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Original Article

Association of Parental, Child, and Environmental Factors with the Occurrence of Childhood Leukemia in Upper Egypt

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Abstract

Background: Leukemia is the most common malignant tumor in children, responsible for nearly one-third of all childhood cancers. However, the exact risk factors of childhood leukemia are unknown.

Objective(s): The aim of this study was to identify risk factors of leukemia among Upper Egyptian children.

Methods: We conducted a case-control study in 2019. Cases included 170 children aged ≤18 years with a confirmed leukemia diagnosis at the South Egypt Cancer Institute. The controls included 170 children matched for age and sex, free from hematological problems, and diagnosed with a mild illness in a pediatric outpatient clinic. Data were collected from children's parents using an interview questionnaire.

Results: The significant predictors for childhood leukemia were abnormal birth weight (<2.5 Kg and >4 kg) (OR = 2.89, 95% CI: 1.46–5.71) and childhood exposure to previous diagnostic radiation (OR = 3.95, 95% CI: 1.37–11.31). The risk increased if the father's occupation was farming (OR = 2.14, 95% CI: 1.04–4.40), household monthly income <2000 LE (OR = 2.22, 95% CI: 1.08–4.56), and a family history of leukemia (OR = 4.37, 95% CI: 1.13–16.94) and other cancer types (OR = 4.71, 95% CI: 2.07–10.72). Childhood exposure to agriculture (OR 5.36, 95% CI 2.87–10.02) and household pesticides (OR = 2.00, 95% CI: 1.12–3.57) had a significantly high odds ratio for developing leukemia.

Conclusion: Abnormal birth weight, father's occupation is farming, exposure to diagnostic radiation and pesticides, family history of leukemia or other cancers, and low income are risk factors for leukemia in Egyptian children.

Keywords: Egypt, childhood leukemia, risk factors

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INTRODUCTION

Globally, childhood cancer is considered the ninth leading cause of childhood disease burden.[1] Leukemia is the most common type of childhood cancer, representing nearly one-third of all pediatric cancers, and acute lymphocytic leukemia (ALL) is the most common subtype of leukemia.[2, 3] In Egypt, childhood leukemia represents 35.6% of all incidents of childhood cancer.[4] ALL is the most common subtype. Most of the affected children are four years or younger.[5]

Early diagnosis of cancer is a crucial priority in health care. Many pediatric leukemia symptoms are similar to symptoms caused by non-leukemia mild diseases. This lack of specific symptoms complicates the diagnostic challenge faced by front-line clinicians, highlighting the need for recognizing the possible signs and symptoms of this disease.[6, 7]

Childhood leukemia's etiology remains largely unclear. Many epidemiological studies associate certain genetic, childbirth, parental, and environmental factors with leukemia risk. Leukemia is assumed to develop in response to multi-factorial interactions between genetic and environmental factors.[8] A positive family history of cancer may predispose children to the development of leukemia.[9] A meta-analysis and review reported subtype-specific leukemia associations with both low and high birth weights.[10] Maternal history of fetal loss and birth by cesarean section were also associated with an elevated risk of childhood leukemia.[11, 12] The oldest or youngest

extremes of parental age reportedly played a role in the epidemiology of specific leukemia subtypes.[13]

Regarding environmental factors, American and Canadian case-control studies associated exposure to postnatal diagnostic radiation with an increased childhood leukemia risk.[14, 15] Parental smoking or passive smoke exposure of mother or child also posed a potential risk for child leukemia.[16, 17] Growing evidence revealed positive associations between childhood leukemia and childhood exposure to household or agriculture pesticides.[18-21]

Published Egyptian studies on risk factors of childhood leukemia are limited, [16] and no previous study explored these risk factors in Upper Egyptian children. This study aimed to identify potential child, parental, and environmental factors that contribute to leukemia risk among Egyptian children in Assiut Governorate.

METHODS

Study design and setting and sampling

We conducted a case-control study in Assiut Governorate in Upper Egypt. The capital city is Assiut, about 375 km south of Cairo. In 2018, the total population of the Assiut Governorate was approximately 4,527,565**.**

The sample size was calculated for the case-control design using the Open Epi program, version 3.01, updated in 2013, based on an odds ratio of 2.01 **[22]**, a confidence interval of 95%, a power of 80%, and control:case ratio of 1:1. The calculated sample size was 156 cases and 156 controls. The sample size was rounded to 170 cases and 170 matched controls.

Inclusion criteria for the cases were leukemic children aged ≤18 years old and recently diagnosed (within one year) at the South Egypt Cancer Institute (SECI) at Assiut University. The leukemia diagnosis was based on a hematological and histopathological examination conducted at SECI. The control group included children matched with cases by age (within a 6-month range) and gender. The control subjects were children diagnosed with mild illness and free from hematological problems (based on complete blood count examination). We recruited the controls from children attending the general outpatient clinic of the Children's University Hospital at Assiut University.

