JRHS
Journal of Research in Health Sciences
journal homepage: www.umsha.ac.ir/jrhs

Original Article

Parental Risk Factors of Childhood Acute Leukemia: A Case-Control Study

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ARTICLE INFORMATION

Article history:
Received: 5 June 2011
Revised: 7 July 2011
Accepted: 7 September 2011
Available online: 13 September 2011

Keywords:
Leukemia
Parents
Child
Lymphoblastic
Myeloblastic

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ABSTRACT

Background: Leukemia is the most common cancer in children, accounting for near to half of all childhood cancers. Different risk factors might be effective in the occurrence of this cancer such as parental characteristics. This study was done in West Azarbaijan Province in order to determine the relation between parental characteristics and acute leukemia in children.

Methods: This matched case-control study was conducted on children less than 15 years affected by acute leukemia from March 20, 2003 to March 20, 2009. Two control groups were selected, one from hospital and the other from the study population. Cases and controls were matched on age and sex. Logistic regression model was used for data analysis.

Results: This study was done on 130 patients, 108 (83.1%) were affected by Acute Lymphoblastic Leukemia and 22 (16.9%) by Acute Myeloblastic Leukemia. Seventy two of the patients were male (55.4%) and 58 were female (44.6%). There was a statistically significant correlation between acute leukemia and variables such as mother's education [OR=4.2, 95% CI: 2.42, 7.34], mother's history of using Oral Contraceptive Pills [OR=1.77, 95% CI: 1.05, 2.82] and parental relationship [OR=2.05, 95% CI: 1.30, 3.23].

Conclusion: It seems that some parental characteristics have an important role in etiology of childhood leukemia.

Citation: Gholami A, Salarilak S, Hejazi S, Khalkhali HR. Parental risk factors of childhood acute leukemia: a case-control study. JRHS. 2011;11(2):69-76.

Introduction

Leukemia is a malignant disease (cancer) of the bone marrow and blood, characterized by the uncontrolled growth of progenitors of white blood cells. Leukemia is the most common type of cancer diagnosed in children less than 15 years, comprising roughly a half of pediatric malignancies[1-10]. While leukemia occurs about 10 times more often in adults than in children, it is the most leading cause of childhood cancer. The major forms of leukemia are divided into four categories. The terms “myeloblastic” and “lymphoblastic” denote the cell type involved. Myeloblastic and lymphoblastic leukemia each has an acute or chronic form. Thus, the four major types of leukemia are acute or chronic Myeloblastic leukemia (AML, CML) and acute or chronic lymphoblastic leukemia (ALL, CLL)[11].

Acute leukemia (AL) is a rapidly progressive disease that primarily affects cells that are not fully developed or differentiated and these immature cells cannot carry out their normal functions. ALL occurs most often in the first decade of life but increases in frequency again

in older individuals[11]. Approximately 3,250 children and adolescents younger than 20 years of age are diagnosed with leukemia each year in the US, of which 2,400 are acute lymphoblastic leukemia[13]. AL occurs at different rates in different geographic locations. Leukemia is more common among developed countries and higher socioeconomic groups[11]. Identifying risk factors for childhood leukemia is an important step in the reduction of the overall burden of childhood diseases.

In most cases, the cause of AL is not evident and few factors have been associated with an increased risk of developing the disease. Genetic susceptibility and environmental factors play potential roles in this process[14]. Most environmental risk factors have been found to be weakly and inconsistently associated with either form of acute childhood leukemia. Chronic exposure to benzene and exposure to high doses of ionizing radiation are well-known leukemia risk factors[15]. In childhood leukemia factors such as parental exposure to ionizing radiation, maternal use of cigarettes, or contraceptives, parental age and education and so on have been suggested as risk factors for leukemia, but these factors have not been definitively linked to leukemia.

In this survey, we investigate parental characteristics as potential risk factors for acute leukemia among childhood in west Azarbaijan Province, the northwest of Iran.

