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INVESTIGATION OF PARENTAL RISK FACTORS IN THE ETIOLOGY OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

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ABSTRACT

Aim: In this case-control study, we investigated parental history and habits in children with acute lymphoblastic leukemia (ALL) and aimed to find possible factors that could affect the risk of leukemia.

Methods: Parents of 105 children treated for ALL over a period of ten years in our Clinic of Pediatric Hematology-Oncology were questioned in terms of age, family history, nutritional habits, maternal supplement intake, smoking, alcohol consumption, X-ray exposure, and accompanying diseases. Results were compared with a control group which consisted of 102 healthy children of similar age and gender.

Results: There was no significant difference between the groups regarding maternal and paternal age. Even though the rates of family history of leukemia and other cancer types were higher in the leukemia group, the difference was not statistically significant. The rate of vitamin and iron supplement intake during pregnancy was significantly lower in the leukemia group (p=0.017; p=0.002). The rate of folic acid and fish oil supplement use was higher in the control group; however, there was no significant difference. There was no difference between the groups in terms of maternal X-ray exposure, infections, and other diseases during pregnancy. Paternal smoking history ≥1 pack/day and ≥20 packs/year; and paternal routine alcohol consumption was significantly higher in the leukemia group (p=0.041; p=0.048; p=0.029).

Conclusion: Leukemia is a disease with a multifactorial etiology that arises from interactions between genes and the environment. Paternal cigarette smoking, alcohol exposure, and maternal iron and vitamin deficiency may be among the factors that increase the risk of childhood ALL.

Keywords: Pediatrics, acute lymphoblastic leukemia, etiology

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancer type seen in the childhood period. It is a heterogeneous disease characterized by proliferation of malignant clones as a result of a pause in the maturation phase of lymphopoietic cells. It involves 25-30% of all childhood cancers, 75% of newly diagnosed leukemia, and 80% of acute leukemia [1]. It is also the most common malignancy among children in Turkey [2]. Although the etiology of leukemia has not been elucidated, it is assumed to be multi-factorial. Besides prenatal, environmental, and immunological factors, infections and genetic factors are suspected to play a role. However, causative factors still remain unclear [3].In this study, we investigated parental history and habits in children with ALL and aimed to find possible factors that could affect the risk of leukemia.

METHODS

The parents of 105 children diagnosed and treated for ALL over a period of ten years in our Pediatric Hematology and Oncology Clinic were questioned in terms of prenatal and perinatal factors related to the parents and results were compared with a control group that consisted of 102 healthy children with similar age and gender. Parents were informed about the content and aim of the study and informed consents were taken. Permission was obtained from the Pediatric Hematology Oncology Department and the study was approved by the institution's ethical committee.

In the questionnaire, prenatal and perinatal X-ray exposure, disease history of mothers (infection, hypertension, infertility), oral contraceptive usage before pregnancy, nutritional habits, and folic acid, iron, vitamin, and fish oil supplementation during pregnancy were questioned. History of abortions, number of siblings, and history of leukemia and cancer in the family were recorded. Mothers were also questioned in terms of prenatal and perinatal exposure of charcoal products and hair dyes, cigarette smoking, and alcohol consumption. Fathers were questioned in terms of prenatal exposure to radiation, smoking, and alcohol consumption.

The Statistical Package for Social Science (SPSS) for Windows 28.0 program was used in statistical analysis [4].In the evaluation of data, besides descriptive statistics (mean, standard deviation, median, minimum, maximum and frequency), Chi-square and Fisher's exact tests were used in the comparison of quantitative data. Data normality was assessed through Shapiro-Wilk test. Pearson chi-square test was used for comparing categorical variables that are independent. Group differences were assessed by a Mann–Whitney U test for analyses that were not normally distributed. The Fisher-Freeman-Halton test was used for sequentially generated contingency tables. The results were evaluated in a 95% confidence interval and $p<0.05$ was accepted as statistically significant.

