

Exclusive breastfeeding as a protective factor of acute lymphoblastic leukemia

Lactancia materna exclusiva como factor protector de la leucemia linfoblástica aguda

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What do we know about the subject matter of this study?

Breastfeeding is known to reduce the risk of developing acute lymphoblastic leukemia in children and adolescents, making it essential to validate this national experience.

What does this study contribute to what is already known?

This article confirms the protective effects of breastfeeding and complete secondary education of the mother on acute lymphoblastic leukemia in children aged 0 to 13 years, where the latter constituting a second finding in the literature.

Abstract

Globally, Acute Lymphoblastic Leukemia (ALL), represents more than 30% of all types of cancers in children aged between 0 and 9 years. In Peru, it has not been evaluated whether exclusive breastfeeding (EB) is a protective factor for ALL. **Objective:** To identify the protective and risk factors associated with acute lymphoblastic leukemia in children aged between 0 and 13 years in a national hospital in Lima, Peru. **Patients and Method:** Observational, analytical study, case-control design. 112 cases diagnosed with ALL and 229 controls were evaluated. The data were collected by interviews with the mothers of both groups. The magnitude of the association between ALL and EB was estimated using the odds ratio (OR) and multivariate logistic regression in Stata v 12. **Results:** 50.9% (57/112) of the cases and 51.5% (118/229) of the controls were male. The mean age of the cases was 6.7 ± 3.2 years and of the controls 5.7 ± 3.5 years. The mean age of the mothers of the cases was 35.9 ± 6.5 and of the controls was 34.1 ± 7.1 years. EB reduces the risk of ALL by 44% compared with those who did not receive it, OR 0.56, $p = 0.017$, 95% CI (0.35-0.90). Complete secondary education reduces the risk of ALL by 62%, OR 0.38 CI 95% (0.15-0.61). **Conclusions:** Exclusive breastfeeding and the mother's complete secondary education are protective factors for the development of ALL in children and adolescents.

Keywords:

Precursor Cell
Lymphoblastic
Leukemia-Lymphoma;
Risk Factors;
Case-Control Studies;
Breastfeeding;
Child;
Peru

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Introduction

Childhood cancer is the leading cause of death in children in the world¹, with an estimated 385,509 new cases reported annually aged between 0 and 19 years². In this group, leukemia is one of the most frequent cancers, accounting for more than 30%, between 0 and 9 years of age². South America reports a specific incidence of 49.8 new cases of leukemia per year in the 0-19 year age group².

Acute lymphoblastic leukemia (ALL) is a group of malignant neoplasms that originate from immature hematopoietic cells, altering the functions of the bone marrow and causing failure of marrow function^{3,4}. Patients present with a leukemic clone that may be of B or T cell type, identified by immunophenotype, and a wide range of genetic alterations³.

The management and treatment of ALL require typing the neoplasm according to the 8 morphological varieties that have been established based on the finding of blasts in the blood count, as well as considering cytochemical, immunophenotypic, cytogenetic, and molecular biology studies⁴.

The incidence of ALL in children of Hispanic origin is higher (40.9 new cases per million) compared with whites (35.6 cases per million), and African Americans (14.8 cases per million), and boys are at higher risk than girls⁵. Although the cure rate of ALL in children is close to 100%⁵, mortality is higher in poor or developing countries, mainly due to poor access to health services, delayed diagnosis, economic barriers to treatment, or lack of health care insurance⁶.

In Peru, between 2006 and 2011, out of 3,801 cases of cancer in children under 15 years of age, 44.2% are of the lymphoid lineage, with a predominance in boys⁷. Between 2004 and 2005, in Lima Metropolitan Area, 635 cases were reported in children under 14 years of age, representing 2.1% of the total cases reported and 35.2% are leukemias with a higher incidence rate in boys⁸. The incidence of ALL in Peru in children under 14 years of age is 270 to 360 new cases per year⁹ and the overall survival rate of 348 children at the Edgardo Rebagliati Martins Hospital at five years was 32.5% with a median follow-up of 27.5 months and an interquartile range of 25-45 months¹⁰.

Environmental risk factors include exposure to ionizing radiation, paints, solvents, smoking, among others^{5,11}, however, these explain a small number of cases⁵. Therefore, there have been studies to identify protective factors such as iron or folic acid supplementation, vitamins, and the consumption of other products by mothers during pregnancy⁹⁻¹². Likewise, breastfeeding for 6 months or more reduces the risk of developing leukemia in children by 10% to 21%^{9,13}.

Breast milk contains all the nutrients an infant

needs during the first 6 months of life, it also contains bioactive factors that increase the response of the baby's immature immune system and protect against different infections¹⁴.