Data collection

Data collection was carried out from February 2017 to March 2019. We collected data for both cases and controls using a semi-structured interview questionnaire completed by the children's mothers. The type of leukemia was obtained from patient sheets in the pediatric unit in SECI. The following data about both controls and cases were collected from the questionnaires:

- Personal and birth characteristics and medical history of children, including age, gender, residence, birth order, weight at birth, breastfeeding, daycare attendance, history of hospital admission before the current illness, history of prior tumor occurrence, previous exposure to diagnostic radiation, and mode of the child delivery.[16, 17, 23-28] We assessed exposure to diagnostic radiation among cases before illness and among controls up to the time of the questionnaire.
- Parental and family factors, including father's and mother's ages at the time of childbirth, parental consanguinity, parent educational level/occupation, family income in Egyptian pounds (LE), and positive family history of cancer and/or leukemia.[16, 23, 27, 29]
- Maternal histories of abortion and radiation exposure before this pregnancy.**[16, 30, 31]**
- Environmental factors, including childhood exposure to paternal smoking and/or other smokers at home **[17]**, childhood exposure to agriculture or household pesticides **[18, 20]**, residence near high voltage power transmission lines ≤200 meters, residence near main roads ≤100 meters, residence near petrol stations ≤one kilometer, and factory construction near the residence area.**[29, 32]**
- For leukemic children, as asked the mothers about the first presented clinical symptom that led them to seek health care.

Statistical analysis

We analyzed the data using SPSS version 25. Chi-square tests (X^2) compared the distribution of frequencies among different groups. Fisher's exact test determined expected counts <5. Based on testing data normality for quantitative variables, Mann–Whitney U test was applied. Multivariate logistic regression analysis identified childhood leukemia predictors. The presence of leukemia (yes/no) was considered the dependent variable. The significant variables resulting from the bivariate analysis were entered as explanatory variables in the multivariate regression model. Odds ratios were calculated to measure the association between the different risk factors and childhood leukemia at 95% confidence intervals. A p-value less than 0.05 was considered statistically significant.

Ethical considerations

The Assiut Medical Ethics Committee approved the study. Researchers complied with the International Guidelines for Research Ethics. The mothers of the recruited children provided written informed consent. Illiterate mothers provided informed consent in the presence of a witness. The study aim was explained individually to each mother before filling out the questionnaire. We preserved the anonymity and confidentiality of all obtained information. The authors have no conflict of interest to declare.

RESULTS

Among leukemic children (n = 170) included in the study, the most common leukemia subtype was ALL (81.8%), followed by acute myeloid leukemia (AML) (17%);

chronic myeloid leukemia represented 1.2% of the studied cases, as illustrated in Figure 1. The first reported complaints of leukemic illness were recurrent fevers (74.1%), joint pain (28.2%), hematological problems (24%), and abdominal enlargement/pain (12.9%), as shown in Figure 2.

Table 1 lists the personal, birth and medical histories of both cases and controls included in the study. Among the cases, nearly 63% of childhood leukemia cases were males, and more than one-third of cases (37.6%) were 5 years or younger. Childhood leukemia was significantly associated with rural residence, abnormal birth weight, and previous exposure of the child to diagnostic radiation (p-value ≤ 0.001). However, leukemia was not significantly associated with birth order, delivery mode, breastfeeding, daycare attendance, or childhood history of other cancers.

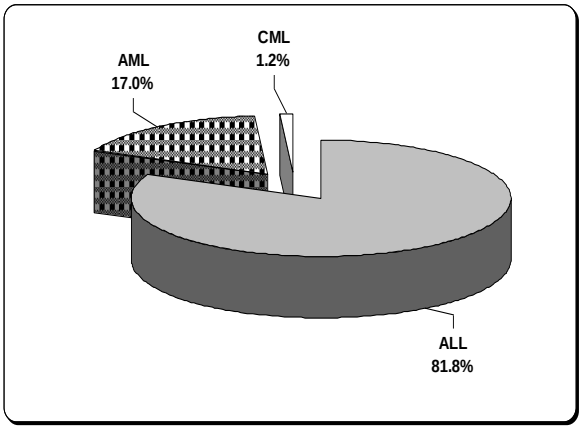

Figure 1: Distribution of leukemic cases according to subtype at the South Egypt Cancer Institute in Assiut Governorate (2017–2019)