RESULTS

Fifty-two (49.5%) of the children with ALL were male, and 53 (50.5%) were female with a mean age of 8.57 ± 3.95 years. The median age at diagnosis was 4.91 years (0.66-16.81 years). In the control group, 50 (49%) were male, 52 (51%) female, and the median age was 6.01 years (0.88-13.31 years). There was no significant difference in terms of age and gender between the groups (p=0.597; p=0.942).The median age of mothers at birth in the study group was 25years (18-38 years), and the mean age of fathers was 29 years (21-45 years). In the control group, the median age of mothers was 24 years (18-38 years), and the median age of fathers was 28 years (20-43 years). There was no significant difference in terms of parental age between the groups (maternal age, p=0.513; paternal age, p=0.332). In 23.8% of the cases (n=25), there was consanguinity between the parents. This ratio was 16.7% (n=17) in the control group. Even though the percentage of consanguinity between the parents was higher in the study group, it was not statistically significant (p=0.201).In the study group, in 26.7% of mothers (n=28) there was a history of abortion. In 19% (n=20) of mothers, there was a history of 1 abortion and in 3.8% there was a history of 2 abortions. One mother had 7, 1 had 5, and 1 had 4 abortions. Three brothers of one patient had died for unknown reasons. The mean abortion ratio was 1.6 and the abortion rate of mothers in the control group was 18.6% (n=19). 13.7% of the mothers had a history of 1, 3.9% of the mothers had a history of 2 abortions. One mother had a history of 3 abortions. The mean abortion ratio was 1.3. Even though the recurrent abortion ratio was higher in the study group, there was no statistically significant difference (p=0.167).

In the study group, 86.7% (n=91) had a sibling, and 53.3% (n=56) had an elder sibling. In the control group 75.5% (n=77) had a sibling and 45.1% (n=46) had an elder sibling. There was no statistically significant difference between the groups in terms of having an elder sibling (p=0.236). In the study group, in 11.4% (n=12) of the patients, there was a history of leukemia in other members of the family. One patient's elder sister had leukemia. There was a history of leukemia in 4.9% (n=5) of the patients in the control group. In 39% (n=41) of the study group and 28.4% (n=29) of the control group, there was a history of other cancer types in the family. Although the percentage of leukemia and other cancer types in the family history was higher in the study group, it was not statistically significant (p=0.087; p=0.112).

In the study group, 86.7 % of the mothers had consumed the desired food. 94.3% of them consumed fresh fruits and vegetables and 83.8% consumed red meat. 70.5% drank tea during the pregnancy and only 8.6 % consumed fast food. In the control group, 90.2% of the mothers had consumed the desired food. Among them, 99% consumed fresh fruits and vegetables, and 88.2% consumed red meat. 73.5% drank tea during pregnancy and 13.7% consumed fast food. There was no statistically significant difference in terms

of nutritional habits between the groups (p=0.428; p=0.06; p=0.359; p=0.625; p=0.238, respectively).Iron and vitamin supplement intake was significantly higher in the control group **(p=002; p=0.017)** (Table 1). There was no significant difference in terms of folic acid and fish oil supplement intake.

Table 1: Iron, folic acid, vitamin and fish oil supplement intake of mothers of children with ALL compared with the control group.

Maternal supplement intake during pregnancy	**Study group n (%)**		**Control group n (%)**	**Test value p**
Iron supplement intake	Yes	66 (62.8%)	84 (82.4%)	χ^2= **9.855**
	No	39 (37.1%)	18 (17.6%)	**p=0.002†**
Vitamin supplement intake	Yes	63 (60.0%)	77 (75.5%)	χ^2=**5.671**
	No	42 (40.0%)	25 (24.5%)	**p=0.017***
Folic acid supplement intake	Yes	5 (4.8%)	11 (10.8%)	χ^2=2.631
	No	100 (95.2%)	91 (89.2%)	p=0.105
Fish-oil supplement intake	Yes	1 (1%)	3 (2.9%)	χ^2=1.080
	No	104 (99%)	99 (97.1%)	p=0.364

