Original Article

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Investigation of the Relationship between Breastfeeding and Leukemia in Children

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Abstract

Background: Leukemia is the most common childhood cancer. This cancer, considering its unknown cause(s), is considered as one of the most important health problems amongst children worldwide. The present study was aimed to determine the relationship between breastfeeding and leukemia in Sistan and Baluchestan province, southeast of Iran.

Materials and methods: This case-control study was implemented on 120 children between 11 months and 17 years old with leukemia as the case group, and 240 children hospitalized due to other non-leukemia-related diseases in the study area (the mean age of children in both groups was about 8 years). The children were categorized according to age and gender. To determine the relationship between variables and the risk of leukemia morbidity, the odds ratio (OR) with 95% confidence intervals was estimated through conditional logistic regression using Chi-square and Fisher's exact test and utilizing SPSS-16.

Results: Out the 120 children with leukemia, about 60% were male and the age group of 5-9 years old was the most frequent age group (45%). The results of the study showed that breastfeeding was significantly associated with leukemia in children, P-value = 0.02(OR = 0.24, CI: 95%, 0.71-0.71).

Conclusion: Regarding the protective role of breastfeeding, the necessary measures for training to maintain and promote breastfeeding and its continuity up to 2 years are required to be taken.

Keywords: Breastfeeding, Children, Leukemia

Introduction

Cancer is a kind of disease, characterized by abnormal cell deformity and loss of cell differentiation (1). The disease, with an annual incidence of 14 million new cases and about 8 million mortalities, is a global problem being responsible for 13% of the world's deaths (2). Cancer is considered as a disabling disease and one of the main causes of children mortality in developing and developed countries (3). The high incidence of cancer is one of the major problems in developing countries among children, which may be due to limited funding for developing a constant nationally established program for early diagnosis and management of the patients in these countries (4). This disease is the second cause of death in children younger than 14 years of age in Iran as well (5). Cancer has different types and leukemia is the most common one during childhood, accounting for almost 35.8% of all types of childhood cancers (6).

The etiology of leukemia in children has remained largely unclear (6). The epidemiologic studies have examined several risk factors, including environmental factors, genetics and infectious agents (ionizing and non-ionizing beams, chemicals, alcohol, tobacco, and narcotics), and other factors such as maternal fertility history, maternal age in pregnancy, birth indices, neonatal

jaundice and birth order, but controversial results have been published (7-9). Breastfeeding may be one of the possible causes of leukemia. Although lactation is considered as a known agent in preventing infections in infancy, its role in preventing leukemia is unknown (10). Some studies have shown the preventive role of breastfeeding in promoting leukemia in children (11), but some other studies have contradicted this finding (12, 13).

Therefore, due to the inconsistency in the results of studies and the importance of preventing leukemia in promoting health status and reducing the treatment expenses, and given the important role of breastfeeding in preventing many diseases, this study was conducted on children admitted to Imam Ali Hospital in Zahedan, Iran aiming at determining the relationship between breastfeeding and leukemia in children.

Materials and Methods

This case-control study was conducted on 120 children with leukemia as the case group and twice as many as this number as the control group between August 2016 and June 2017 in Sistan and Baluchestan province. Considering the facts that the number of children with leukemia is limited in Sistan and Baluchestan province and that the only reference hospital in this province which provides the patients with all health services, including chemotherapy, is Imam Ali Hospital in Zahedan, 120 children, who were diagnosed at the age of 0 to 17 years and whose diseases were confirmed by bone marrow aspiration and flow cytometry, were selected among all the children with leukemia referred to Imam Ali Hospital in Zahedan from 2011 to 2017 by easy accessible method as the case group; the control group consisted of 240 children aged 0 to 17 when referred to the pediatric ward of Imam Ali Hospital in Zahedan and 8 other provincial hospitals, with different types of diseases, except for blood related diseases, Immunologic ones, Solid tumors, Leukemia, Lymphoma, and heart diseases (Figure 1).