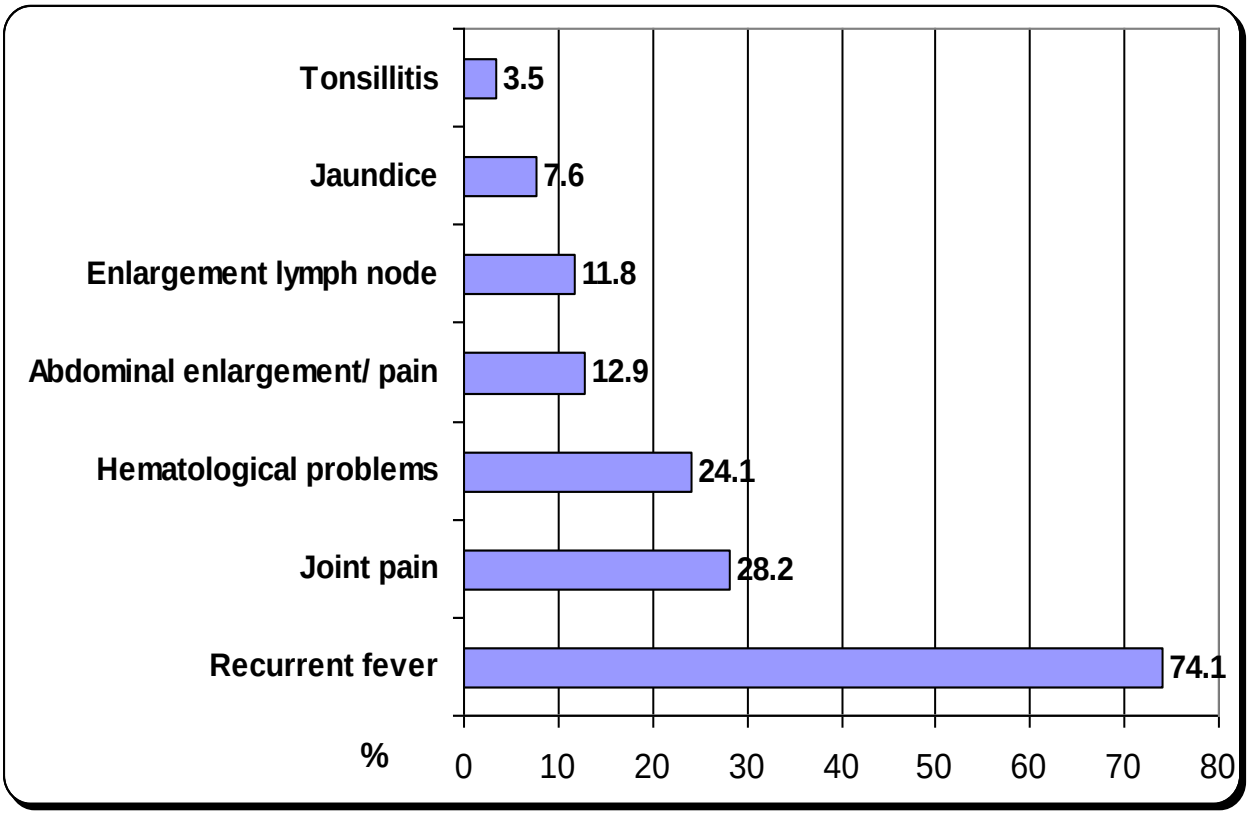

Figure 2: The first complaints leading to seeking health care by leukemic children at the South Egypt Cancer Institute in Assiut Governorate (2017–2019)

More than one response was allowed. Hematological problems were as follows: pallor, epistaxis, ecchymosis, and petechia.

Table 1: Personal, birth, and medical histories of studied children in Assiut Governorate (2017–2019)

	Cases (n = 170)		Controls (n = 170)		*p*-value
	No.	%	No.	%	
Age of child					
5 years or less	64	37.6	64	37.6	1.000 (matched variable)
6–10 years	50	29.4	50	29.4	
More than 10 years	56	32.9	56	32.9	
Gender					
Male	107	62.9	107	62.9	1.000 (matched variable)
Female	63	37.1	63	37.1	
Residence					
Rural	136	80.0	107	62.9	<0.001*
Urban	34	20.0	63	37.1	
Birth order					
1st	46	27.1	47	27.6	0.897
2nd	39	22.9	42	24.7	
3rd or more	85	50.0	81	47.6	
Mode of delivery					
Vaginal	120	70.6	109	64.1	0.203
Cesarean section	50	29.4	61	35.9	
Birth weight					
Less than 2500 g	24	14.1	22	12.9	<0.001*
2500–4000 g	124	72.9	147	86.5	
More than 4000 g	22	12.9	1	0.6	
Breastfeeding					
Yes	164	96.5	166	97.6	0.521
No	6	3.5	4	2.4	
Admission to hospital for another disease					
Yes	33	19.4	39	22.9	0.426
No	137	80.6	131	77.1	
History of other tumors in children					
Yes	5	2.9	0	0.0	0.061#
No	165	97.1	170	100.0	
Previous exposure to diagnostic radiation					
Exposed	23	13.5	6	3.5	0.001*
Not exposed	147	86.5	164	96.5	
Daycare attendance					
Yes	7	4.1	4	2.4	0.358
No	163	95.9	166	97.6	

p value for Chi-square test # Fisher's exact test

Table 2 presents parental criteria, family history of malignancy, and monthly household income among studied children. There were no significant differences between cases and controls regarding the ages of the mother and father at the time of childbirth, the father's educational level, parental consanguinity, the mother's work, and previous fetal loss before the index child. However, childhood leukemia was significantly associated with maternal education; 58.8% of case-patient mothers were illiterate than 41.2% of control patient mothers (*p*-value = 0.004).

