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Original Article

Risk factors of childhood leukemia

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Abstract

Background The incidence of childhood leukemia has increased annually. Recent studies have shown that childhood leukemia is initiated in utero, and have focused on prenatal risk factors such as birth weight and parental age. Exposure to pesticides and radiation, as well as parental smoking, breastfeeding, and the number of older siblings have also been suggested as risk factors for childhood leukemia.

Objective To evaluate possible risk factors for childhood leukemia, including birth weight, parental age, and other risk factors.

Methods This case-control study was conducted from October 2011 to February 2012 in Haji Adam Malik Hospital, Medan. Case subjects were children aged below 18 years and diagnosed with leukemia. Control subjects were children aged below 18 years who were diagnosed with any non-cancerous acute illnesses in this hospital, and individually matched for age and gender to the case subject group. Patients and parents were asked to fill a structured questionnaire. Data was analyzed using conditional logistic regression.

Results A total of 140 subjects were eligible, with 70 subjects in each group. Birth weight ≥4000 g and maternal age ≥35 years were significant risk factors with OR 10.13 (95%CI 1.124 to 91.27) and OR 4.98 (95%CI 1.276 to 19.445), respectively. Paternal age of ≥35 years was not a significant risk factor. Exposure to pesticides was also noted as another significant risk factor (OR=6.66; 95%CI 2.021 to 21.966).

Conclusion High birth weight, advanced maternal age, and exposure to pesticides are risk factors of childhood leukemia. **[Paediatr Indones. 2014;54:358-64.]**

Keywords: *childhood leukemia, birth weight, parental age, risk factors*

Cancer is the second leading cause of death among children. Each year 175,000 children worldwide are diagnosed with cancer, of which an estimated 90,000 will die from the disease.[1] Leukemia is the most common type of childhood cancer, accounting for 30% of all cancers diagnosed in children younger than 15 years.[2,3] The incidence of childhood leukemia has increased annually, but the exact number of new cases is not known because in many countries not all children with cancer are registered and many are not diagnosed correctly. These figures are staggering, given the fact that 70% of all childhood cancers are curable when diagnosed and treated early.[1] Therefore, knowing the symptoms and risk factors of childhood leukemia is important for early detection and increased cure rates.

The etiology of childhood leukemia remains unclear. Epidemiologic studies have examined a number of possible risk factors (e.g., environmental, genetic, or infectious) in an effort to determine the etiology of the disease.[2] There is now growing evidence

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that some childhood leukemia may be explained by a "two-hit model", the first "hit" occurring in utero and often causing a chromosomal translocation and formation of a fusion gene. Any subsequent necessary "hits" are thought to occur postnatally, causing proliferation of the leukemic clone.[4] Birth weight is one of the few prenatal factors reported to be related to the risk of childhood leukemia. High birth weight has been reported to be associated with this disease in many,[4-6] although not all previous studies.[7,8] One interesting hypothesis offered to explain this finding is that high birth weight may be related to production of insulin-like growth factor (IGF-1) in the infant, which may stimulate the growth of myeloid and lymphoid cells.[9] Parental age at birth of more than 35 years has also been reported to be associated with increased risk of childhood leukemia related to germ line mutation, but with inconsistent results.[10-12] Several factors that have been associated with childhood leukemia include exposure to radiation and pesticides, as well as breastfeeding, parental smoking, first born, and infections.[2] However, in Indonesia such studies have not been done. Therefore, this study was conducted to evaluate potential prenatal risk factors, mainly birth weight and parental age, and other risk factors for childhood leukemia.

Methods

We conducted a case–control study from October 2011 to February 2012 in the Pediatrics Department at Haji Adam Malik Hospital, Medan. Children aged below 18 years were included as subjects by consecutive sampling. Case subjects were children diagnosed with all types of leukemia, while control subjects were children diagnosed with any non-cancerous acute illnesses in the hospital. Control subjects were individually matched based on age and gender. Parents and children provided informed consent and filled questionnaires. Those who did not fill the questionnaires completely or suffered other types of cancer were excluded. This study was approved by the Medical Ethics Committee of the University of Sumatera Utara Medical School.

