the patients, exposure to pesticides and electromagnetic fields, living in proximity to high power voltage lines were all obtained for the patients and the control group either by inquiry to the parents or from the medical records of the patients not in follow-up. The results were analysed by the "Epi-Info" computer program, chi-square and Fisher's exact chi-square tests and by estimating Odd's ratio if necessary.

Results

Male to female ratio in patients was 1.32. Mean age was 7.35±3.8 in the patients and 5.35±3.5 in controls. Since the difference between the mean age in the patients and the control subjects was statistically significant ($p < 0.0002$), age adjusted Odd's ratio was calculated to compare the parameters between the two groups. The socioeconomical status of the patients and the control group did not show a significant difference, with approximately 75% belonging to lower socioeconomical status. The most common parental occupation in patients with ALL was farming (40%), whereas farming comprised of only 10% of parental occupation in the control group. Tradesman's calling was the most common (45%) parental occupation in the control group. The maternal education status was significantly lower in the ALL group than that in the control group. Fifty-eight percent of children with ALL were from rural areas whereas only 10% of the control group were living in rural areas. The estimated risk for development of ALL was 1.6 times higher in girls than the boys (p:0.023). The distribution of prenatal, perinatal and genetic risk factors in the children with ALL and the controls are shown in table 1.

Although, increased birthweight, malignant disease among close relatives and increased paternal age were found to be significantly associated with development of ALL, maternal age did not seem to influence its development. There was 3.3 and 3.99 fold increased risk of ALL in children with increased paternal age (over 40 years) and in children with birthweight over 4 kg, respectively.

Table 1
Distribution of paternal age and birthweight in ALL and control groups

	ALL		Control	
	No	%	No	%
Birthweight				
≤4 kg	20	17.2	20	5
>4 kg	96	82.8	380	95
Total	116	100	400	100
Paternal age at the time of delivery				
<40 years	9	7.8	12	3
≥40 years	107	92.2	388	97
Total	116	100	400	100

Birthweight: OR: 3.96 (1.95 - 8.03), Adj OR: 3.99 (CI: 2.01 - 7.94), P: 0.00001. Paternal age at the time of delivery: OR: 2.72 (CI: 1.02 - 7.14), Adj OR: 3.30 (CI: 1.28 - 8.51), P: 0.031.

Maternal smoking during pregnancy, fetal loss, plural gravidity did not seem to be significant factors in development of ALL in our study group. In contrast, there was a significant relationship between the development of ALL and the occurrence of maternal febrile illnesses with rash, physical trauma during gestation, and the use of various medications (Table 2).

Table 2
The distribution of maternal factors in children with ALL and control group

	ALL		Control		OR	Adj OR	p
	n	%	n	%	CI (%95)	CI (% 95)	
Spontaneous fetal loss (+)	21	18.1	59	14.8	1.28	0.89	0.77
Spontaneous fetal loss (-)	95	81.9	341	85.2	(0.71-2.28)	(0.5-1.57)	
Multiple gravidity (+)	4	3.4	3	0.7	4.73	0.28	0.05
Multiple gravidity (-)	112	96.6	397	99.3	(0.88-2.7)	(0.06-1.27)	
Smoking (+)	7	6.1	27	6.8	0.89	1.41	0.8
Smoking (-)	109	93.9	373	93.2	(0.34-2.21)	(0.56-3.55)	
X-Ray (+)	2	1.7	-	0	*	*	0.005
X-Ray (-)	114	98.3	400	100			
Febrile illness with rash (+)	6	5.2	-	0	*	*	0.00001
Febrile illness with rash (-)	110	94.8	400	100			
Medication (+)	10	8.6	9	2.3	4.1		0.0033
Medication (-)	106	91.4	391	97.8	(1.6-10.3)		
Trauma (+)	4	3.4	1	0.3	14.25)		0.01
Trauma (-)	112	96.6	399	99.7	(1.49-338.14)		

*Could not be calculated

Among several environmental factors, pesticide exposure was found to be associated with increased risk of ALL ($p < 0.05$), whereas no relationship was detected between development of ALL and living in proximity to higher voltage power lines and also with habit of watching television too close (Table 3). There was history of maternal diagnostic X-ray exposure (dental in one, and extremity

in the other) during pregnancy in two patients with ALL whereas none of the subjects in the control group had prenatal X-ray exposure. Therefore, no conclusion was yielded in the present study regarding the hazards of ionizing radiation in the development of ALL.

Table 3
Distribution of environmental factors in the ALL and control groups

	ALL		Control		OR	Adj Or	p
	n	%	n	%	CI (%95)	CI (%95)	
Breast-feeding (+)	8	6.9	25	6.2	1.1	1.22	0.8
Breast-feeding (-)	108	93.1	375	93.8	(0.45-2.68	(0.5-2.97)	
Living proximity to high power voltage (+)	12	15.2	56	14	1.10	0.92	0.78
Living proximity to high power voltage (-)	67	84.5	344	86	(0.53-2.26	(0.31-8.9)	
Television habit (+)	77	97.5	381	95.3	1.92	1.67	0.55
Television habit (-)	2	2.5	19	4.7	(0.42-12.2	(0.31-8.9)	0.55
Exposure to pesticide (+)	19	24.1	-	0	*	*	0.000
Exposure to pesticide (-)	60	75.9	400	100			

*Could not be calculated

Discussion

It has been shown that the incidence of ALL is higher among boys than girls (2). The male preponderance is particularly significant in T cell ALL with an increasing male to female ratio of 4/1. Young et al (2) have demonstrated that the incidence of ALL was 1.4 times higher in boys than girls among children of age 14 years. Consistent with the established data the risk for development of ALL was found to be 1.6 times higher among boys than girls in this study.

