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Modifiable and Non-Modifiable Factors Affecting the Risk of Childhood Leukemia: An Overview of Meta-Analysis

Rana Tafrishi[1], Benyamin Seyfari[2], Rahele Rahimi[3], Zahra Chaichi[1], *Amirreza Dehghan Tarazjani[4], Nahid Marvi[5], Mahbubeh Maazallahi[6], Zari Dolatabadi[7], Farzane Ashrafinia[8]

[1]Pediatrician, Department of Pediatrics, Faculty of Medicine, Mashhad university of Medical Sciences, Mashhad, Iran. [2]Department of Surgery, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran. [3]Fellowship of Pediatric Intensive Care, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [4]General Physician, Mashhad University of Medical Sciences Mashhad, Iran. [5]MSc Counseling in Midwifery, Department of Nursing and Midwifery, Neyshabur University of Medical Sciences, Neyshabur, Iran. [6]Nursing Research Center, Department of Critical Care Nursing, Kerman University of Medical Sciences, Kerman, Iran. [7]Department of Reproductive Health and Midwifery, School of Nursing and Midwifery, Iran University of Medical Sciences, Tehran, Iran. [8]Student Research Committee, Kerman University of Medical Sciences, Kerman, Iran.

Abstract

Background: Numerous meta-analyses of childhood leukemia have been published, but no comprehensive study has examined the factors influencing childhood leukemia. We aimed to scrutinize the modifiable and non-modifiable factors affecting the risk of childhood leukemia.

Materials and Methods: In this overview, two independent researchers screened the articles studying the effect of modifiable and non-modifiable factors on the childhood leukemia from the related databases, including Scopus, EMBASE, Cochrane, Web of Science, and Medline, without time and language restrictions from inception up to March 10, 2020.

Results: Eight meta-analyses were included in this overview. Breastfeeding compared with non-breastfeeding was associated with 9% reduction in the risk of childhood leukemia (OR = 0.91). The children with the birth weight of ≥4,000 g were at a higher risk of acute lymphoblastic leukemia compared with those with low birth weight (OR = 1.26, 95% CI = 1.17, 1.37). There was a significant relationship between childhood leukemia and residential pesticide exposure (SOR=1.57). There was a relationship between influenza during pregnancy and higher risk of ALL (POR=3.64; 95% CI = 1.34-9.90), and childhood leukemia (POR=1.77). The childhood AML had a statistically significant relationship with no alcohol consumption during pregnancy. The SOR of childhood ALL had an association with paternal smoking. A statistical relationship exists between magnetic field intensity of ≥0.4 μT and childhood leukemia. The exposure to NO_2 and benzene exhibited the OR of 1.64 (95% CI = 0.91-2.95) and 1.21 (95% CI = 0.97-1.52), respectively.

Conclusion: Decreased breastfeeding, high birth weight, viral infections during pregnancy, alcohol consumption, maternal exposure to direct and indirect smoking, and exposure to electromagnetic fields and airborne pollutants are found to be significant risk factors for childhood leukemia.

Key Words: Affecting factors, Childhood, Leukemia, Risk factors.

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Corresponding Author:

Amirreza Dehghan Tarazjani, MD, General Physician, Mashhad University of Medical Sciences Mashhad, Iran.

Email: Armdehghan@gmail.com

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1- INTRODUCTION

Leukemia is caused by the transformation of a hematopoietic cell and is categorized into four major types, depending on the type of the cell (either lymphoid or myeloid), and the acute or chronic nature of disease: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), and chronic lymphoid leukemia (CLL) (1). Although childhood leukemia is classified as a relatively rare disease (2), it is the most common type of cancer in children, accounting for 30% of childhood cancers under the age of 15. Among the different types, ALL is seen in 80%, and AML in 20% of children. According to World Health Organization (WHO), the annual incidence of leukemia in the world is 250,000 and its global mortality rate is 76%.

The cost of treatment, the length of hospital stay, and the psychological problems caused by this disease indicate the resulting heavy economic and social burden. In Iran, leukemia is likewise a common type of cancer and its prevalence has increased over time. Accordingly, numerous etiological studies have been conducted in different countries, and a significant relationship has been identified in some cases between the disease and genetic, environmental, and demographic factors (1). After cardiovascular diseases, cancer is the second leading cause of death in the world. The prevalence of hematological cancers is increasing in Western countries. Toxic agents exert their carcinogenic effects by damaging the DNA of blood progenitors and eventually lead to malignancy (3).

Although the exact causes of leukemia have not yet been determined, age-related factors at the time of diagnosis, white blood cell counts, parental occupations, radon and benzene, pesticides, ionizing radiation and magnetic fields (MFs), nutritional factors, and genetic and chromosomal abnormalities (e.g., Down syndrome) play a role in the risk of this cancer (4). Various strengths of electric and magnetic fields (EMFs) increase the risk in the blood system. Acute childhood leukemia worsens near high-voltage power lines (225-400 kV). The causes of leukemia are still controversial in different studies (5). Numerous meta-analyses evaluated the association of leukemia with weight (6), residential pesticide exposure (7), influenza (8), alcohol consumption (8), smoking (9), and NO_2 exposure (10).

