



RELATIONSHIP BETWEEN ALLERGIC DISEASES AND ATOPY WITH LEUKEMIA IN CHILDREN

Paediatrics

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ABSTRACT

Background: Allergic diseases is a risk factor for leukemia but can also become a protective factor. Immune response activation induce preleukemia cells or allergic diseases increases the capacity of the immune system to detect and destroy aberrant cells.

Objective: To determine the relationship of allergic diseases and atopy with the occurrence of leukemia in children.

Methods: A case-control study conducted in pediatric allergy immunology and hemato-oncology division November 2013 to February 2014. Children aged 3-17 years old with leukemia in the study group, and children without leukemia as the control group. The diagnosis of leukemia was established by bone marrow puncture. Skin prick tests to assess atopy and International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to assess allergic diseases. We used the x2 test, and Fischer exact, logistic regression for statistical analysis.

Results: Examination of 70 subjects at 35 of leukemia and 35 children without leukemia. One child found allergic disease and atopy in 13 children in the case group, while in the control group we found 9 allergic disease and atopy in 31 children. There was a relationship between allergic diseases with leukemia ($P=0.006$). There was a significant relationship between atopy with leukemia ($P=0.0001$). Atopy in children is a protective factor against leukemia ($OR < 1$).

Conclusion: There was significant relationship between allergic diseases and atopy with leukemia and atopy acts as a protective factor against leukemia.

KEYWORDS

Leukemia children, atopy, allergic disease

Introduction

Leukemia is blood cell malignancy which comes from bone marrow, identified by the proliferation of white blood cell with manifestation of abnormal cells in peripheral blood.¹ Leukemia was divided into acute and chronic which was distinguished from acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML), based on the domination of myeloblast or lymphoblast cells.² The prevalence of acute leukemia in childhood was around 30-40% of the malignancy.¹

Allergic diseases is referred to clinical forms such as asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis, and food allergy which were caused by the mechanism of immunology.³ Data ecology analysis from *The International Study of Asthma and Allergies in Childhood* (ISAAC) reveals that the environmental aspects such as economic development, food factors, climate, and infection influence some of these variations.⁴

Several studies indicated that atopic disease became the protection for ALL in childhood.⁵⁻⁷ Another study showed that allergic disease became the risk factor for ALL in childhood,⁸ but there is no relationship between allergy and leukemia development.⁹ It was not clear whether the immunology mechanism of allergic disease can influence the risk for leukemia. One of the possibilities was that allergic condition can increase alertness of immune system in monitoring to identify, eliminate, and destroy cell deviation in order to avoid the development of malignant cells in childhood.¹⁰⁻¹¹ The objective of the study was to determine the relationship of allergic diseases and atopy with the occurrence of leukemia in children.

Methods

A case-control study was conducted at H. Adam Malik Hospital, Medan, from November 2013 to February 2014. The subjects were children with leukemia as the case and children without leukemia as the control, which were adjusted for age and sex. The inclusion criteria were children who did not consume steroid, not use topical steroid in the last one day, and not use antihistamine in the last three days. The exclusion criteria was children with dermatographism. The study was

approved by the Ethics Committee of Medical School, University of Sumatera Utara.

We explained about the study and the examination which would be conducted. The subjects of the study received permission from their parents by fill out and sign an informed consent. Skin prick test was performed by researcher using ten allergens, including food allergens such as crabs, shrimps, cow's milk, chicken, chocolate, peanuts, and chicken egg white, and inhalan allergens such as yeast, chicken feather, and house dust mites in order to examine the atopy.¹² ISAAC questionnaires which had been modified were distributed to find out the manifestation of allergic diseases: they were bronchial asthma (BA), allergic rhinitis (AR) and atopic dermatitis (AD).

The data were analyzed by using Chi Square test or Fisher exact test in order to assess the relationship of allergic disease and atopy with leukemia. Odds Ratio (OR) was used to assess the risk factor with multivariate analysis, using logistic regression test at the significance interval of 95% and p-value < 0.05 which was considered statistically significant.