It should be noted that the controls were matched in groups with the cases based on age and sex (±2 years). Since hospitalized children were used as the control group, there was a probability of Burkson's bias. This type of bias was prevented largely in this study given that nearly all children with leukemia who were referred to Imam Ali Hospital were put into the case group and children whose illnesses were not related to the considered exposures were put into the control group.

The data were collected through reviewing medical records and a validated researcher-made questionnaire, including demographic characteristics, child-related and child's mother-related questions, and medical information checklist through interviewing with one of the parents, preferably the mother.

Statistical analysis

For analyzing the data, the Chi-square test was used when there was a univariate and when Chi-square test assumptions were not available, Fisher's exact test was utilized; in multivariate tests, conditional logistic regression was used.

Odds ratio (OR) with 95% confidence intervals was used to show the relationship between the independent variables and the outcome (leukemia). Because of the large number of variables compared to the sample size, the relationship between single independent and dependent variables was assessed and then variables with P-value < 0.25 were entered into the model by Forward: Conditional method. The data was analyzed using SPSS-16 with a significant level of ≤ 0.05.

Results

In this study, 120 children with leukemia were selected as the case group. These children were classified into 5 groups at the age of diagnosis of leukemia morbidity. The most frequent age group

was 2-4 years old with 40%, and the lowest frequency was related to the age groups of 15-17 years old with 5%. The age groups of 5-9 years old with 32.5%, 10-14 years old with 13.3%, and under 2 years old with 9.2% were in between.

Moreover, 92.5% of morbidities were due to acute lymphoblastic leukemia (ALL) and the rest were acute and chronic (AML and CML) types. Furthermore, 74.2% of patients were Baluch, 22.5% were from Sistan (Sistanis) and 3.3% of patients were from other ethnicities and considering the gender, about 60% of the case group were male patients. In the age group of less than 5 years old, 69.2% of the cases and 66.7% of the controls, in the age group of 5-9 years old, 55.6% of the cases and 54.5% of the controls, in the age group of 10-14 years old, 52% of the cases and 50% of the controls and in the age group of 15-18 years old, 53.3% of the cases and 54.2% of the controls were boys. Table I shows the frequency distribution of demographic variables in the subjects under study. As it is shown, the monthly income variable ($p < 0.001$) and residence place ($p = 0.03$) are related to the incidence of leukemia in children, so that the risk of developing leukemia in children with low income families (Family monthly income ≤ 250 $) compared to children living in high-income families (Family monthly income ≥ 250 $) was 2.33 higher, and the chance of promoting this cancer in children living in rural areas (Population < 5000 Person (14)) was 1.64 times higher than children living in urban areas (Population > 5000 Person). Table II is related to other probable variables related to leukemia in children using univariate analysis, and tables III, IV and Figure 2 show the chance of developing leukemia in terms of the overall duration of breastfeeding and the duration of exclusive breastfeeding of the child, respectively. In the present study, multiple logistic regression analysis was used to investigate the relationship between independent variables together and control probable and potential confounders and calculate adjusted OR.

The results are shown in Table V. According to this table and regarding the factors associated with leukemia, only breastfeeding variables, history of childhood allergies, and monthly household income level were identified as predictors of children leukemia.

Table I: Comparing the demographic characteristics of case and control groups in univariate analysis

Demographic variables		Case n (%)	Control n (%)	p-value	OR(95% CI) Univariate
Child sex	Male	69(57.5)	135(56.2)	0.821	1.05(0.67-1.63)
	Female	51(42.5)	105(43.8)		Ref
	Total	120(100.0)	240(100.0)		
Age at the beginning of the study (year)	0-4	26(21.7)	54(22.5)	0.913	0.77(0.34-1.70)
	5-9	54(45.0)	112(46.7)		0.77(37-1.58)
	10-14	25(20.8)	50(20.8)		0.80(0.35-1.78)
	15-17	15(12.5)	24(10.0)		Ref
Birth Order	1-2	62(51.7)	118(49.2)	0.655	1.10(0.71-1.71)
	≥3	58(48.3)	122(50.8)		Ref
Residence Place	Village	53(44.2)	78(32.5)	0.03	1.64(1. 04-2.57)
	City	67(55.8)	162(67.5)		Ref
Family monthly income($/Month)	0-250	91(75.8)	124(51.7)	<0.001	2.93(1.80-4.78)
	≥250	29(24.2)	116(48.3)		Ref