Numerous meta-analyses of childhood leukemia have been published, but no comprehensive study has examined the factors influencing childhood leukemia. In order to introduce these factors to the medical community and patients, this overview aims to scrutinize the modifiable and non-modifiable factors affecting the risk of childhood leukemia.

2- MATERIALS AND METHODS

In this overview, all meta-analyses evaluating the association between effective factor and childhood leukemia were searched on the electronic databases of Scopus, EMBASE, Cochrane, Web of Science, and Medline (via PubMed) with no language or time restrictions (up to March 10, 2010). Two independent researchers performed the search process and a supervisor resolved any discrepancies in this regard. Two reviewers initially reviewed the abstracts of searched articles, downloaded their full texts to review carefully, and chose the relevant studies independently. Finally, the articles that met the inclusion criteria were enrolled in the review, and relevant references were reviewed to find further studies. The third reviewer resolved possible discrepancies.

3- RESULTS

Eight related meta-analyses were selected for our overview. In the first

meta-analysis on 15 studies (11), breastfeeding compared with non-breastfeeding was associated with 9% reduction in the risk of childhood leukemia (Odds ratio (OR) = 0.91; 95% confidence interval (CI) = 0.80-1.04).

In the second meta-analysis on 18 studies from 1962 to 2002 including 10,282 children with leukemia, the children with the birth weight of ≥4,000 g were at a higher risk of acute lymphoblastic leukemia compared with those with low birth weight (OR = 1.26, 95% CI = 1.17-1.37). In addition, the findings were in line with a dose-response effect (OR = 1.14/ birth weight increase of 1,000g, 95% CI = 1.08-1.20) (6).

In the third meta-analysis, combining all studies showed a significant association between childhood leukemia and residential pesticide exposure (summary odds ratio (SOR) = 1.57; 95% CI= 1.27-1.95) with no publication bias. There was a significant elevation in the risk factors of all types of leukemia, particularly pregnancy exposure, indoor exposure, and prenatal exposure to insecticides (7).

In the fourth meta-analysis on 20 studies (12), there was an association between influenza during pregnancy and higher risk of ALL (pooled OR (POR) = 3.64; 95% CI=1.34-9.90), and childhood leukemia (POR = 1.77; 95% CI = 1.01-3.11). There was an association between higher risk of childhood leukemia and rubella (POR = 2.79; 95% CI = 1.16-6.71), and varicella (POR = 10.19; 95% CI = 1.98-52.39) infection.

In the fifth meta-analysis on 21 trials within categorical and dose-response (8), the childhood AML had a statistically significant association with no alcohol consumption during pregnancy (OR = 1.56; 95% CI = 1.13-2.15).

In the sixth meta-analysis, the SOR of childhood ALL had an association with paternal smoking with a value of 1.25 (95% CI = 1.08-1.46) for preconception, 1.24 (95% CI = 1.07-1.43) during pregnancy, 1.24 (95% CI = 0.96-1.60, %) after birth, and 1.11 (95% CI = 1.05-1.18) during any time period (9).

In the seventh meta-analysis stratifying 11,699 cases and 13,194 controls from nine studies based on various cut-off points of exposure (5), it was found that a statistically significant association exists between magnetic field intensity ≥0.4 μT and childhood leukemia regarding the reference <0.1 μT (OR = 2.43, 95% CI = 1.30–4.55 for ALL, and OR = 1.57, 95%CI = 1.03-2.40, for total leukemia).

In the eighth meta-analysis (10), an increased risk of childhood leukemia was seen in subjects who were stuck in traffic congestion, as the criteria for evaluating exposure, within the highest exposure group (OR = 1.07, 95% CI = 0.93-1.24), though there was evidence of publication bias. The exposure to NO_2 and benzene exhibited the OR of 1.64 (95% CI = 0.91-2.95), and 1.21 (95% CI = 0.97-1.52), respectively.

4- DISCUSSION

The role of the most important factors influencing the childhood leukemia, despite different studies on its risk factors, remains a question. The sources and references of the present study are the findings of eight meta-analyses reviewing the modifiable (genetic predispositions) and non-modifiable (environmental) risk factors. Aminity et al. (2015) reported that breastfeeding and its continuation are effective factors in preventing leukemia. The presence of breast milk stem cells expressing embryonic stem cell-like characteristics and their absorption in neonatal organs have added to the hypothesis of the important role of breastfeeding in reducing the risk of leukemia (11). Hjalgrim et al. (2003) showed a significant association between ALL and the presence of specific

chromosomal translocation associated with weight gain in children, but the evidence in AML was unclear. The sequence of weight gain was hypothesized following an increase in growth factors and the association of elevated growth factor with increased bone marrow volume and high risk of hematopoiesis in these studies. This association was significant with the ratio of increase in odds ratio per 1000 grams of birth weight gain (6).