Childhood leukemia was significantly associated with the mother's preconception exposure to radiation, the father working as a farmer, a family history of leukemia, and a family history of other types of malignancies (*p*-value < 0.05). The median monthly household income among leukemic cases (800 LE) was significantly lower than that among controls (1200 LE) (*p*-value < 0.001).

Table 3 shows the relationship between childhood leukemia and exposure to environmental factors. A significantly higher proportion of leukemic cases were exposed to paternal smoking and other home smokers than exposure among controls (*p*-value < 0.001). Moreover, a significantly higher proportion of leukemic cases were exposed to household and/or agricultural pesticides than exposure in controls (p-value < 0.05). Similarly, residence near power line/substations (≤200 M) was significantly associated with childhood leukemia (*p*-value = 0.002). On the other hand, there was no significant association between living near benzene stations, main roads, or factories and childhood leukemia (*p*-value > 0.05).

Table 2: Parental risk factors, family history of malignancy, and household monthly income among studied children in Assiut Governorate (2017–2019)

	Cases (n = 170)		Controls (n = 170)		*p*-value
	No.	%	No.	%	
Father age at the time of delivery (years)					
<30	75	44.1	70	41.2	0.120
30 -	71	41.8	86	50.6	
40+	24	14.1	14	8.2	
Father level of education					
Illiterate/ write and read	65	38.2	52	30.6	0.394
Primary / Preparatory school	24	14.1	33	19.4	
Secondary school	66	38.8	70	41.2	
University degree or more	15	8.8	15	8.8	
Occupation of father:					
Farmer	50	29.4	21	12.4	<0.001*
Not farmer	120	70.6	149	87.6	
Age of mother at delivery					
<25	90	52.9	89	52.4	0.699
25 -	39	22.9	47	27.6	
30 -	27	15.9	23	13.5	
35+	14	8.2	11	6.5	
Consanguinity					
Yes	91	53.5	88	51.8	0.745
No	79	46.5	82	48.2	
Mother education:					
Illiterate/ write and read	100	58.8	70	41.2	0.004*
Primary / Preparatory school	18	10.6	33	19.4	
Secondary	40	23.5	58	34.1	
University	12	7.1	9	5.3	
Mothers work					
Yes	16	9.4	13	7.6	0.560
No (Housewife)	154	90.6	157	92.4	
Maternal exposure to diagnostic radiation before this pregnancy (within one year)					
Yes	10	5.9	2	1.2	0.019*
No	160	94.1	168	98.8	
Mother history of fetal loss: (abortion)					
Yes	65	38.2	49	28.8	0.066
No	105	61.8	121	71.2	
Family history of leukemia					
Positive	13	7.6	4	2.4	0.025*
Negative	157	92.4	166	97.6	
Family history of other type of malignancy					
Yes	38	22.4	13	7.6	<0.001*
No	132	77.6	157	92.4	
Family monthly income (LE)					
Median (Inter Quartile Range)	800 (500–1200)		1200 (800–2000)		<0.001*≠

p value for Chi-square test
≠Mann–Whitney test
LE: Egyptian pound

Table 3: Exposure to environmental factors for childhood leukemia among studied children in Assiut Governorate (2017–2019)

	Cases (n = 170)		Controls (n = 170)		*p*-value
	No.	%	No.	%	
Paternal smoking					
Yes	109	64.1	91	53.5	0.047*
No	61	35.9	79	46.5	
Presence of other smokers at home					
Yes	51	30.0	8	4.7	<0.001*
No	119	70.0	162	95.3	
Child exposure to smoking at home: (paternal smoking and/or others smoker at home)					
Yes	123	72.4	94	55.3	0.001*
No	47	27.6	76	44.7	
Exposure to household pesticides					
Exposed	81	47.6	53	31.2	0.002*
Not exposed	89	52.4	117	68.8	
Family exposure to agricultural pesticides					
Exposed	122	71.8	51	30.0	<0.001*
Not exposed	48	28.2	119	70.0	
Child exposure to agricultural pesticides					
Exposed	107	62.9	33	19.4	<0.001*
Not exposed	63	37.1	137	80.6	
High power/ substation line near to house (<200 m)					
Yes	54	31.8	29	17.1	0.002*
No	116	68.2	141	82.9	
Benzene station near to house (< 1 km)					
Yes	12	7.1	11	6.5	0.829
No	158	92.9	159	93.5	
Main road (less than 100 M)					
Yes	52	30.6	69	40.6	0.054
No	118	69.4	101	59.4	
Nearby factory					
Yes	7	4.1	7	4.1	1.000
No	163	95.9	163	95.9	

p value for Chi-square test

Table 4 shows the multivariate logistic regression model for childhood leukemia risk factors. Predictors of childhood leukemia exposure to agricultural pesticides (OR = 5.369), household pesticides (OR = 2.009), or previously exposed to diagnostic radiation (OR = 3.951). Moreover, the significant predictors of childhood leukemia included farmer occupation of the father (OR = 2.148), having a family history of leukemia (OR = 4.379), having a family history of other malignancies (OR = 4.717), abnormal birth weight (OR = 2.891), and low monthly family income (less than 2000 LE) (OR = 2.227).