Table II: Comparison of variables related to leukemia among case and control groups in univariate analysis

variables related to leukemia		Case n (%)	Control n (%)	p-value	OR(95% CI) Univariate
Maternal age in pregnancy	35<	98(81.7)	208(86.7)	0.21	Ref
	≥35	22(18.3)	32(13.3)		1.45(0.80-2.64)
Neonatal jaundice	Yes	45(38.1)	84(35.1)	0.58	1.13(0.72-1.79)
	No	73(61.9)	155(64.9)		Ref
Allergy	Yes	11(9.2)	40(16.7)	0.04	0.50(0.24-1.02)
	No	109(90.8)	200(83.3)		Ref
Breastfeeding	Yes	113(94.2)	235(97.9)	0.06	0.34(0.10-1.10)
	No	7(5.8)	5(2.1)		Ref
Breastfeeding at Birth	Yes	111(93.3)	233(97.1)	0.09	0.41(0.14-1.17)
	No	8(6.7)	7(2.9)		Ref
Exclusive Breastfeeding	Yes	107(91.5)	224(93.3)	0.52	0.76(0.33-1.74)
	No	10(8.5)	16(6.7)		Ref

Table III: The odds ratio of leukemia morbidity according to the duration of breastfeeding in univariate analysis

Duration of breastfeeding (Month)	Case n (%)	Control n (%)	p-value	OR(95% CI) Univariate
1<	7(6.4)	6(2.5)	0.07	2.87(0.91-8.96)
1-6	12(11.0)	32(13.3)	0.83	0.92(0.44-1.93)
7-12	12(11.0)	23(9.6)	0.52	1.28(0.59-2.77)
13-19	20(18.3)	43(17.9)	0.67	1.14(0.61-2.13)
20-24	50(45.9)	123(51.2)	-	Ref
>24	8(7.3)	13(5.4)	0.38	1.51(0.59-3.87)
Total	109(100.0)	240(100.0)		

Table IV: The odds ratio of leukemia morbidity according to the duration of exclusive breastfeeding in univariate analysis

Duration of **exclusive** breastfeeding (Month)	Case n (%)	Control n (%)	p-value	OR(95% CI) Univariate
0	9(7.8)	16(6.7)	0.50	1.34(0.56-3.18)
<1	9(7.8)	16(6.7)	0.50	1.34(0.56-3.18)
1-3	18(15.7)	34(14.2)	0.47	1.26(0.66-2.38)
4-6	70(60.9)	167(69.6)	-	Ref
≥7	9(7.8)	7(2.9)	0.03	3.06(1.09-8.56)