Data were collected using a structured questionnaire conducted in the hospital. Parents or guardians of the children were interviewed using the questionnaire, which included questions on age, sex, age at diagnosis, parental age at birth, birth weight, history of pesticide and radiation exposures, breastfeeding, number of older siblings, parental occupation, parental smoking during pregnancy, family history of leukemia, socio-demographic, and economic characteristics. Secondary data about diagnosis of the children were retrieved from the hospital medical records. Leukemia was diagnosed by clinical symptoms and bone marrow aspiration. History of pesticide and radiation exposures was obtained from the prenatal, during pregnancy and postnatal periods.

Data were processed and analyzed by *Epi Info v.3.4.1* computer software. Univariate analysis was done to assess percentage distributions of characteristics in the case and control groups. Bivariate and multivariate analyses using conditional logistic regression were performed to assess associations between the risk factors and childhood leukemia. Associations are presented as odds ratio (OR) with 95% confidence intervals (CI), with an OR > 1 indicating increased risk for childhood leukemia. All risk variables in the bivariate analysis with a significance level of $P < 0.25$ were included in the multivariate analysis.

Results

Initially, 142 subjects enrolled in the study, 71 with leukemia and 71 without leukemia. From the 142 children, 2 were excluded because they suffered from

Table 1. Demographic data of subjects

Characteristics	Case (n=70)	Control (n=70)
Mean age (SD), years	7.1 (3.84)	7.1 (3.84)
Gender, n (%)		
Male	37 (52.9)	(52.9)
Female	33 (47.1)	33 (47.1)
Ethnicity, n (%)		
Batak	31 (44.3)	38 (54.3)
Jawa	23 (32.9)	21 (30.0)
Aceh	10 (14.3)	2 (2.9)
Melayu	3 (4.3)	6 (8.6)
Padang	1 (1.4)	3 (4.3)
Nias	1 (1.4)	-
Ambon	1 (1.4)	-
Family history of leukemia, n (%)		
Yes	3 (4.3)	0 (0.0)
No	67 (95.7)	70 (100.0)

Table 2. Characteristics of subjects with leukemia

Characteristics	ALL n=50	AML n=20
Mean age (SD), year	7.7 (3.66)	5.6 (3.96)
Gender, n		
Male	25	11
Female	25	8
Diagnosis, n		
ALL FAB L1	49	
ALL FAB L2	1	
AML FAB M0		2
AML FAB M1		13
AML FAB M2		1
AML FAB M4		4
Age at diagnosis, n		
< 2 years	5	6
2-5 years	20	6
6-10 years	17	7
11-15 years	8	1
Family history of leukemia, n		
Yes	2	1
No	48	19

ALL=acute lymphoblastic leukemia, AML=acute myeloblastic leukemia, FAB=French-American-British

other types of cancer. The 140 children who fulfilled the inclusion criteria were divided into two groups: 70 with leukemia as the case group and 70 without leukemia as the control group, individually matched for age and gender.

The mean age in both groups was 7.1 years, and there were more boys (52.9%) than girls (**Table 1**).

Table 2 shows the characteristics of subjects with leukemia, consisting of 50 acute lymphoblastic leukemia (ALL) and 20 acute myeloblastic leukemia (AML) patients. In terms of diagnosis, they were mostly ALL FAB L1 and AML FAB M1. The most common ages at diagnosis were 2–5 years for ALL patients (40%), and 6–10 years for AML patients 7/20.

Table 3 shows the crude odds ratio for the relationship between childhood leukemia and history of pesticide and radiation exposures, birth weight, parental age, breastfeeding, parental smoking, and

