RESEARCH ARTICLE

Maternal Factors and Risk of Childhood Leukemia

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Abstract

Background: Although the cause in most cases of childhood leukemia is not known, the contribution of environmental risk factors in the context of genetic predisposition has been reported with inconsistent results. The aim of this study was to examine association of childhood leukemia with maternal factors especially during pregnancy, to help in avoiding risk factors. Materials and Methods: This case-control study included children younger than 18 years diagnosed with leukemia from 2008 to 2012. Controls were randomly selected and individually matched to cases with respect to age, sex, and residency. All variables were compared between cases and control to determine any significant association with leukemia. Results: Statistically significant associations between risk of childhood leukemia with mother's education (p=0.001), occupation (p=0.0005) and pesticides exposure (p=0.005) during pregnancy were found. However, there were no significant links with maternal age (p=0.090), history of fetal loss (0.85), history of radiography during pregnancy (p=0.400), history of drug intake (p=0.689) and infection (p=0.696) during pregnancy. Conclusions: The results showed increased risk of leukemia in children whose mothers were working in agriculture and were exposed to pesticides during pregnancy. The further study needs to be investigated to know association of various maternal risk factors with leukemia which remained unknown in this study.

Keywords: Childhood leukemia - maternal factors - pesticide exposure during pregnancy - occupation

Asian Pac J Cancer Prev, **15 (2)**, 781-784

Introduction

Leukemia is the most common childhood cancer, accounting for nearly one-third of all cancers among children aged <15 years (Ries et al., 1999; Kim et al., 2006; Belson et al., 2007). Acute leukemia accounts for the majority of pediatric cases, with 80% acute lymphoid leukemia (ALL) and 20% acute myeloid leukemia (AML) (Pui, 1999). It is the primary cause of childhood cancer mortality in the United States and approximately 6000 new cases are diagnosed each year (Podvin et al., 2006; Dores et al., 2012). Leukemia accounts for 25-40% of all childhood cancer in India (Arora et al., 2009). Leukemia is not a single disease but a group of diseases perhaps with many different causes. Some doctors believe that leukemia develop from a combination of genetic and environmental factors. Although the cause in most cases of childhood leukemia is not known, certain prenatal and postnatal risk factors like inherited diseases, exposure of ionizing radiation, pesticides, and high birth weight have been suggested to contribute to susceptibility (OU et al., 2002; Hjalgrim et al., 2004; Belson et al., 2007).

The risk of childhood leukemia associated with maternal exposure to a number of possible risk factors including environmental, genetic and infection has been studied extensively. Some prenatal risk factors in mothers before or during pregnancy have been found associated with increased risk of childhood leukemia (Belson et al., 2007). An increased risk of childhood leukemia has been reported in children whose mothers had an exposure to ionizing radiation, pesticides and drugs during pregnancy (Murray et al., 2002; Podvin et al., 2006;Belson et al., 2007; Bartley et al., 2010). Links between most environmental risk factors and childhood leukemia are inconsistent. However, researches present conclusive link between pesticides exposure and leukemia (Infante-Rivard et al., 1999; Menegaux et al., 2006).

The objective of this study was to examine the relationship between maternal characteristics and environmental exposures with childhood leukemia. Knowledge of these particular risk factors can be helpful in alleviating potentially harmful exposures and reducing the risk of diseases.

Materials and Methods

In this case-control study, children younger than 18 years suffering from acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) were included. The patients were diagnosed at Pt.B.D Sharma University of Health Sciences, Rohtak, India between 2008-12.The control chosen by random sampling were individually matched to the cases with respect to age, sex and residency. The mothers of both cases and control were interviewed for information regarding mother's age at the time of childbirth, education, occupation, history of drug

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intake during pregnancy, history of fetal loss, exposure of pesticides during pregnancy in agricultural activity or house hold activity, history of radiography during pregnancy and infection during pregnancy. Chi-Square test was used for data analysis. Various maternal risk factors were compared between cases and controls by test of proportion (z-test) to find any significant association with leukemia. P value less than 0.05 was considered significant. The data were analyzed with SPSS software (version 11.5).