Breastfeeding is a protective factor for children aged between 0 and 17 years for developing both ALL and acute myeloid leukemia (AML)^{13,15,16}, in children under 2 years of age¹⁷ and other types of cancer¹⁸; however, some reports do not find an association with a lower risk¹⁹. The protective effect would be greater if breastfeeding is for 7 to 9 months. In contrast, maternal age, smoking during pregnancy, among other factors, can increase the risk of childhood leukemia²⁰. Both long- and short-duration breastfeeding would be protective for ALL and AML²¹.

The objective of this study is to evaluate the protective effect of exclusive breastfeeding on the risk of acute lymphoblastic leukemia in children under 14 years of age in a national hospital in Lima, Peru.

Patients and Method

Study design

Case-control study of 1:2 ratio. This design was used because ALL is a rare disease of long duration or latency that allows the evaluation of several risk factors for the same pathology²²⁻²³.

We considered as a case those children diagnosed with ALL through myelogram by bone marrow aspiration (blasts $\geq$ 25%), and in cases with abundant proliferation, corroborated by biopsy. The control was defined as children with no history of cancer who had another diagnosis and who attended the Pediatric Emergency Department of the same hospital where the cases were identified due to another cause on an outpatient basis.

Population, sample, sample selection, and selection criteria

Patients with a diagnosis of ALL, aged between 0 and 13 years, seen during 2015 at the Outpatient Childhood Chemotherapy Clinic and the Pediatric Emergency Department of the Edgardo Rebagliati Martins Hospital in Lima, Peru.

339 participants were selected by convenience criteria, among them 112 were cases and 225 were controls. Incident or prevalent cases of ALL (0 to less than 14 years of age), who attended the Outpatient Childhood Chemotherapy Clinic of the hospital during 2015, were consecutively included. Those hospitalized children due to cancer or congenital malformation and those whose mothers did not complete the survey due to anxiety about the patient's diagnosis, and adoptive mothers were excluded.

The controls were also between 0 and 13 years of age and selected from among those seen at the outpatient pediatric emergency department of the hospital on the same day as the cases were selected. They had no history of cancer or Down syndrome.

Variables

The dependent variable was ALL and the independent variables were history of exclusive breastfeeding (EBF), the age of the child at the last care, sex, age of the mother at the time of the last care of her child, age of the mother at the time of delivery of the child included in the study, educational level of the mother, origin referral unit, and history of suffering a negative life or traumatic event (psychological trauma of the mother during gestation). EBF was defined as when the child was exclusively breastfed during the first 6 months of life.

Data collection procedures

Data collection was performed using a questionnaire that was validated to assess its relevance by nine experts (in breastfeeding and other experts in leukemia). The questionnaire was applied by the main author (MMSB) to the mother of children and adolescents under 14 years of age with leukemia (case) at the Outpatient Childhood Chemotherapy Clinic and to the mother of children without ALL (control) at the Pediatric Emergency Department of the hospital after informed consent.

Data analysis

The variables were coded and tabulated into a database in MS Excel 2007, and the analysis was performed with STATA software version v 12. A descriptive analysis of absolute and relative frequencies was performed for categorical variables and an analysis of central tendency measures, dispersion, and summary measures was performed for the numerical ones.

The normality of the mother's age at delivery and the child's age was assessed by the Shapiro-Wilks test and the homogeneity of variances by the Levene test.

To identify the associated variables, a bivariate analysis was first performed by calculating the crude Odds Ratio (COR) at a 95% confidence interval. For categorical variables, we used the Chi-square test, and a < 0.05 p-value was considered statistically significant. For the multivariate logistic regression analysis, a 95% confidence level was used, and both the coefficients and the adjusted Odds Ratio (AOR) were calculated.

Ethical considerations

This study was approved by the Ethics Committee of the Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru. The mothers of all participants included in

this study were informed of the objective of the study and were asked to participate. The mothers who accepted signed the informed consent form. In addition, the ethical considerations of the World Medical Association and the Declaration of Helsinki were respected.

Results

341 children aged from 0.3 to 13 years were included in the study, 112 of them were cases (with ALL diagnosis) and 229 were controls without ALL. Table 1 shows the characteristics of the cases and controls.

Table 2 shows the COR results in the bivariate analysis. The age of the children and adolescents and the age of the mother were considered variables not associated with risk factors. Regarding the child, for each additional year of age, the risk of having the disease increased by 1.09 times ($p = 0.10$); while regarding the mother, for each additional year of age, the risk of the child having ALL increases by 1.03 times ($p = 0.056$).

In contrast, the variables that were associated with maternal protective factors were having completed secondary education and exclusive breastfeeding. Mothers with completed high school would reduce the risk of developing ALL by 70% in the sample ($p < 0.000$). Likewise, EBF reduces the chance of having ALL by 44% compared with those who did not have EBF. ($p = 0.012$).