Table 4: Multiple logistic regression model of risk factors for childhood leukemia among the studied children in Assiut Governorate (2017–2019)

	Ref. group	OR (95% CI)	*p*-value
Residence (Rural)	Urban	1.139 (0.573–2.264)	0.710
Mother education (Did not receive education)	Educated	1.098 (0.593–2.031)	0.766
Diagnostic radiation before pregnancy (Yes)	No	3.862 (0.672–22.207)	0.130
Child exposure to smoking from father and other sources (Yes)	No	1.594(0.898–2.828)	0.111
Child previous exposure to diagnostic radiation (Yes)	No	3.951 (1.379–11.319)	0.010*
Occupation of father (Farmer)	Other jobs	2.148 (1.047–4.408)	0.037*
Family history of leukemia (Yes)	No	4.379 (1.132–16.948)	0.032*
Family history of other types of cancer (Yes)	No	4.717 (2.076–10.721)	<0.001*
Child exposure to household pesticides (Yes)	No	2.009 (1.128–3.579)	0.018*
Child exposure to agricultural pesticides (Yes)	No	5.369 (2.874–10.028)	<0.001*
Power line (< 200 M) (Yes)	No	1.700 (0.894–3.233)	0.105
Birth weight (< 2.5 kg and > 4 kg)	2.5–4.0 kg	2.891 (1.464–5.710)	0.002*
Monthly family income (< 2000 LE)	≥2000	2.227 (1.087–4.562)	0.029*

DISCUSSION

Childhood leukemia is the most common cancer among children. This case-control study's objective was to identify potential associations between child, family, and environmental factors and the risk of leukemia among Egyptian children ≤18 years. In the current study, the most common leukemia subtype was ALL, which represented about 82% of leukemia, and the most affected age group was children 5 years or younger. This is consistent with American, Brazilian, Libyan, and Canadian reports showing that ALL formed about three-fourths or more of leukemia cases in children and teens, and childhood leukemia was more common in children less than four years of age.[23, 32-34] Greaves explained the disease occurrence at an early age by in utero exposure to possible maternal and perinatal risk factors.[35]

The earliest presentations of childhood leukemia are nonspecific symptoms. These nonspecific symptoms may mislead general practitioners. The first complaints that led to seeking health care in this study were fever (74%), joint/ bone pain (28%), hematological problems such as pallor and petechia (24%), and abdominal enlargement (12.9%). The common symptoms and signs were similar to other studies but with different orders of frequency. A meta-analysis study showed that the five predominant signs and symptoms in more than 50% of children were hepatomegaly (64%), splenomegaly (61%), pallor (54%), fever (53%), and bruising (52%) [6]. A retrospective Iraqi study reported the initial presenting features of childhood leukemia were fever (81.8%), pallor (67.3%), hepatosplenomegaly (56.4%), lymphadenopathy (49.1%), bone pain (40%), anorexia (36.4%), and mucocutaneous bleeding (27.3%).[36]

Reports vary on the relationship of residence with childhood leukemia. Our study showed that residence was not a risk factor for childhood leukemia. Consistent with our report, there was no significant impact of residence (urban/rural) on the incidence of childhood leukemia in another Egyptian case-control study carried out in 2016.[16] In contrast, there is a theory that children living in rural areas tend to have higher leukemia rates. This might be explained by the immunologically active rural environment.[30]

In the present study, children with an abnormal birth weight (less than 2500g and more than 4000g) had a significantly higher risk for developing childhood leukemia. Similarly, other studies reported that high birth weights or both high and low extremes of birth weights (U-shaped) elevate the risk of childhood leukemia.[9, 10] High birth weights might be associated with a higher rate of cell proliferation and, subsequently, an increase in the precursor cells at risk for malignant changes.[9]

Children with previous exposure to diagnostic radiation had a significantly higher risk of developing childhood leukemia. Consistent with this result, American and Canadian case-control studies associated exposure to postnatal diagnostic radiation with an increased risk of childhood leukemia.[14, 15]

In the current study, protective childhood factors, such as breastfeeding and daycare attendance, were not significantly associated with childhood leukemia. These results disagreed with an American case-control meta-analysis and review studies. These studies showed that breastfeeding and daycare attendance were associated with reduced childhood leukemia risk.[26, 27, 37] The protective role of daycare attendance could be explained by Greaves' delayed infection hypothesis.[35] Daycare attendance increases the occurrence of common infections. Common infections early in life may play a protective role against acute leukemia. In the current study, the protective effects of breastfeeding and daycare attendance may be concealed; a vast majority of studied mothers of both cases and controls breastfed their children and did not send their children to daycare centers.