Results

There were 70 subjects that fulfill the inclusion and exclusion criteria. 35 children with leukemia which consist of 12 acute myeloid leukemia (AML), 5 chronic myeloid leukemia (CML), and 18 acute lymphocytic leukemia (ALL). Other 35 children without leukemia as control. Skin prick test was examined and ISAAC questionnaires were distributed.

Table 1. Characteristics data of subjects

VARIABLE	LEUKEMIA (N = 35)	CONTROL (N = 35)
AGE, MEAN(SD), YEARS	9.4 (4.83)	9.6 (4.74)
AGE, N		
BOYS	19	19
GIRLS	16	16
WEIGHT, MEAN (SD), KG	28.1 (13.14)	32.4 (15.38)

HEIGHT MEAN (SD), CM	128.0 (23.76)	130.9 (25.54)
NUMBER OF SIBLINGS, MEAN (SD)	2.7 (1.86)	2.3 (1.45)
BIRTH ORDER, N		
1	10	14
2	12	8
3	3	5
>4	10	8
TYPES OF LEUKEMIA, N		
ALL	18	-
AML	12	-
CML	5	-
ALLERGIC DISEASES, N		
BRONCHIAL ASTHMA	0	3
ALLERGIC RHINITIS	1	7
ATOPIC DERMATITIS	0	1
ATOPY, N	13	31

Table 1. showed the characteristics of the study subjects consisted of mean age, sex, weight, number of siblings and birth order did not difference between groups of leukemia compared with controls.

Table 2. Relationship between allergic disease and atopy with leukemia

VARIABLE	LEUKEMIA (N = 35)	CONTROL (N = 35)	95%CI	P
ALLERGIC DISEASE				
YES	1	9	0.01 - 0.714	0.006
NO	34	26		
ATOPY				
YES	13	31	0.215 - 0.567	0.0001
NO	22	4		

Table 2. showed that there was significant relationship between allergic disease and leukemia (P= 0.006 and 95%CI= 0.01-0.714). There was a significant relationship between atopy with leukemia (P = 0.0001 and 95%CI=0.215-0.567).

Table 3. Relationship between types of allergic diseases with leukemia

ALLERGIC DISEASES	LEUKEMIA (N = 35)	CONTROL (N = 35)	95% CI	P
BRONCHIAL ASTHMA				
YES	0	3	1.630 – 2.690	0.239
NO	35	32		
ALLERGIC RHINITIS				
YES	1	7	0.014 – 1.014	0.055
NO	34	28		
ATOPIC DERMATITIS				
YES	0	1	1.597 – 2.578	1.000
NO	35	34		

Table 3. showed there was significant relationship between three types of allergic disease with leukemia (P>0.05)

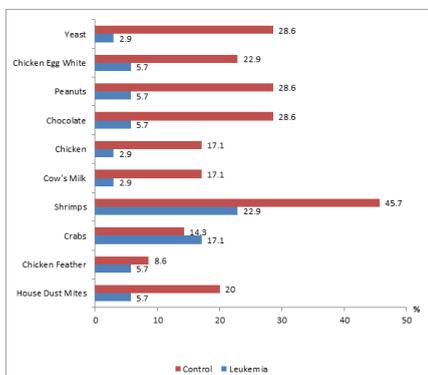


Figure. Histogram graph percentage of the result of skin prick test

The percentage of the positive result on skin prick test in leukemia group mostly found in allergens such as shrimp and crab, while in the control group, the result of positive skin prick test mostly found in the allergens such as shrimp, chocolate, peanut, chicken egg white, and yeast.