In the complete multivariate logistic regression model (Table 3), we found that the age of the child increases the risk by 1.08 times for each year of increase, keeping the other variables constant ($p = 0.06$), but it is not a risk factor. The fact that the mother has completed secondary education reduces the possibility of having ALL in the child by 62% compared with children with mothers with primary or incomplete secondary education, which was statistically significant ($p = 0.007$). Likewise, EBF reduces the risk of the child having ALL by 44% compared with those who did not have EBF ($p = 0.017$).

Discussion

The results of this study show that EBF is associated as a protective factor for developing ALL (OR 0.56). EBF reduces the risk of developing ALL in children by 44%. These results are very important given the extent of the issue in Peru^{7,9,24}.

In our study, the reduction in the risk of developing ALL was similar to those reported by other investigators (48%¹⁷ and 50.2%²⁰), but more than double that those found by other authors²³. However, in two

studies breastfeeding was a risk factor^{25,26}. It has been suggested that breastfeeding and delayed introduction of formula milk may reduce the risk of ALL¹⁷. The differences between the studies could be explained by the different timing of EBF, the sample size, and the age of the children included in the studies. In our study, EBF was considered up to 6 months of age. The duration of EBF could likely influence the magnitude of the association of the variables.

Systematic reviews and meta-analyses that have evaluated the risk of developing ALL with breastfeeding of 6 months or more conclude that prolonged breastfeeding has a protective effect for ALL (OR 0.76, OR 0.81), with a reduction in the risk of developing leukemia between 19% and 5% in breastfed children^{21,27-29}.

In Peru, the prevalence of EBF in newborns aged 0-5 months varies between 60-79%^{30,31}. The WHO has recommended protecting, promoting, and supporting EBF for 6 months and continued breastfeeding until 2 years of age or older¹⁴. EBF would provide more beneficial immunological effects than

breastfeeding supplemented with milk formula³². In France, in a study of 617 cases and 1,225 controls in children ≥ 1 year, the results support the hypothesis that conditions that promote maturation of the immune system in childhood have a protective role against ALL³³.

One of the arguments for promoting EBF is the cost of caring for a child with leukemia. In the USA, it was estimated that the direct cost of caring for a child with leukemia is US\$136,444.00 and the total cost is US\$153,617.00³⁴. In the same country, another study estimated that if the "Healthy People" health plan (HP20) were implemented with an increase in 82% of children who have ever been breastfed, 52 (19.4%) new cases of leukemia would be prevented, which means a saving of US\$197.8 million³⁵.

At the family level, it is described that up to 77% of parents interrupt their jobs, and between 11% and 35% have to quit in order to care for their sick children with leukemia, even bringing the families to the poverty line³⁶.

In this study, having completed secondary edu-

Table 1. Characteristics of cases and controls included in the study, 2015

Variable	Cases (With Acute Lymphoblastic Leukemia)		Controls (Without Acute Lymphoblastic Leukemia)	
	n = 112	%	n = 229	%
Child's age (years)				
Median (RIQ), mean $\pm$ SD, range	6 (5), 6.7 $\pm$ 3.2, 1-13		5 (6), 5.7 $\pm$ 3.5, 0.3-13	
Gender				
Female	55	49.1	111	48.5
Male	57	50.9	118	51.5
Mother's age (years)*				
Median (RIQ), mean $\pm$ SD	36 (10), 35.9 $\pm$ 6.5		33 (10), 34.1 $\pm$ 7.1	
Mother's age at time of delivery (years)				
Median (RIQ), mean $\pm$ SD	30 (8), 29.1 $\pm$ 6.3		28 (10), 28.6 $\pm$ 6.4	
Mother's level of education				
Incomplete Elementary/high school	28	25.0	30	13.4
High school completed	24	21.4	86	37.6
Superior incomplete and complete	60	53.6	113	49.3
Exclusive breastfeeding				
No	57	50.9	84	36.7
Yes	55	49.1	145	63.3
Traumatic event				
No	98	87.5	206	89.9
Yes	14	12.5	23	10.1

IQR = Interquartile range *Non-normal distribution

Table 2. Bivariate analysis between cases and controls and crude odds ratio results

Variable	Cases n = 112	Controls n = 229	p-value	ORc (95% CI)
Child's age (years)				
Media	6.7	5.7	0.010	1.09 (1.02-1.17)
Gender of child				
Female	55	111		Reference
Male	57	118	0.816	1.05 (0.65-1.70)
Mother's age (years)				
Media	35.9	34.1	0.056	1.03 (1.00-1.07)
Mother's level of education				
Incomplete elementary/high school	28	30		Reference
High school completed	24	86	0.000	0.30 (0.15-0.61)
Superior incomplete and complete	60	113	0.066	0.57 (0.34-0.91)
Exclusive breastfeeding				
No	57	84		Reference
Yes	55	145	0.012	0.56 (0.34-0.91)
Traumatic event				
No	98	206		
Yes	14	23	0.493	1.28 (0.58-2.272)

c = Crude.