The mode of delivery was not significantly associated with childhood leukemia. This finding disagreed with an Egyptian case-control study that reported the association between pediatric leukemia and cesarean section [16]. Also, an American case-control study reported significantly increased odds of ALL for cesarean section, while there was no significant effect of cesarean section on AML risk.[28] Likewise, there was no significant association between parental age (father and mother age) at the time of delivery and childhood leukemia. This finding disagreed with several studies showing that advanced parental age is associated with childhood risk of ALL.[13, 16, 38] Maternal age was associated with the risk of childhood AML in a U-shaped manner at both oldest and youngest extremes.[13]

Maternal educational level was not a predictor of pediatric leukemia. Variations in the association of childhood leukemia with maternal education were reported. Childhood leukemia was significantly associated with low maternal education in India.[31] In contrast, an Egyptian study reported that children of mothers with secondary or higher educational levels had significantly higher odds for developing acute leukemia [16]. This study explained the association of maternal education level with childhood leukemia as a reflection of an association with western lifestyle.[16] Other studies showed a link between childhood leukemia and higher socioeconomic status.[42-43]

Father occupation, especially agricultural work, had a significant impact on the risk of childhood leukemia. Children of farmer fathers had a significantly higher odds ratio for having childhood leukemia. Mexican and Iranian case-control studies reported similar results.[39, 40]

Previous abortion before the index child was not significantly associated with childhood leukemia. Along that same line, there were no significant links between fetal loss and childhood leukemia in Indian and American case-control studies.[31, 41] Contrary results were reported in a Greek case-control study conducted on 1099 ALL cases and 131 AML cases. Statistically significant exposure and disease subtype-specific associations of previous

miscarriage(s) were exclusively associated with AML, and stillbirths were associated with ALL in the Greek study.[11]

A history of fetal loss may reflect genetic predisposition, abnormal intrauterine environment, or the effects of a common environmental exposure.[41] During the preconception period, mothers' exposure to diagnostic radiation was not a risk factor for childhood leukemia. An American case-control study reported similar results; exposure to x-rays during the maternal preconception was not a risk factor for AML.[14]

Family monthly income less than 2000 LE was a risk factor for developing childhood leukemia in the present study. Similarly, other studies reported a relationship between family poverty and the occurrence of childhood leukemia. A Malaysian case-control study found that family income ≥2000 RM resulted in a significantly lower risk for childhood leukemia.[29] An Iranian case-control study reported a negative association between acute childhood leukemia and family income.[42] A Norwegian cohort study showed that family poverty during the first two years of life was a risk factor for developing lymphoid leukemia before the age of 15 years (odds ratio: 1.72, 95% CI: 1.11–2.64).[43]

There is a growing evidence for the role of potential genetic factors in the occurrence of childhood leukemia [8]. In this study, a family history of leukemia and/or other types of malignancies resulted in a significantly higher odds ratio for childhood leukemia. These results were consistent with Greek, Iranian, Malaysian, and Canadian case-control studies reporting a familial contribution to childhood leukemia.[9, 29, 40, 44]

The relation between parental smoking and pediatric leukemia remains unclear. In the current study, there were significant differences between cases and controls. The cases had significantly higher proportions of paternal smoking and/or other smokers' presence at home (p-values 0.047 and <0.001, respectively). However, exposure to smoking was not a risk factor for childhood leukemia with adjusted regression. A Chinese case-control study reported contradictory results; in this report, childhood exposure to smoking significantly increased the risk of developing acute pediatric leukemia.[17] Also, father smoking was a risk factor for acute leukemia in Malaysian children.[29]

In this study, the proportion of children exposed to household and/or agriculture pesticides was significantly higher in the leukemia cases than that of the control group. These results are consistent with other studies that linked exposure to household pesticides with an elevated risk of childhood leukemia.[17, 20, 45] Consistent with these studies, a Costa Rican case-control study found an association between elevated childhood leukemia incidence and maternal insecticide use in the home and pesticide spraying on nearby farms before and after the child's birth.[46] An Italian case-control study showed an increase in leukemia risk among children residing close to arable crops. This study emphasized the need for further investigations into the role of passive exposure to herbicides and pyrethroids in disease occurrence in the majority of cases.[18] The risk of pediatric leukemia upon exposure to certain types of pesticides, either in utero or after birth, could be explained by the probability of pesticide inhibition topoisomerase II and oxidative stress production, which lead to single- and double-strand DNA breaks and, consequently, chromosomal aberrations in hematopoietic stem and progenitor cells. However, this evidence supports the triggering of infant leukemia, but not childhood leukemia, which involves further postnatal events for overt disease.[47]

Regarding residence of the children close to power lines, residence within 200 m of power lines was not a significant predictor of childhood leukemia. This result disagreed with results from Malaysian and British case-control studies in which children living within 200 m of power lines/substations had an increased risk of childhood leukemia.[29, 48]

CONCLUSION AND RECOMMENDATIONS

In the current study, environmental, genetic, and social factors, including exposure to pesticides and diagnostic radiation, low family income, positive family history of cancer or leukemia, and the father's occupation as a farmer play a role in childhood leukemia. Parents should be educated about the safe use and storage of pesticides, alarming signs for childhood leukemia, and the avoidance of unnecessary diagnostic radiation exposure in children.