χ^2:Chi square test *p<0.05 †p<0.01

When maternal X-ray exposure in the study group was questioned, 12.4% (n=13) had the anamnesis of having an X-ray before pregnancy (av. 2.07 times). In the control group, 18.6% (n=19) had anamnesis of having an X-ray before pregnancy (av. 1.78 times). None of the mothers had an X-ray or radiotherapy during pregnancy. There was no significant difference between the groups in terms of X-ray exposure (p= 0.214). In the study group, 5.7% (n=6) of the mothers had infection during pregnancy. Three of them had urinary tract infection (UTI), 1 typhoid fever, 1 bronchitis, and 1 had tooth abscess. This rate was 3.9% (n=4) in the control group. Two of

them had UTI, 1 had upper respiratory tract infection + UTI and 1 had HBs Ag positivity. There was no significant difference between the groups in terms of history of infection during pregnancy (p=0.548).In the study group, 8.6% (n=9) of the mothers were under follow-up for gestational hypertension, 2.9% (n=3) had the threat of miscarriage, 1 had undergone treatment for cervical nodules, 1 had gestational diabetes, 1 had polyhydramnios, and 1 had insufficient weight gain. One mother's elder daughter was diagnosed with ALL when the mother was in the 6^{th} week of pregnancy. In the control group, 5 mothers (4.9%) had gestational hypertension, 1 had gestational diabetes and 1 had food poisoning (overall 4%). There was no significant difference between the groups in terms of gestational hypertension and other diseases (p=0.293; p=0.058).

Only 12.4% (n=13) of the mothers in the study group had used hair dyes before pregnancy and three of them used hair dye during pregnancy. In the control group, 10.8% had used hair dye before pregnancy and none had used hair dye during pregnancy. There was no significant difference between the groups (p=0.720).In the study group, 18.3% (n=19) of the mothers were smokers. Only 1 of them had smoked over 1 pack/day. The average time of smoking was 11.15 ± 6.44 years (2-24 years). In the control group, 17.6% (n=18) of mothers were smokers. 90% smoked less than 1 pack/day and 10% smoked 1-2 packs/day. The average time of smoking was 11.22 ± 5.57 years. There was no significant difference in terms of smoking between the groups (p=0.907). There was no history of alcohol or drug abuse among mothers in both groups.80% (n=84) of the patients had charcoal heaters in their houses. This rate was 74.5% (n=76) in the control group. There was no significant difference between the groups (p=0.346).

Among fathers in the study group, 59% (n=62) were smokers (Table 2). The average duration of smoking among fathers was 17 ± 7.04 years. In the control group, the average rate of smoking among fathers was 55.9% (n=57). The average duration of smoking was 15.35 ± 5.9 years. When overall smoking ratios were compared, there was no statistically significant difference between the groups (p=0.211). However, the rate of smoking ≥1 pack/day was significantly higher in the study group **(p=0.041).** When smoking duration was also evaluated together with smoking habits, smoking ≥20 pack/years was significantly higher in the study group **(p=0.048)**(Table 2). According to the anamnesis taken from the mothers, 11.4% (n= 12) of the fathers were regularly consuming alcohol (Table 2). The average duration was 15.25 years. The rate of alcohol consumption in the study group was significantly higher **(p=0.011)** (Table 2). There was no history of drug abuse among fathers in both groups.

Table 2: Comparison of paternal smoking habits and alcohol consumption.