Methods

This matched case-control study was conducted on the patients with ALL and AML less than 15 years diagnosed from March 20, 2003 to March 20, 2009 in west Azerbaijan Province. Peripheral blood and bone marrow cells were examined by light microscope to diagnose AL. In order to identify the lymphoblastic or myelocytic origin of the cells, the histochemical staining (Myeloproxidase and Sudan block B) as well as flow cytometry of peripheral blood and/or bone marrow cells were done.

The data collection tool was a questionnaire included various question regarding demographic information, type of cancer, and potential risk factors of leukemia. Indeed, the data collection tool was modified version of Washington Health Department questionnaire[16] adjusted for the study population after consultant with epidemiologists and oncologist. In addition, a pilot study was done to increase the validity of questionnaire. Data collection was formed via face-to-face interview with patients' mothers and that of controls.

We selected two control groups (one from hospital and the other from the study population). Hospital control group were selected from children ward and children clinic center in Motahari hospital in the city of Urmia. Population control group were selected from children who came to Urmia Health Centers for routine health cares. Cases and controls were frequently matched on sex and age using the same three age groups (less than 5, 5 to 9, 10 to14 years old).

Inclusion criteria for cases included: (a) having AL, (b) AL diagnosis from March 20, 2003 to March 20, 2009, (c) aged less than 15 years at time of diagnosis, (d) residence in west Azerbaijan Province at time of diagnosis. Inclusion criteria for controls included: (a) not having AL or other blood diseases, (b) age less than 15 years at time of data collection, (c) residence in west Azerbaijan Province.

Logistic regression model was used to investigate the relation between leukemia and parental characteristics including both parents' age, education level, cigarette smoking and their relationship as well as history of oral contraceptive (OCP) use, drug use, number of previous pregnancies, abortion and exposure to X-ray during pregnancy. We reported odds ratio (OR) with 95% confidence interval (CI). Chi-square test for developing leukemia was used to comprise education levels and OCP use (before pregnancy of surveyed child) with specified reference. We used SPSS software version 16 for all statistical analysis.

Results

During the study period, 138 children with leukemia were detected. Of these, eight patients were excluded from the study, one because of parents' disagreement and seven because of changing their addresses.

Accordingly, 130 patients remained for analysis including 108 (83.1%) patients with ALL and 22 (16.9%) patients with AML. Seventy two patients (55.4%) were males and 58 (44.6%) were females. At the time of diagnosis, 52.3% of the families lived in urban areas and 47.7% in rural areas. Most of male patients (48.6%) aged less than 5 years (Figure 1) while most of the female (43.1%) aged 5 to 9 years age group (Figure 2).

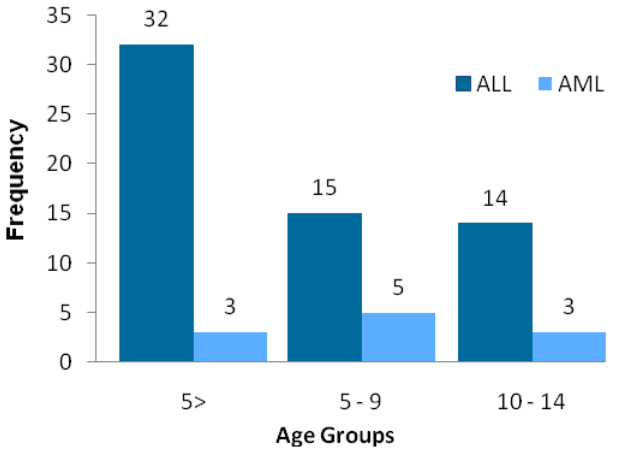

Figure 1: Frequency of acute lymphblastic leukemia (ALL) and acute Myeloblastic leukemia (AML) in male patient by age

The correlation between AL and the following variables was statistically significant: the mother's age (P<0.016), the mother's education (P<0.001), the father's education (P= 0.001), OCP use by mothers (P<0.001), parental relationship (P=0.002) and number of the mother's pregnancy (P<0.05) (Table 1). The correlation between AL and the following variables was not statistically significant according to univariate logistic regression model: father's age, the mother's smoking status, the father's smoking status, X-ray exposure by the mother during pregnancy and the mother's abortion (Table 1).