Limitation of the study

The study results are vulnerable to recall bias, as the case-control study design was applied.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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REFERENCES

1. Force LM, Abdollahpour I, Advani SM, Agius D, Ahmadian E, Alahdab F. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. Lancet Oncol. 2019;20(9):1211-25.
2. American Cancer Society. Cancer facts & figures; 2017. Available from: https://www. facts- and-figures/2017/cancer-facts-and-figures-2017.pdf.
3. Imbach P, Kühne T. Pediatric oncology. 3rd ed. Switzerland: Springer International Publishing; 2014.
4. Ibrahim A, Mikail N, Khaled H, Baraka H, Abdeen M, Bishara A, et al. Cancer profile in Aswan, Egypt, Methodology and Results chart book 2008. 2010 ed; 2010.
5. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014:437971.
6. Clarke RT, Van den Bruel A, Bankhead C, Mitchell CD, Phillips B, Thompson MJ. Clinical presentation of childhood leukaemia: a systematic review and metaanalysis. Arch Dis Child. 2016;101(10):894-901.
7. ACS, American Cancer Society. Signs and symptoms of childhood leukemia; 2019. Available from: https://www.cancer.org/cancer/leukemia-in-children/detection-diagnosis-staging/signs-and-symptoms.html
8. Ntzani EE, Ntritsos G, Evangelou E, Tzoulaki I. Literature review on epidemiological studies linking exposure to pesticides and health