Table 3. Bivariate analysis between risk factors and childhood leukemia

Risk factors		Case n (%)	Control n (%)	OR	95% CI	P value
Birth weight, grams	< 2,500	3 (4.3)	2 (2.9)	1.5	0.25 to 8.98	0.657
	2,500 – 3,999	58 (82.9)	67 (95.7)	Ref.	-	-
	≥ 4,000	9 (12.9)	1 (1.4)	8.99	1.15 to 70.76	0.037
Maternal age, years	<20	6 (8.6)	4 (5.7)	1.5	0.42 to 5.32	0.529
	20 – 34	53 (75.7)	61 (87.1)	Ref.	-	-
	≥35	11 (15.7)	5 (7.1)	2.2	0.79 to 0.54	0.144
Paternal age, years	20 – 34	50 (71.4)	56 (80.0)	Ref.	-	-
	≥ 35	20 (28.6)	14 (20.0)	1.55	0.72 to 3.29	0.261
Exposure to pesticides	Yes	23 (32.9)	5 (7.1)	5.25	1.80 to 15.29	0.002
	No	47 (67.1)	65 (92.9)	Ref.	-	-
Radiation exposure	Yes	1 (1.4)	6 (8.6)	0.17	0.02 to 1.38	0.097
	No	69 (98.6)	64 (91.4)	Ref.	-	-
Breastfeeding	No	18 (25.7)	20 (28.6)	1.22	0.51 to 2.95	0.655
	Yes	52 (74.3)	50 (71.4)	Ref.	-	-
Paternal smoking	Yes	54 (77.1)	53 (75.7)	1.08	0.49 to 2.37	0.841
	No	16 (22.9)	17 (24.3)	Ref.	-	-
Birth order	First born	26 (37.1)	26 (37.1)	1.0	0.49 to 2.05	1.0
	Not first born	44 (62.9)	44 (62.9)	Ref.	-	-

Table 4. Multivariate analysis between risk factors and childhood leukemia

Risk factors	Coefficient	Adjusted OR	95% CI	P value
Birth weight ≥4,000 grams	2.315	10.13	1.12 to 91.27	0.039
Maternal age ≥35 years	1.606	4.98	1.28 to 19.45	0.021
Exposure to pesticides	1.896	6.66	2.02 to 21.97	0.002

number of older siblings. We found that exposure to pesticides and birth weight ≥ 4000 g were significantly associated with increased risk of childhood leukemia with OR 5.25 (95%CI 1.8 to 15.29) and OR 8.99 (95%CI 1.15 to 70.76), respectively.

Table 4 shows the adjusted odds ratios from multivariate analysis with conditional logistic regression for childhood leukemia. We found that children with birth weight ≥ 4,000 g, maternal age at birth ≥ 35 years, and exposure to pesticides significantly increased the risk for childhood leukemia with OR 10.13 (95%CI 1.12 to 91.27), OR 4.98 (95%CI 1.28 to 19.45), and OR 6.66 (95%CI 2.02 to 21.97), respectively.

Discussion

We found statistically significant associations between high birth weight, advanced maternal age, and exposure to pesticides to increased risk of childhood leukemia. Maternal smoking was not analyzed because none of the subjects' mothers smoked during or before pregnancy. Socioeconomic factor was also not analyzed because most patients in Haji Adam Malik Hospital were of low socioeconomic background and did not accurately represent the general population.

Birth weight in our study was divided into three categories: low birth weight (< 2,500 g), normal birth weight (2,500 – 3,999 g), and high birth weight (≥ 4,000 g). It has been hypothesized that very low birth weight may be associated with childhood cancer, because these children are exposed to multiple medical interventions in NICUs at a time when their antioxidant capacity is decreased and xenobiotic metabolizing enzyme expression is variable.[13,14] However, we found no significant association between low birth weight and childhood leukemia (OR 1.5; 95%CI 0.25 to 8.98). In fact, we found a strong association between high birth weight (≥ 4,000 g) and the risk of childhood leukemia (OR 10.13; 95%CI 1.124 to 91.27). This result was consistent with that of other studies.[4-6,15-17] High birth weight may result from high levels of growth factors in utero. These growth factors might increase the risk of childhood leukemia by inducing proliferative stress on the bone marrow. Biologic data demonstrate that birthweight is positively correlated with circulating levels of IGF-1.[9,18] Insuline growth factor-1 is important for blood formation and regulation and has been shown to stimulate the growth of both myeloid and lymphoid cells in culture.[9]

The risk of childhood leukemia in high birth weight children has also been associated with gestational age. A German study reported a higher risk of childhood leukemia in children with high birth weight and large for gestational age (LGA).[19] High birth weight has also been associated with some maternal factors including maternal weight, multi-parity, diabetes, race, ethnicity, maternal diet, and smoking during pregnancy. A study in New York reported that high birth weight was associated with childhood leukemia only when mothers were not overweight (< 80 kg) during pregnancy.[20] We did not analyze this factor because of the difficulty in obtaining information on maternal status during pregnancy.