Results

In this case control study, 132 children younger than 18 years were diagnosed with leukemia between 2008-12. Out of 132 cases, 79 children were suffering from acute lymphocytic leukemia and 53 were suffering from acute myeloid leukemia. Male were more than females in both ALL and AML. The demographic characteristics of both cases and controls are shown in Table 1.There was significant difference between the case and control groups regarding mother's education (p=0.001) and occupation (p=0.0005). However, significant difference was not observed in maternal age at the time of childbirth (p=0.090). Agriculture was the major occupation in mothers of cases and education level of mothers in cases was lower than control, particularly when primary school and university degrees were concerned.

Table 2 shows the frequency of various risk factors in mothers of cases and control calculated by test of proportion. History of fetal loss was observed in mothers of 12.9% cases and 21.2% controls which was not statistically significant (p=0.071). The children with leukemia whose mothers had exposure of pesticides during pregnancy were at higher risk of developing leukemia, this association was statistically significant (p=0.005). The history of drug intake during pregnancy, particularly chloramphenicol was observed in more cases than control but difference was not statically significant (p=0.695). No association was observed in maternal history of radiography (p=0.400) and infection (p=0.696) during pregnancy with increased risk of childhood leukemia.

Table 1. Demographic Characterstics of Cases and Controls

Variables	Cases Frequency(%)	Controls Frequency(%)	p value[A]
Age(years)			Matched variable
<5	19(14.4)	19(14.4)	
6 to 10	43(32.6)	43(32.6)	
11 to 15	36(27.3)	36(27.3)	
16 to 18	34(25.7)	34(25.7)	
Sex			Matched variable
Male	92(69.7)	92(69.7)	
Female	40(30.3)	40(30.3)	
Residency			Matched variable
City	84(63.6)	84(63.6)	
Village	48(36.4)	48(36.4)	
Maternal age(years)			p=0.090
<20	26(19.7)	22(16.7)	
21-25	40(30.3)	47(35.6)	
26-30	35(26.5)	46(34.8)	
>30	31(23.5)	17(12.9)	
Maternal education			p=0.001
Illiterate	8(6)	7(5.3)	
Primary school	38(28.7)	16(12.1)	
Secondary school	63(47.7)	64(48.4)	
University Degree	23(17.4)	45(34)	
Mother's occupation			p=0.0005
Agriculture workers	56(42.4)	31(25.5)	
House wife	18(13.6)	41(31)	
Workers	40(30.3)	35(26.5)	
Industry	18(13.6)	25(18.9)	

[A], Based on Chi-square test

Table 2. Proportion of Various Risk Factors in Mothers of Cases and Controls

Variables	Cases n (%)	Controls n (%)	p value[B]
History of fetal loss	17 (12.9)	28 (21.2)	0.071
History of radiography during pregnancy	32 (24.2)	38 (28.8)	0.4
Exposure to pesticides during pregnancy	28 (21.2)	12 (9.1)	0.005
Drug in take during pregnancy	41 (31.1)	38 (28.8)	0.689
History of infection during pregnancy	14 (10.6)	16 (12.1)	0.696

[B]Based on Z-test

Discussion

Leukemia as the most common childhood cancer occurs when the genetic and environmental factors interact in a multistage sequence. Although, the recent increase in the childhood leukemia cases may be partly explained by more accurate diagnostic practice and better reporting scheme, the role of new environmental risk factors must be more clearly elucidated.

The predominance of acute lymphocytic leukemia and male cases in our study was previously reported by other researchers (Greaves and Alexander, 1993; Margolin et al., 2001; Arora et al., 2009; Dores et al., 2012).The peak occurrences of leukemia were in 6-10 years old children, which include over 33 percent of children in this case. Hassanzadeh and workers have reported higher frequency of children in age group of 5-9 years followed by < 4 years and 10-14 years (Hassanzadeh et al., 2011) while others have reported peak in 2-5 years, followed by a small peak between 11-15 years(Hanson and Mulvihill, 1980; Draper et al., 1994). This is relatively compatible with the theory that young children (under 10 years of age) have less developed immune system and are more vulnerable to common childhood infections. This study has found an association of mothers having lower education with increased risk of leukemia in children. However, such association was not reported in earlier studies (Bartley et al., 2010; Hassanzadeh et al., 2011).