Table 4. Relationship between type of allergic diseases and atopy with leukemia

VARIABLE	OR	95% -CI
BRONCHIAL ASTHMA	0.000	0.000 - .
ALERGIC RHINITIS	0.200	0.018 - 2.283
ATOPIC DERMATITIS	0.000	0.0001 - .
ATOPY	0.097	0.026 – 0.359

Table 4. showed that, based on the result of multivariate analysis, using logistic regression test, there was relationship between variables of bronchial asthma, allergic rhinitis, atopic dermatitis, and atopy with leukemia. Among the four variables, only atopy which showed significant relationship with leukemia as a protective factor (OR = 0.097 and 95% CI 0.026 - 0.359).

Discussion

In this study, subjects were assessed characteristics did not differ between the groups with the control leukemia. Type of leukemia were observed in this study that most types of ALL and the highest manifestation of allergic disease in the control group. The study was consistent with previous studies in which the population controls matched for age and sex with the case. Data obtained from questionnaires on most types of leukemia group ALL.⁶

In this study there was significant relationship between allergic diseases with leukemia (P = 0.006). There was significant relationship between atopy with leukemia (0.0001). The results of positive skin prick tests with the highest number on shrimp and crab allergens in children leukemia, whereas the control group the number of allergens most shrimp, chocolate, peanuts, egg white chicken and yeast. This research is in accordance with previous studies, in which the percentage of allergies increased in the control group and vice versa allergy percentage decreased in cases of leukemia.^{13,14} Results of previous studies using data retrieved from the medical records, there atopy before the children suffering from leukemia was significantly relationship with ALL. Significant relationship was also found in atopic or eczema and bronchial asthma after suffering from leukemia.⁹ In the third study showed allergic diseases are bronchial asthma, allergic rhinitis, and atopic dermatitis no significant relationship with leukemia (P> 0.05). In the study there were two control groups of children who have more than one type of manifestation of allergic disease, whereas in children leukemia there is only one type of manifestation of allergic disease.

The results of this study was not consistent with previous ones which showed increasing the risk of ALL was related with the number of allergies and the types of allergy such as allergic rhinitis, asthma and urticaria.¹⁴ Other study also assessed the relationship between allergy and leukemia. The allergy which was asthma, allergic rhinitis, food or medicine allergy, and eczema. More than one allergic disease was related to the risk of leukemia. The risk of leukemia decreased when a child had two or more allergies for all age group and all types of leukemia. Generally the risk of leukemia decreased when a child had more than one allergic diseases and the number of siblings.¹⁰ The previous studies assessed all types of leukemia with the history of allergy which was related with the decrease in the risk of leukemia, but the relationship between allergic disease and the types of leukemia was not found.¹² Multivariate analysis in this study with multiple variables assessment atopy only show a significant association with leukemia (OR = 0.097 and IK95% = 0.026-0.359). Atopy have protective factors with the occurrence of leukemia (OR <1).

The study was appropriate with previous studies which showed that there was relationship between atopy and ALL in childhood, while the possibility for atopy was 31% lower in the case than the control group and 21% lower for asthma, 26% lower for eczema, and 45% lower for allergic rhinitis.¹¹ The prevalence of atopy significantly decreased in ALL type of leukemia which indicated that atopy was the protector for ALL development.^{15,16} In general, there appeared to be a small protective effect for each of the allergy-related disorders with respect

to CLL.¹⁷ The result of the previous study also showed that allergy could protect from the incidence of acute leukemia, and allergic disease in a child statistically had significant relationship with his parents.^{18,19}

In the study, relationship between leukemia and history of allergy in family was not assessed. Besides that, questionnaires and skin prick test were not conducted to the parents and siblings so that the risk of allergy in a leukemia child and the control group was not known. The limitation of the study by using a number of small samples and case-control design could not conclude the causality and analyze the length or the amount of protective factor of allergic disease and atopy against the incidence of leukemia. The study used questionnaires in providing diagnoses of bronchial asthma, allergic rhinitis, and atopic dermatitis which might have more recall bias. Nevertheless, this study used the translation of ISAAC questionnaires which had been validated and standardized to be used in epidemiology researches throughout the world.²⁰

Conclusion

There was significant relationship between allergic diseases and atopy with leukemia, and atopy acts as a protective factor against leukemia. there was no significant relationship between the type of allergic disease with leukemia.