We evaluated the correlation between different variables and AL using multivariate logistic regression model with Forward method. Variables with significant relations were as follows: the mother's education, the mother's history of OCP use and parental relationship (Table 2). As seen in Table 3, there was a positive correlation between the risk of AL and duration of OCP use (P<0.001) and a negative correlation between the risk of AL and the mother's education level (P<0.001) (Table 3).

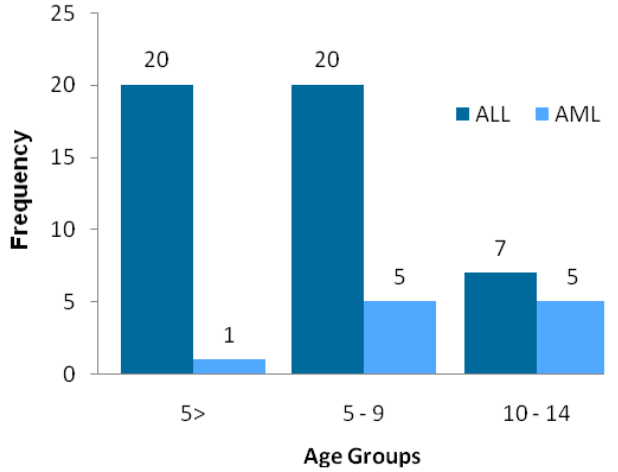

Figure 2: Frequency of acute lymphoblastic leukemia (ALL) and acute Myeloblastic leukemia (AML) in female patients by age

Discussion

In this study, we examined 130 children with AL who were diagnosed in west Azarbaijan Province. Seventy two patients (55.4%) were male and 58 (44.6%) were female. In Hjalgrim study, 52.9% of patients were male and 47.1% of were female[17]. In Paolo study conducted on patients with ALL; 57% were male and 43% were female[18]. In Natali Mallol study, 54.4% were male and 45.6% were female[19]. According to the results of this study and the studies mentioned previously, it seems that leukemia is more common in males than in females.

Of the children in this study, 108 patients (83.1%) were affected by ALL and 16.9% by AML. In Emi study, 88% of patients were affected by ALL, 10% by AML and 2% by acute unknown lymphoblastic leukemia (ANLL)[20]. In Milne study, done in west Australia; 86.8% of children were affected by ALL and 13.2% by AML[21]. In all previous as well as the present study, almost 80% of AL were ALL type. Most cases (43%) in this study aged five years which was similar to the results of Westergard [7], Hjalgrim, and[17] Zolala[22] studies.

In this study, the number of patients in urban areas (52.3%) was more than that of rural areas (47.7%). In Auvinen's study, 24% lived in rural areas, 32% in urban areas and 44% in suburbs[23]. In addition, based on the resulths of Zolala's study, 63.5% of the patients lived in urban areas compared to 36.5% who lived in rural areas[22].

Table 1: Odds ratio (OR) estimates of leukemia based on the univariate logistic regression model