effects. Eur Food Saf Authority EFSA Supporting Publications. 2013;10(10):497E.
9. Kyriakopoulou A, Meimeti E, Moisoglou I, Psarrou A, Provatopoulou X, Dounias G. Parental occupational exposures and risk of childhood acute leukemia. Mater Sociomed. 2018;30(3):209-14.
10. Caughey RW, Michels KB. Birth weight and childhood leukemia: a metaanalysis and review of the current evidence. Int J Cancer. 2009;124(11):2658-70.
11. Karalexi MA, Skalkidou A, Thomopoulos TP, Belechri M, Biniaris-Georgallis SI, Bouka E, et al. History of maternal fetal loss and childhood leukaemia risk in subsequent offspring: differentials by miscarriage or stillbirth history and disease subtype. Paediatr Perinat Epidemiol. 2015;29(5):453-61.
12. Hyde MJ, Mostyn A, Modi N, Kemp PR. The health implications of birth by Caesarean section. Biol Rev Camb Philos Soc. 2012;87(1):229-43.
13. Sergentanis TN, Thomopoulos TP, Gialamas SP, Karalexi MA, Biniaris-Georgallis S-I, Kontogeorgi E, et al. Risk for childhood leukemia associated with maternal and paternal age. Eur J Epidemiol. 2015; 30: 1229-61.
14. Bartley K, Metayer C, Selvin S, Ducore J, Buffler P. Diagnostic X-rays and risk of childhood leukaemia. Int J Epidemiol. 2010;39(6):1628-37.
15. Infante-Rivard C. Diagnostic x rays, DNA repair genes and childhood acute lymphoblastic leukemia. Health Phys. 2003;85(1):60-4.
16. Ezzat S, Rashed WM, Salem S, Dorak MT, El-Daly M, Abdel-Hamid M, et al. Environmental, maternal, and reproductive risk factors for childhood acute lymphoblastic leukemia in Egypt: a case-control study. BioMid Cent Cancer. 2016;16(1):1-7.
17. Zhang Y, Gao Y, Shi R, Chen D, Wang X, Kamijima M, et al. Household pesticide exposure and the risk of childhood acute leukemia in Shanghai, China. Environ Sci Pollut Res Int. 2015;22(15):11755-63.
18. Malagoli C, Costanzini S, Heck JE, Malavolti M, De Girolamo G, Oleari P, et al. Passive exposure to agricultural pesticides and risk of childhood leukemia in an Italian community. Int J Hyg Environ Health. 2016;219(8):742-8.
19. Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ Health Perspect. 2007;115(1):138-45.
20. Bailey HD, Infante-Rivard C, Metayer C, Clavel J, Lightfoot T, Kaatsch P, et al. Home pesticide exposures and risk of childhood leukemia: findings from the childhood leukemia international consortium. Int J Cancer. 2015;137(11):2644-63.
21. Turner MC, Wigle DT, Krewski D. Residential pesticides and childhood leukemia: a systematic review and metaanalysis. Environ Health Perspect. 2010;118(1):33-41.
22. Obeid HL, Habib OS, Hassan GG. Childhood Cancer (Leukaemias and Lymphoma) in Basrah-A case-control study. Thi-Qar. Med J. 2008;2(1):1-9.
23. Reis RdS, Silva NdP, Santos MdO, Oliveira JFP, Thuler LCS, de Camargo Bd, et al. Mother and child characteristics at birth and early age leukemia: a case-cohort population-based study. J Pediatr (Rio J). 2017;93(6):610-8.
24. Kutanzi KR, Lumen A, Koturbash I, Miousse IR. Pediatric exposures to ionizing radiation: carcinogenic considerations. Int J Environ Res Public Health. 2016;13(11):1057.
25. Marcotte EL, Ritz B, Cockburn M, Yu F, Heck JE. Exposure to infections and risk of leukemia in young children. Cancer Epidemiol Biomarkers Prev. 2014;23(7):1195-203.
26. Maia Rda R, Wünsch Filho V. VInfection and childhood leukemia: review of evidence. Rev Saude Publica. 2013;47(6):1172-85.
27. Urayama KY, Ma X, Selvin S, Metayer C, Chokkalingam AP, Wiemels JL, et al Early life exposure to infections and risk of childhood acute lymphoblastic leukemia. Int J Cancer. 2011;128(7):1632-43.
28. Francis SS, Selvin S, Metayer C, Wallace AD, Crouse V, Moore TB, et al. Mode of delivery and risk of childhood leukemia. Cancer Epidemiol Biomarkers Prev. 2014;23(5):876-81.
29. Abdul Rahman HIA, Shah SA, Alias H, Ibrahim HM. A case-control study on the association between environmental factors and the occurrence of acute leukemia among children in Klang Valley, Malaysia. Asian Pac J Cancer Prev. 2008;9(4):649-52.
30. Jin MW, Xu SM, An Q, Wang P. A review of risk factors for childhood leukemia. Eur Rev Med Pharmacol Sci. 2016;20(18):3760-4.
31. Kumar A, Vashist M, Rathee R. Maternal factors and risk of childhood leukemia. Asian Pac J Cancer Prev. 2014;15(2):781-4.
32. Gusbi A, Elouzi A, BenOmran E, Arhima M, Zekre EB, BenAyad E. Risk factors of childhood leukemia at Tripoli Medical Center in Libya. Am J Pharm Am J Pharm Pharmacol Acy Pharmacol Acy Pharmacol. 2014;1(2):17-22.
33. MacArthur AC, McBride ML, Spinelli JJ, Tamaro S, Gallagher RP, Theriault GP. Risk of childhood leukemia associated with vaccination, infection, and medication use in childhood: the Cross-Canada Childhood leukemia Study. Am J Epidemiol. 2008;167(5):598-606.
34. ACS, American Cancer Society. Key statistics for childhood leukemia; 2019. Available from: https://www.cancer.org/cancer/leukemia-in-children/about/key-statistics.html.
35. Greaves M. Aetiology of acute leukaemia. Lancet. 1997;349(9048):344-9.
36. Shalal HH, Mahmood NS, Alchalabi MAQ. Clinical, hematological, and laboratory presentation of acute lymphoblastic leukemia of children in Diyala Province/Eastern Iraq. Int J Res Med Sci. 2017;5(10):4227-33.
37. Urayama KY, Buffler PA, Gallagher ER, Ayoob JM, Ma X. A metaanalysis of the association between daycare attendance and childhood acute lymphoblastic leukaemia. Int J Epidemiol. 2010;39(3):718-32.
38. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental age and risk of childhood cancer: a pooled analysis. Epidemiology. 2009;20(4):475-83.
39. Perez-Saldivar ML, Ortega-Alvarez MC, Fajardo-Gutierrez A, Bernaldez-Rios R, Del Campo-Martinez Mde L, Medina-Sanson A, et al. Father's occupational exposure to carcinogenic agents and childhood acute leukemia: a new method to assess exposure (a case-control study). BioMid Cent Cancer. 2008;8:7.
40. Hassanzadeh J, Mohammadi R, Rajaeefard AR, Bordbar MR, Karimi M. Maternal and prenatal risk factors for childhood leukemia in southern of iran. Iran Red Crescent Med J. 2011;13(6):398-403.
41. Ross JA, Potter JD, Shu XO, Reaman GH, Lampkin B, Robison LL. Evaluating the relationships among maternal reproductive history, birth characteristics, and infant leukemia: a report from the Children's Cancer Group. Ann Epidemiol. 1997;7(3):172-9.
42. Dehghani K, Poormovahed Z, Dehghani H. Socioeconomic status and childhood leukemia. Iran J Pediatr Hematol Oncol. 2011;1(4):152-8.
43. Del Risco Kollerud R, Blaasaas KG, Claussen B. Poverty and the risk of leukemia and cancer in the central nervous system in children: A cohort study in a high-income country. Scand J Public Health. 2015;43(7):736-43.
44. Infante-Rivard C, Guiguet M. Family history of hematopoietic and other cancers in children with acute lymphoblastic leukemia. Cancer Detect Prev. 2004;28(2):83-7.
45. Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B, et al. Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med. 2006;63(2):131-4.
46. Hyland C, Gunier RB, Metayer C, Bates MN, Wesseling C, Mora AM. Maternal residential pesticide use and risk of childhood leukemia in C osta R ica. Int J Cancer. 2018;143(6):1295-304.
47. Hernández AF, Menéndez P. Linking pesticide exposure with pediatric leukemia: potential underlying mechanisms. Int J Mol Sci. 2016;17(4):1-16.
48. Draper G, Vincent T, Kroll ME, Swanson J. Childhood cancer in relation to distance from high voltage power lines in England and Wales: a case-control study. Br Med J. 2005;330(7503):1-5.