REFERENCES

1. Permono B, Ugrasena IDG. Leukemia Akut. In: Permono HB, Sutaryo, Ugrasena IDG, Windiastuti E, Abdulsalam M, editors. Buku Ajar Hemato-Onkologi Anak. Jakarta: Ikatan Dokter Anak Indonesia, 2005. p. 236-47
2. Kim AS, Eastmond DA, Preston RJ. Childhood acute lymphocytic leukemia and perspectives on risk assessment of early-life stage exposures. *Mutation Res.* 2006;613: 138-160
3. McGeady SJ. Immunocompetence and allergy. *Pediatrics.* 2004;113:1107-13
4. Asher MI, Montefort S, Bjorksten B, Lai CKW, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet.* 2006;368:733-43
5. Rudant J, Orsi L, Manegaux F, Petit A, Baruchel A, Bertrand Y, et al. Childhood acute leukemia, early common infections, and allergy: The ESCALE. *Am J Epidemiol.* 2010;172:1015-27
6. Schuz J, Morgan G, Bohler E, Kaatsch P, Michaelis J. Atopic disease and childhood acute lymphoblastic leukemia. *Int J Cancer.* 2003;105:255-60
7. Linabery AM, Jurek AM, Duval S, Ross JA. The Association between atopy and childhood/Adolescent leukemia: A meta-analysis. *Am J Epidemiol.* 2010;171:749-64
8. Wen W, Shu XO, Linet MS, Neglia JP, Potter JD, Trigg ME, et al. Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States). *Cancer Causes and Control.* 2000;11:303-07
9. Spector L, Groves F, Destefano F, Liff J, Klein M, Mullooly J, et al. Medically recorded allergies and the risk of childhood acute lymphoblastic leukemia. *Eur J Cancer.* 2004;40:579-84
10. Hughes AM, Lightfoot T, Simpson J, Ansell P, McKinney PA, Kinsey SE, et al. Allergy and risk of childhood leukemia: Results from the UKCCS. *Int J Cancer.* 2007;121:819-24
11. Lindelof B, Granath F, Tengvall-Linder M, Ekblom A. Allergy and cancer. *Allergy.* 2005;60:1116-20
12. Arbes SJ, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: Results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol.* 2005;116:377-83
13. Soderberg KC, Jonsson F, Winquist O, Hagmar L, Feychting M. Autoimmune diseases, asthma, and risk of haematological malignancies: A nationwide case-control study in Sweden. *Eur J Cancer.* 2006;42:3028-33
14. Chang JS, Tsai YW, Tsai CR, Wiemels JL. Allergy and Risk of Childhood Acute Lymphoblastic Leukemia: A population-based and record-based study. *Am J Epidemiol.* 2012;1-8
15. Musolino C, Allegra A, Minciullo PI, Gangemis. Allergy and risk of hematologic malignancies: associations and mechanisms. *Leukemia Research.* 2014; 38:1137-44
16. Cooper GS, Kamel F, Sandler DP, Davey FR, Bloomfield CD. Risk of adult acute leukemia in relation to prior immune-related conditions. *Cancer Epidemiol, biomarkers & prevent.* 1996; 5:867-72
17. Linet MS, McCaffrey LD, Humphrey RL, Brookmeyer R, Van Natta ML, Tielsch JM, et al. Chronic lymphocytic leukemia and acquired disorders affecting the immune system: A case-control study. *JNCI.* 1986; 77:371-8
18. Schuz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Association of childhood leukemia with factors related to the immune system. *British J Cancer.* 1999; 80:585-90
19. Rosenbaum PF, Buck GM, Brecher ML. Allergy and infectious disease histories and the risk of childhood acute lymphoblastic leukemia. *Paed and Perinatal Epidemiol.* 2005;19:152-64
20. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J.* 1995;8:483-91