Genetic factors are presumed to play a significant role in development of acute leukemia including ALL. Some inborn chromosomal defects have been shown to be associated with high risk of ALL such as trisomy 21 Down Syndrome (16,17,18). When a sibling of a child develops ALL, the risk of the disease in that child has been found to be 2-4 times higher than the risk in normal population (13). The concordance of acute leukemia in identical twins has been estimated to be 20-25%. These findings suggest that leukemogenesis originates in utero and blood born metastases may also occur from one twin to the other. On the other hand, shared environmental exposures to leukomogens may play a role in the increased incidence of leukemia between siblings and other family members. Families with constitutional p53 abnormalities have been noted to have children with both AML and ALL (19). Based on the above data, we investigated whether the incidence of the malignant disorders among close relatives of children with ALL was higher than those in controls and showed that it was 5.36 fold increased in ALL group.

There have been conflicting results in the literature about the influence of increased maternal and paternal age in the development of ALL (3). In the

present study, although no relationship was detected between the maternal age and the risk of ALL, increased paternal age (over 40 years old) has been shown to be associated with 3.5 fold increased risk.

The association of higher birthweight and the risk of the development of ALL is an area of controversy as well (5,7). Daling et al (5) have reported an increased incidence of ALL among children between the ages of 2-4 years whose birthweight was higher than normal, however, beyond the age of 4 years such an association disappeared. In contrast, Mc Mohan et al (6) have found no association between the risk of ALL and the birthweight of children. In this study, the risk of ALL was found to be 3.9 fold increased in children born with a weight over 4 kg. However, no significant effect of birthweight on different age groups was detected as shown by Daling et al.

Spontaneous fetal loss particularly prior to the birth of a child has been shown by a number of investigators to be with 2 fold increased leukemia risk in that child (3). No such relationship was demonstrated in this study. Furthermore, history of maternal smoking during pregnancy also did not seem to influence the development of ALL. In contrast to our results, Stjernfeldt et al (20) have reported two fold increased risk of leukemia in children with history of maternal smoking during gestation; however, some other investigators have not confirmed this finding (21,22).

Large epidemiological studies have documented that ionizing radiation under certain conditions of exposure induces human cancers including leukemia (11,15). In a study by the American National Academy of Science (12) prenatal exposure to ionizing irradiation during the first trimester was found to be associated with five fold increased risk of childhood cancers and when the exposure occurred beyond the first trimester, the risk has been shown to be increased 1.5 folds.

Several investigators have reported that intrauterine exposure to 0.3 - 0.8 cGy radiation was associated with significantly increased risk of ALL (10,12). Since the effect of ionizing radiation on development of cancer is well-established, large measures are taken to avoid exposure to radiation, and nowadays ionizing radiation is underrepresented as a risk factor among leukemia cases. Thus, in this study a history of diagnostic X-ray during gestation was present in only two cases. Consequently, no conclusive statement could be yielded regarding the relationship between in-utero exposure to radiation and the risk of ALL.

The role of viral infections in the pathogenesis of leukemia has frequently been brought to the attention. Although it has not been confirmed in humans, many viruses have been shown to induce leukemogenesis in animals. The Ebstein Barr virus (EBV) infection has been shown to contribute, at least partially to development of African Burkitt Lymphoma and ALL with L3 morphology. In immunocompromised individuals this virus has been shown to cause lymphoproliferative disorders, and in its most aggressive form, EBV infections can result in chromosomal breaks, translocation and malignant transformation to a monoclonal proliferation (23). In our study group, we tried to identify if there was an association between in-utero exposure to viral agents and risk of ALL. Indeed, we have found significantly higher incidence of history of acute febrile infections with rash during gestation in the ALL group than in

controls. Not only maternal febrile infections but also the incidence of physical trauma and medication usage during gestation were found to be increased in the ALL group when compared to controls. However, this finding may represent a recall bias due to the possibility of mothers of leukemic children to remember such gestational events much more than those mothers in the control group. When the effect of breast-feeding was analysed, we did not find a difference in the incidence of being devoid of breast-feeding between the groups with ALL and controls as shown by Shu et al (7) in 1995.

The effects of paternal occupation and exposure to some chemicals including pesticides on the development of childhood cancers have also been studied. Contaminations in drinking water, food additives, pesticides in environment can expose children particularly living in rural area (3). In the present study, the finding of higher incidence of living in rural area and having paternal occupation of farming in the ALL group may suggest an association between pesticide exposure and risk of ALL. However, a selection bias may also be considered.

Exposure to electromagnetic fields has been shown to induce chromosomal breaks and lymphoblastic transformation in experimental studies (8,14,24). However, the results of clinical studies are conflicting. Measurement of exposure is difficult, given that electromagnetic field not only exists near high voltage powerlines, but is also generated by several equipments including computers, television monitors and cellular phones. We compared the rates of living proximity to high voltage powerlines and habit of watching television too close among ALL and control groups, but did not show a significant difference. Although a similar method was also used in several previous studies, we believe that more sensitive and reliable methods would be more informative.

In conclusion, our present study suggests that sex, paternal age, existence of malignant disorder among close relatives, higher birthweight, and exposure to pesticides is associated with increased risk of ALL in children.

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