In contrast to what Dockerty and colleagues described (Dockerty et al., 2001), this study does not support existence of a link between advanced maternal age and risk of childhood leukemia. Some other researchers have also reported results similar to our study (Bartley et al., 2010;Hassanzadeh et al., 2011). This could be partly explained by younger age of marriage and pregnancy especially in rural areas and the effect of genetics and other environmental factors.

As stated earlier, we discovered significant difference between the case and control groups in regard to mother's occupation during pregnancy especially in agricultural working. This may be due to prolonged pesticide exposure or other unknown environmental hazards. However, there is inconclusive evidence regarding parent's occupational exposures and risk of developing leukemia. Results from the different Child Cancer Study shows a small increased risk of childhood leukemia associated with parental occupational exposure to exhaust fumes, inhaled particulate hydrocarbons and pesticides(Schuz et al., 2000; Cordier et al., 2001; McKinney et al., 2003 Metayer et al., 2013).

Children whose mothers had an exposure to pesticides during pregnancy were at greater risk of developing leukemia than controls. Several studies have reported increased risk leukemia in children whose mothers had frequent prenatal exposure of pesticides in garden and home (Daniel et al; 1997; Zaham and Ward 1998,Infante-Rivard et al., 1999; Menegaux et al., 2006; Metayer et al., 2013). Van Maele-Fabry et al have reported increased risk of childhood leukemia with maternal occupational exposure to pesticides (Van Maele et al;2010). In a recent study from Brazil, use of pesticides during pregnancy was found associated with increased risk of childhood leukemia(Ferreira et al;2013). This suggests that embryo in uterus may be particularly sensitive to carcinogenic effects of pesticides

The maternal history of fetal loss and risk of childhood leukemia have been pursued in several studies and have reached contradictory results (Kaye et al., 1991; Ross et al., 1997). A history of fetal loss may reflect genetic predisposition, abnormal intrauterine environment, or the effect of a common environmental exposure (Ross et al., 1997). While some studies similar to this study did not show any significant associations (Kaye et al., 1991; OU et al., 2002) others suggest it as a possible risk factor (Yeazel et al., 1995;Podvin et al., 2006;Specter et al., 2007). These controversies may be explained as follows: First, the characteristics of leukemia cases in different studies varied. Second, such information was gathered through interviews in some studies which may be subjected to recall biases.

Several studies have assessed the risk of in utero exposure to ionizing radiation and the development of childhood leukemia (Doll and Wakefold, 1997; Bunch et al., 2009; Schonified et al., 2012). However, such association was not shown in our research, similar to what described by other investigators (Meinert et al., 1999; Shu et al., 2002; OU et al., 2002; Bartley et al., 2010). This apparent decrease in risk over time may be attributable to declining exposures to ionizing radiation (decreased dose) and to the increasing use of diagnostic ultrasound in place of diagnostic X rays during pregnancy (Shu et al., 2002).

The role of infection has been shown by several studies (Greaves and Alexander 1993; Greaves et al., 2002). A specific virus has been posted as a candidate etiologic agent for childhood ALL, with leukemia occurring as a consequence of primary infection of women during pregnancy that lead to in utero infection and to subsequent increased risk of developing ALL in early childhood (Smith, 1997). However, such association was not observed in this study.

A study has reported 10-fold increased risk of childhood AML and ALL with use of maternal marijuana before and during pregnancy (Robinson et al., 1989). Recently, Couto et al have reported an association between maternal exposure to hair straightening cosmetics in the first trimester of pregnancy and acute lymphocytic Leukemia(ALL) at early age(<2 years)(Couto et al., 2013). However, there was no association of childhood leukemia with drug intake during pregnancy in this study.

This study presented an existence of a link between mother's education, occupation and pesticides exposure during pregnancy. The contradiction presented in different studies regarding different variables is partly explained by the influence of genetic predisposition and leukomogenic translocations. Furthermore, the multi-center matched case-control studies are recommended to clarify the ambiguous aspects of this complex subject.

Acknowledgements

We would like to express our special thanks to Dr.Pankaj abrol, Professor & Head, Department. of Pediatrics, and Dr.P.S.Gahlot, Head, Department of Medicine, Pt.B.D.University of Health Sciences,Rohtak(India) for helping us in data collection.

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