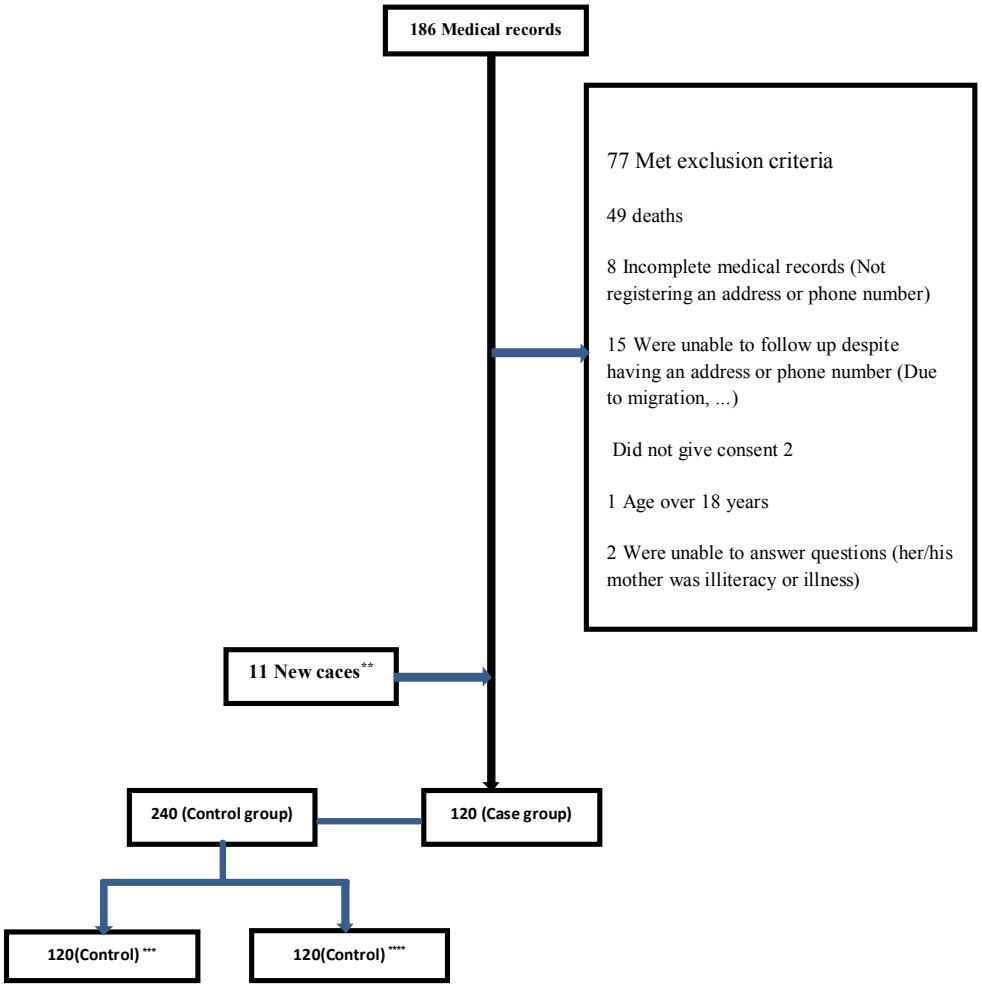

Figure 1. Selection of case and control groups. *There were 186 medical records for the diagnosis of childhood leukemia in Imam Ali Hospital in Zahedan when this study was started. ** Cases were detected during the study (August 2016 - June 2017). ***120 patients from only Imam Ali Hospital in Zahedan. ****120 patients from the rest of hospitals of all over the province (including 8 hospitals).

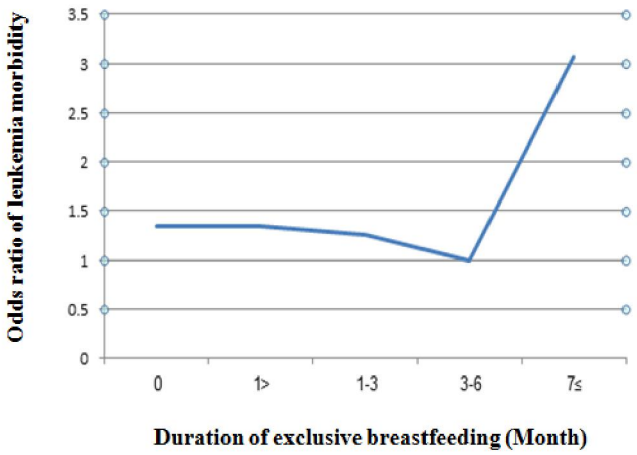

Figure 2. The odds ratio of leukemia morbidity according to the duration of exclusive breastfeeding

Discussion

Based on the findings of this study, breastfeeding, the positive history of allergies and family income level were identified as predictors of children leukemia. The "delayed infection" hypothesis suggested by Greaves, states that "the incidence of common infections and exposure to indirect markers and exposure to infection in early postnatal years may play a protective role against ALL, especially the subgroup of c-ALL". At the same time, limited exposure to infection during this period of life increases the risk of disease by increasing the likelihood of abnormal immune responses to infections transmitted from the environment (15, 16). Therefore, in this study, the effect of infections (neonatal jaundice and childhood allergies) and infection exposure indicators, including birth order and duration of breastfeeding, on leukemia were investigated in children.