		Study group n (%)	**Control group n (%)**	**Test value p**
	None	43 (41.0%)	45 (44.1%)	
Paternal	**< 1pack/day**	32 (30.5%)	40 (39.2%)	χ^2=4.510
smoking habits	**≥ 1pack/day**	26 (24.8%)	15 (14.7%)	p= 0.211
	≥ 2packs/day	4 (3.8%)	2 (2%)	
	≥1pack/day	30(28.6%)	17 (16.7%)	χ^2**=4.178** **p= 0.041***
	≥20packs/year	32(30.5%)	19 (18.6%)	χ^2**=3,912** **p=0.048***
Paternal alcohol	**None**	93 (88.6%)	100 (98.0%)	
consumption	**Once/ week**	6 (5.7%)	2 (2.0%)	**p=0.011****
	Everyday	6 (5.7%)	--	

*:Chi square test p<0.05 **:Fisher-Freeman-Halton test

In the study group 21.9% (n=23) of the fathers had an X-ray before conception. One of the fathers had undergone radiotherapy for 4 years before conception. This ratio was 18.6% (n=19) in the control group. There was no significant difference between the groups in terms of X-ray exposure (p=0.558).

DISCUSSION

The etiology of childhood leukemia is assumed to be multifactorial. According to one hypothesis, the primary causes are during the prenatal period, and natal and postnatal factors turn this susceptibility to disease. This means that leukemia occurs as a result of gene-environment interactions [5].Therefore, it is important to determine the chemical, physical, or biological factors that cause unrepairable damage in DNA

and lead to chromosomal breaks. The hypothesis that 'as maternal age increases, accumulation of chromosomal aberrations and mutations during maturation of germ cells may cause an increment in the risk of leukemia' has been tested in many studies. In a study from Sweden, it was reported that maternal age > 35 years increased the risk of leukemia by 50% [6]. In another study of 1842 children with ALL, maternal age <20 years was found to be related to increased risk. Only pre –B ALL was found to be related to both young and old maternal age[7]. There are also studies on increased paternal age and leukemia [8]. However, we did not find any relation between parental age and leukemia risk in our study.

Considering that genetic factors may have a role in the etiology of leukemia, it is assumed that consanguinity between parents may increase the risk of leukemia. In a study by Benner et al, the consanguinity rate of parents of children with ALL was found to be significantly higher when compared to the normal population [9]. In another study by Hoffman et al, the ALL rate was significantly higher among families in which consanguineous marriages were frequent and the term "familial leukemia" was applied[10].In our study, even though the rate of consanguinity was higher in the study group, it was not statistically significant.

In a study by Perrillat et al of 242 children with ALL, the incidence of hematologic malignancies and solid neoplasms in families of children with ALL was found to be significantly higher when compared to the normal population [11]. In our study, even though the incidence of leukemia and other solid neoplasms in families of children with ALL was higher in the study group, this was not statistically significant. This may be due to the relatively small sample size. One of our patient's elder sisters was also treated for leukemia and this supports the hypothesis that genetic factors may play a role. There are studies on the relationship between the abortion history of the mother and leukemia occurring at a young age. In a case-controlled study of 1753 cases with acute leukemia, abortion history in the mother was significantly related to leukemia, especially in children diagnosed before 2 years of age. Every previous aborted fetus increased the risk 5-fold. It is reported that leukemia diagnosed at an early age may be related to genetic abnormalities and chronic environmental exposures [12]. In a study by Dorak et alof 732 children with cancer (225 were ALL), the abortion history was higher in the study group, but it was only statistically significant for males [13]. In our study, the abortion rate was higher in the study group, but this was not statistically significant. In the study group, one mother had 4, one had 5 and one had 7 abortions but in the control group no mother had more than 3.

According to one hypothesis, congenital leukemia may occur as a result of exposure of mothers to topoisomerase II inhibitors in drugs or food, causing chromosomal breaks. DNA topoisomerase II inhibitors are found in certain vegetables and fruits, in soya, coffee, tea, cacao, pesticides, solvents, and drugs. In a study by

Spector et al, it is reported that there was a decrease in the risk of congenital leukemia in children of mothers consuming fresh fruits and vegetables, but an increase in the risk when mothers consumed some specific foods containing DNA topoisomerase II inhibitors [14]. In our study, in both groups, the nutritional habits of the mothers were consistent with the normal population. Most consumed fresh fruits, vegetables, and tea, and few consumed coffee, soy products and fast food. There was no significant difference between the groups in terms of dietary habits. In a study of 1842 children with ALL, it was reported that vitamin and iron supplement intake of mothers during pregnancy decreased the risk of ALL in the child [15]. In another study, iron was also reported as a protector against leukemia [16]. In our study, vitamin and iron supplement intake was significantly lower in the study group (p:0.017; p:0.002).