Variables	Cases N=130	Hospital controls N=130	Populations Controls N=130	Total controls N=260	OR (95% CI) based on hospital controls	OR (95% CI) based on population controls	OR (95% CI) based on total controls
Number of previous pregnancy [a]							
0	34	57	64	121	Reference	Reference	Reference
1	44	39	34	73	1.89 (1.03, 3.46)	2.44 (1.32, 4.49)	2.15 (1.26, 3.66)
2	20	11	19	30	3.05 (1.3, 7.13)	1.98 (0.93, 4.21)	2.37 (1.2, 4.69)
≥ 3	32	23	13	36	2.33 (1.18, 4.62)	4.63 (2.15, 9.98)	3.16 (1.72, 5.82)
Mother's age (year) [b]							
≤ 35	106	124	121	245	Reference	Reference	Reference
> 35	24	6	9	15	3.1 (1.18, 8.16)	2.23 (0.87, 4.70)	2.46 (1.19, 5.10)
Father's age (year) [b]							
≤ 35	82	99	101	200	Reference	Reference	Reference
> 35	48	31	29	60	1.47 (0.85, 2.54)	1.6 (0.92, 2.8)	1.54 (0.96, 2.46)
Mother's education [b]							
≥ high school	19	54	66	120	Reference	Reference	Reference
< high school	111	76	64	140	4.15 (2.28, 7.55)	6.03 (3.32, 10.9)	5.01 (2.91, 8.63)
Father's education [b]							
≥ high school	36	53	64	117	Reference	Reference	Reference
< high school	94	77	66	143	1.8 (1.07, 3.02)	2.53 (1.51, 4.24)	2.14 (1.35, 3.69)
Parental Relationship							
No	82	95	108	203	Reference	Reference	Reference
Yes	48	35	22	57	1.59 (0.94, 2.7)	2.87 (1.61, 5.14)	2.08 (1.31, 3.31)
History of the mother's OCP use [a]							
No	61	87	91	178	Reference	Reference	Reference
Yes	69	43	39	82	2.29 (1.39, 3.78)	2.64 (1.59, 4.39)	2.46 (1.59, 3.78)
History of the mother's drug use [c]							
No	84	99	91	190	Reference	Reference	Reference
Yes	46	31	39	70	1.75 (1.02, 3.00)	1.28 (0.76, 2.15)	1.49 (0.95, 2.34)
History of the mother's X-ray exposure [c]							
No	127	128	129	257	Reference	Reference	Reference
Yes	3	2	1	3	1.51 (0.25, 9.20)	3.05 (0.31, 29.7)	2.02 (0.40, 10.2)
History of the mother's abortion [a]							
No	107	98	100	198	Reference	Reference	Reference
Yes	23	32	30	62	0.66 (0.36, 1.20)	0.72 (0.39, 1.32)	0. 69 (0.40, 1.17)
History of the mother's smoking [a]							
No	126	129	130	259	Reference	Reference	Reference
Yes	4	1	0	1	4.1 (0.45,37.2)	No data	8.22 (0.91, 74.3)
History of the father's smoking [a]							
No	67	75	78	153	Reference	Reference	Reference
Yes	63	55	52	107	1.28 (0.79, 2.10)	1.41 (0.86, 2.31)	1.35 (0.88, 2.95)

[a] Before pregnancy of surveyed child

[b] At the birth time of surveyed child

[c] During pregnancy of surveyed child

Table 2: Odds ratio (OR) estimates of leukemia based on the multivariate logistic regression model

Variables	Cases N=130	Hospital controls N=130	Populations Controls N=130	Total controls N=260	OR (95% CI) based on hospital controls	OR (95% CI) based on population controls	OR (95% CI) based on total controls
Mother's education [a]							
≥ high school	19	54	66	120	Reference	Reference	Reference
< high school	111	76	64	140	3.75 (2.28, 7.55)	5 (2.70, 9.26)	4.2 (2.42, 7.34)
Parental Relationship							
No	82	95	108	203	Reference	Reference	Reference
Yes	48	35	22	57	-	2.64 (1.40, 4.27)	2.05 (1.30, 3.23)
History of the mother's OCP use [b]							
No	61	87	91	178	Reference	Reference	Reference
Yes	69	43	39	82	1.96 (1.16 , 3.31)	2.44 (1.39, 5.00)	1.77 (1.05, 2.82)

[a] At the birth time of surveyed child
[b] Before pregnancy of surveyed child

One of the major advantages of this study was that the subjects in the control group were randomly selected from the children ward and from the Children Clinic Center in Motahari Hospital in Urmia city and from children who came to Urmia health centers for routine cares rather than from recruited volunteers as in most case control studies.