Table 3. Multivariate logistic regression analysis between cases and controls

Variable	Cases n = 112	Controls n = 229	p-value	ORa (95% CI)
Child's age (years)				
Media	6.7	5.7	0.060	1.08 (1.00-1.16)
Gender of child				
Female	55	111		Reference
Male	57	118	0.865	0.96 (0.60-1.54)
Mother's age (years)				
Media	35.9	34.1	0.567	1.01 (0.97-1.05)
Mother's level of education				
Incomplete elementary/high school	28	30		Reference
High school completed	24	86	0.007	0.38 (0.15-0.61)
Superior incomplete and complete	60	113	0.159	0.64 (0.34-1.19)
Exclusive breastfeeding				
No	57	84		Reference
Yes	55	145	0.017	0.56 (0.35-0.90)
Traumatic event				
No	98	206		
Yes	14	23	0.769	1.28 (0.54-2.33)

a = adjusted.

cation of the mother reduced the risk of developing ALL by 62% in children compared with children of mothers with incomplete primary or secondary education. In a systematic review, it was found that the educational level of the mothers was negatively associated ($p < 0.001$) with the risk of developing ALL in 11 of 18 case-control studies³⁷.

Our results are similar to a study conducted in Greece, where the association was strongly positive with a relative risk (RR) of 0.54 95%CI for mothers with 7-14 years of education and a RR of 0.38 for mothers with ≥ 14 years of education³⁸. In our research, mothers with complete and incomplete higher education did not have a protective effect on ALL. This could be because they would work between 6 to 10 hours and would not have the time to exclusively breastfeed their children. Mothers with a higher level of education likely have greater access to the use of milk formulas, which has been identified as a factor associated with the abandonment of EBF³⁹. Future studies need to test our findings and assess the association between mothers' jobs and EBF with ALL.

In Iran, in 125 children up to 15 years of age with ALL matched with 130 children for age, sex, and residence location, the authors found that children with parents who were not highly educated had a risk of OR 2.67, 95% CI (1.10-6.45) compared with children with parents who were highly educated⁴⁰. In China, researchers found a high risk among those with no or low educational level²⁰. In another similar study in children under 18 years of age in North Dakota and Wisconsin, USA, mothers who completed high school had a higher risk, OR 1.61 95% CI (1.05-2.48) compared with those with a higher level of education⁴¹.

In this study, the sex and age of children under 14 years of age, the age of the mother, and history of traumatic events were also evaluated, which were not associated with ALL. Other researchers have also found no association between the sex of children or adolescents and the risk of developing ALL^{38,40}. It has been identified that the peak incidence of ALL is between 2 and 5 years of age⁴². The subtypes of ALL were not identified in this study.

In a case-control study, the older or advanced age of the parents increased the risk of childhood cancer, showing a positive linear trend relationship for the age of the mother and the increased frequency of seven neoplasms in children, including ALL with an OR 1.08 (1.05-1.11)⁴³. Although the mean age of both cases (29.1 years) and controls (28.6 years) in our study is similar to that of the aforementioned authors (26.9 years vs. 26.7 years, respectively)⁴³, likely, the sample size causes not finding an association with ALL in this study. In Egypt, mothers older than 30 years had an

OR 1.8 95% CI (1.1-2.8) of their children developing ALL⁴⁴. In contrast, in Ecuador, no association was found with the risk of ALL in children among mothers older than 35 years compared with 35 years or younger⁴⁵.

The mother's history during pregnancy of having experienced a negative or stressful life event (traumatic event) was not associated with the risk of ALL. This could probably be explained by the small sample size. In Medellin, Colombia, a history of being a victim of domestic violence, parental separation, and maternal depression had an OR 2.57 95% CI (1.23-5.39) for developing ALL compared with those without this background⁴⁶.

One of the limitations of this study is not having calculated the sample size to identify the expected risk, despite cohort studies with sample sizes similar to ours have been published^{38,40}. However, the identification of EBF as a protective factor is consistent with previous findings^{13,17,20} and the finding of the educational level is also consistent with a previous study³⁸. Future studies should evaluate whether having completed high school is a confounding variable.

The sample size calculated for a matched study considering the history of breastfeeding with 27.5% of exposed cases, 3.7%²⁰ of exposed controls, 80% of power, and 95% CI resulted in 38 pairs, far below the size used in this study, however, the variable was not measured in the same way. Future studies are required to identify other risk factors not included in this study and to corroborate our results.

In this study, the hypothesis that EBF has a protective effect on ALL (OR 0.56) is accepted, as well as completed secondary education which protects from ALL (OR 0.38).

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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