Advanced parental age has generally been associated with higher risk of childhood leukemia, but not all studies have observed this relationship.[21-24] One study reported an increased risk of childhood leukemia in children with maternal age < 20 years at time of delivery.[13] The independent associations of maternal and paternal age on childhood cancer risk are difficult to separate, but most studies found an association to maternal age, in particular.[11,12,23] We found a statistically significant association between childhood leukemia and maternal age ≥ 35 years at the time of delivery (OR 4.98; 95%CI 1.28 to 19.45), but not with the paternal age (OR 1.55; 95%CI 0.72 to 3.29).

Similar to previous studies,[25,26] we found a statistically significant association between exposure to pesticides and risk for childhood leukemia (OR 6.66; 95%CI 2.02 to 21.97). The risk of childhood leukemia has been seen particularly in paternal exposure to pesticides, because of a direct effect on sperm DNA and accumulation of pesticides in the seminal fluid.[25,27] The parental occupation of farming may indicate a potential history of exposure to pesticides. Household exposure to pesticides was assessed by maternal use of insecticides at home. However, we did not analyze the frequency or duration of exposure because of difficulty in obtaining accurate data.

We also investigated other possible risk factors for childhood leukemia but found no significant

associations with factors such as radiation exposure, breastfeeding, paternal smoking, and number of older siblings. Radiation exposure was found to not be associated with increased risk of childhood leukemia (OR 0.17; 95%CI 0.02 to 1.38), in contrast to previous studies.[28,29] This apparent contradiction may have been due to the control group having been collected from the outpatient clinics, especially from the Division of Respirology and Gastroenterology, where most patients had undergone radiologic imaging.

Breastfeeding was found to not be associated as a protective factor for childhood leukemia. Previous studies have shown inconsistent results between breastfeeding and leukemia.[30-32] Parental smoking was also not associated with increased risk of childhood leukemia in our study. Results from previous studies were also inconsistent.[33-36] The number of cigarettes smoked per day was shown to be associated with the increased risk of childhood leukemia.[33] We did not analyze for an association between the increased risk and number of cigarettes smoked per day because of the difficulty in collecting accurate information.

The association between birth order and childhood leukemia has been debated for a long time. Greaves' delayed-infection hypothesis suggested that children with older siblings who have contact with infectious agents in infancy are less likely to develop leukemia than first born or only children.[37] However, other results from other studies have been inconsistent.[10,38,39] We found no evidence of an association between number of older siblings and childhood leukemia. One of the reasons for this might be because of the low socioeconomic status of subjects. They mostly live in crowded areas, so even first born children may have been exposed to early infection in infancy.

Several limitations that usually occur in hospital-based, case-control studies have been identified. First, study subjects were not representative of all cases within the population. Second, some selection bias may have been present, as the control group was limited to hospital patients. It would have been better if the controls had been from the general population. Third, information recall bias may occur in case-control studies, since some information is based on memory. However, in our study, the case and control groups were individually matched for age and gender, and information about paternal age was collected from the identity cards of each family, in order to reduce bias.

To our knowledge, this is the first study in Indonesia to assess prenatal risk factors of childhood leukemia, such as birth weight, parental age at birth, and other factors. Our findings showed that high birth weight, advanced maternal age, and exposure to pesticides were associated with increased risk of childhood leukemia. Awareness of these risk factors may help in early detection and prevention of childhood leukemia. However, leukemia is assumed to be a multifactorial disease that occurs when all risk factors interact. Knowing the risk factors of childhood leukemia is important, especially for general practitioners, for early detection and increased cure rates. Further studies can be done on a larger scale with a prospective cohort to assess the risk factors for childhood leukemia.

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