In this study, after using of Multivariate logistic regression model, we observed a strong positive correlation between the mother's education and AL risk. In Xiao Ou Shu[24] and Wan-Qing[25] studies, there was a negative correlation between OR estimates of ALL and AML and Mother's Education level and according to the results of Amy study, the mother's education level in cases group was lower than that of controls group[26]. Some studies did not report any significant relation between the mother's education and leukemia[19,22,27,28]. It seems that the education level of parents, especially the mother's education level, can probably be one of the potential risk factors that may affect the childhood leukemia. Mothers with higher education level are probably more careful in taking care of their children i.e. they are more careful to children not to be exposed to chemical materials, more pursuing for timely diagnosis and treatment of the childhood diseases, providing timely vaccination, and accurate nutrition of the child and so on.

In this study, we observed a significant relationship between AL and the History of Mother's OCP use (before being pregnant for the surveyed child). OCP use has a weak relation to the breast and cervical cancers but the relation between mother's OCP use and childhood leukemia probably caused by estrogen and progesterone passes through placenta to fetus. The results of Pombo and colleagues[29] shows that the percentage of contraceptive use during pregnancy is higher among mothers of infants with acute leukemia (approximately 6%), that can probably be caused by estrogen passes (as a teratogenic) through the placenta to the fetus, and then use of OCP during the pregnancy can be dangerous. As long as this study is concerned we surveyed the relation between the mother's OCP use before pregnancy and childhood leukemia. This field requires further studies to investigate this type of relation.

We observed a significant relationship between AL and parental relationship. In Zolala study[22], no significant relation between AL and parental relationship was reported. On the contrary, in Berger[30] and Hadi[30] studies a significant relation between AL and parental relationship was reported. Accordingly, it seems that

the relationship between parents is one of the factors that probably have an effect on childhood leukemia.

Conclusion

It seems that some parental characteristics probably have important roles in the etiology of childhood leukemia and that this subject can be useful for early diagnosis and prevention of the disease.

Table 3: Odds ratio (OR) of developing acute leukemia according to the mother's education level and time of oral contraceptive (OCP) use by mother

Variables	Cases N=130	Hospital controls N=130	Population Controls N=130	Total controls N=260	OR (95% CI) based on hospital controls	OR (95% CI) based on population controls	OR (95% CI) based on total controls	*P* value
Mother's education level [a]								
Illiterate	55	16	15	31	Reference	Reference	Reference	<0.001
Elementary	36	31	29	60	0.34 (0.16, 0.70)	0.34 (0.16, 0.72)	0.34 (0.19, 0.62)	
Guidance	20	29	20	49	0.2 (0.09, 0.45)	0.27 (0.12, 0.63)	0.23 (0.12, 0.46)	
High	14	42	40	82	0.1 (0.04, 0.22)	0.1 (0.04, 0.22)	0.1 (0.05, 0.20)	
Collage	5	12	26	38	0.12 (0.04, 0.40)	0.05 (0.02, 0.16)	0.07 (0.03, 0.21)	
Time duration of OCP use by mother [b]								
Don't use	61	87	91	178	Reference	Reference	Reference	<0.001
5>	43	34	34	68	1.8 (1.03, 3.15)	1.89 (1.08, 3.29)	1.85 (1.14, 2.98)	
5-10>	24	8	5	13	4.28 (1.8, 10.16)	7.16 (2.60, 19.8)	5.39 (2.58, 11.2)	
10≤	2	1	0	1	2.85 (0.25, 32.2)	No data	5.84 (0.52, 65.5)	

[a] At the birth time of surveyed child
[b] Before pregnancy of surveyed child

Acknowledgments

We appreciate the respectable staff of Hematology Ward in Motahari teaching Hospital and also the patient and control groups' families.

Conflict of interest statement

There were no conflicts of interest to be stated.

Funding

This study was funded by the Urmia University of Medical Sciences.

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