Ionizing radiation is a well-known factor in cancer formation and there are many studies on parental exposure to radiation and leukemia. In a study of 1842 children with ALL, no relationship was found between parental exposure to radiation before pregnancy, intrauterine and postnatal exposure to radiation, and leukemia [17]. Even though studies on parents working in power plants have reported that radiation may increase the risk to some extent, there is no powerful evidence [18-19]. In our study, none of the mothers had exposure to X-rays during pregnancy. There was also no significant difference between the groups in terms of parental exposure to radiation before conception.

Ras proto-oncogene mutations are associated with many cancer types. In a case-controlled study of 837 patients with ALL, parental intake of drugs like LSD, amphetamine, diet pills, and exposure to solvents, plastic, oil, and coal products are reported to be related to ras mutations in leukemic cells of children[20]. In another study of 1138 children with ALL, maternal exposure to dye and varnish during pregnancy was associated with an increased risk of leukemia [21]. In our study group, no parents had used amphetamines, diet pills or LSD; one mother reported that she had used bleach very often in cleaning during pregnancy. One mother was working in a rubber factory and one in a leather factory.

There are studies reporting that maternal infections during pregnancy like influenza, pneumonia, and lower genital region infections are associated with an increased risk of leukemia [16,22]. In our study, no significant relation was found in terms of maternal infections and diseases during pregnancy and the risk of leukemia.

Cigarette smoke contains over 60 carcinogenic substances for animals and humans and is associated with many cancer types in adults including myeloid leukemia [23]. It is reported that chromosomal abnormalities are more common in children of smoking mothers [24]. Smoking also causes aneuploidy in sperm cells of humans by increasing oxidative DNA damage [25]. In a meta-analysis from China, it was

reported that paternal smoking was significantly related to childhood ALL [26]. In another study from England of 1630 cases with leukemia and 6987 controls, the risk was found to be increased, but it was not statistically significant [27]. There are other studies relating smoking and ALL and AML risk [28]. In our study, the rate of smoking was low among mothers both before and during pregnancy and there was no significant difference between the groups. When fathers were compared, the rate of smoking more than 1 pack/day and more than 20 packs/year was significantly higher in the study group. In a systematic review and meta-analysis by Karalexi MA et al, a significant dose-response association of maternal alcohol consumption during index pregnancy and AML risk was reported [29]. In a study by Orsi et al, alcohol consumption during pregnancy was found to be non-significantly related to AML, but not ALL [30]. Although paternal preconceptional alcohol consumption was associated with brain tumors in the offspring, no significant relation was found for ALL [31]. In our study, none of the mothers used alcohol either before or during pregnancy, however routine alcohol consumption among fathers was significantly higher in the study group.

Limitations

This study was retrospective and was based on anamnestic data. Therefore, no measurements could be done in terms of vitamin, iron, and folate deficiency. In addition, the sample size was notlarge enough to reach significance for some of the parameters. More extensive studies based on measurements should be carried out.

CONCLUSION

Leukemia has a multifactorial etiology and occurs as a result of gene-environment interrelations. According to our study, paternal cigarette smoking and alcohol consumption before conception were significantly related to an increased risk of leukemia in children. Maternal iron and vitamin deficiency are also likely to be associated with an increased risk. Consanguinity between parents, the abortion rate of mothers and the presence of leukemia and other cancer types in the family were higher in the study group, but no significant difference was found.

Conflicts of interest: The authors have nothing to disclose.

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