The first predictor of childhood leukemia was breastfeeding. Breast milk reduced the chances of child leukemia morbidity. It has been long time determined that breast milk contains many beneficial biological agents, such as antimicrobial, anti-inflammatory and immunization agents, so breastfeeding is considered to be a known agent in preventing infections in the neonatal period, but its role in prevention of acute leukemia is unknown (17). Studies have shown paradoxical results about exclusive breastfeeding, the duration of breastfeeding, and its impact on leukemia morbidity in children (10). Some of these studies have shown that there is no relationship between breastfeeding and the risk of developing leukemia (12, 13) but some studies have reported significant association of the variable with leukemia in children (10, 11).

Moreover, the results of this study showed that as the duration of breastfeeding increases by up to 24 months (after birth), the chance of leukemia morbidity decreases, but if breastfeeding continues after 24 months, this probability increases. This finding also applied to the exclusive breastfeeding of a child; if children are exclusively breastfed for the first six months of their lives, their chance of developing leukemia decreases, but if exclusive breastfeeding continues for more than 6 months, the chance of leukemia morbidity increases in the children. According to the WHO, as breast milk is the best source of food for children, during the first six months of life a child should be exclusively breastfed. However after 6 months of age, the child would also need other sources of nutrients to cover the nutritional needs, especially the iron, because exclusive breastfeeding for more than 6 months results in anemia and malnutrition which may be associated with an increased risk of developing leukemia in the child (18).

Allergies are of other predictors of leukemia which cause significant reduction in the risk of leukemia morbidity in children. Allergy is a hypersensitivity reaction of individuals to foreign substances by immunological mechanisms (allergies to food and medicine, skin allergies, seasonal allergies, asthma, etc.) (19). Allergy data were collected through a review of the pediatric medical records. Most of the studies (such as the meta-analysis of the other studies during the years 1952 to 2009) reported an inverse relationship between allergies and leukemia (20). In contrast, another study in this field showed that there was a positive association between hives and asthma and leukemia in children. This finding suggested that allergies and leukemia may have similar biological mechanisms, for example, allergic reactions had a positive effect on the destruction of neo-plastic cells and lymphoid cells (21).

The other examined variable in this field was the birth order. Children with higher birth orders were exposed to infectious agents at an earlier age than those with

lower birth orders (22). Therefore, the birth order was considered as an indicator of the rate of infection acquired during infancy (7). However, in this study, there was no significant relationship between birth order and the risk of childhood leukemia.

Other results of this study showed the predictive role of low household income in children leukemia morbidity. Poverty and low socioeconomic status along with low birth weight, malnutrition, mental health problems, and higher exposure of the child to unfavorable environmental factors such as air pollution, and use of illegal drugs and tobacco, etc. affected the health of the individual especially in early life, and even these factors themselves may act as a risk factor for childhood leukemia (23, 24).

The results of the studies by Raaschou - Nielsen O, R. Del Risco Kollerud and Pan IJ also showed that low household income increased the probability of leukemia morbidity in children (23, 25, 26). However, the study by Borugian MJ et al. did not match these findings. The higher incidence of leukemia in higher income families may be due to better and earlier diagnosis of leukemia (27).

The limitation of this study was related to small sample size due to the rarity of this cancer, so more extensive and multi-center studies are suggested simultaneously.

Conclusion

Considering the protective role of breastfeeding in children leukemia, necessary measures are needed to be taken for training to preserve and promote breastfeeding and maintaining it until the age of 2. Efforts for improving health status by promoting hygiene, nutrition, and other issues related to the economic situation and the income level of familie, are also essential to reduce the probability of leukemia morbidity in children.

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Conflict of interest

The author(s) declare that they have no conflict of interests

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