Van Maele-Fabry (2018) stated that exposure to pesticides, especially during the prenatal period, can be a potential risk factor for both acute types of leukemia (ALL and AML / ANLL), which has been evaluated in previous studies. In this meta-analysis, domestic and residential exposure to domestic insecticides, herbicides, and other environmental pesticides revealed a positive and significant association with childhood leukemia. There is documented evidence of the impact of chemical exposure in the laboratory on the incidence of chromosomal abnormalities in stem cells derived from umbilical cord (prenatal exposure) and bone marrow (childhood exposure) followed by abnormal hematopoietic processes in Leukemia (13).

Jian-Rong He et al. (2020) showed a significant association between influenza, varicella, and rubella infections and an increased risk of ALL, while a stronger association was reported between influenza and leukemia compared to other infections. The involvement of genetic and immune mechanisms following exposure to intrauterine infections and the occurrence of B-cell synthesis impairment in the adaptive immune response to viral loads were mysteriously proposed in the development of childhood leukemia (12).

Latino-Martel et al. (2010) showed the association of maternal alcohol consumption with the risk of AML, though the association between ALL and alcohol consumption during pregnancy was not reported. This could be due to the limited number of studies and their study design. Some studies have suggested that the dosage and type of alcohol may be involved in the development of the disease (14). The findings of a review study by Liu et al. (2011) did not find a clear and significant association in evaluating the risk factor of active and passive smoking of the mother before and during pregnancy, but totally supported the relationship between exposure to smoking and the risk of ALL. In these studies, there were reports of a possible mechanism of mutation in the sperm gene content and changes in the pattern of cell gene expression in the direct and indirect exposure of parents to smoking before and after pregnancy and an increased risk of ALL (9). The increasing use of cellphones and personal communication services has made it necessary to increase the number of transmitters to support these devices (15). The potential association between childhood leukemia and EMFs has been the focus of both the scientific community and the general public. Many researchers have hypothesized that exposure to EMFs is an environmental risk factor for childhood leukemia and have therefore conducted scientific studies to investigate this association. With the increasing prevalence of childhood leukemia over the past 40 years, efforts to reduce the overall burden of the disease are essential (2).

Zhao et al. (2014) suggested a positive association between EMFs and childhood leukemia risk based on the results of homogeneous review studies. The results of these studies found that exposure to radiation between 0.2 and 0.4 μT could have adverse effects (16). Merzenich et al. (2008) found no significant increase in the risk of exposure to radiofrequency electromagnetic fields (RF-EMF) emitted from broadcast towers and childhood leukemia (17). In an epidemiological study by Feychting (2011) on cell phones and radio fields and its health effects on

children, it has been strongly recommended to monitor and control the development of brain tumors (18). The findings of a meta-analysis by Filippini et al. (2015) showed an increased risk of various types of leukemia, especially ALL and AML, as a result of exposure to air pollutants caused by potentially toxic vehicle exhaust gas and NO2 emissions.

Some findings showed a greater impact of prenatal exposure and effects of postnatal exposure on the risk of leukemia. The benzene metabolite para-benzoquinone has a strong association with destruction of the genetic content of cells. In the literature review, gene mutations and translocations following the binding of airborne toxic metabolites are similar to cellular changes in leukemia. In addition, the immune response to these compounds emphasizes the importance of their carcinogenic potential (19). In general, the results of meta-analyses indicated the limitations of the case-control design of the reviewed studies. Although there is a significant association between the risk of childhood leukemia and prenatal or postnatal environmental exposure, carefully monitoring the impact of confounding factors on cancer risk and the need for prospective studies are important in examining the importance of risk factors and their prevention.

Based on data published in various studies on risk factors for leukemia, the results of some studies have been consistent and some have been treated with skepticism, despite control over other factors. Given that most results were derived from retrospective studies, it is necessary to conduct future investigations. In each study, the exact dose and duration of exposure were discussed and recommended in subsequent studies. In addition, most studies have focused on the two types of ALL and AML, which, despite their similarities, are reported to be affected by various risk factors in different ways. Therefore, the need for more extensive studies with more accurate control of factors affecting the incidence of childhood leukemia should be considered.

5- CONCLUSION

The findings of the present meta-analysis reported different risk factors for childhood leukemia, especially ALL and AML. Decreased breastfeeding, high birth weight, viral infections during pregnancy, alcohol consumption, maternal exposure to direct and indirect smoking, and exposure to electromagnetic fields and airborne pollutants are known to be significant risk factors for childhood leukemia. Due to the limitations of previous meta-analyses, it is recommended to conduct prospective studies and carefully control of other modifiable and non-modifiable confounding factors.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Madmoli M. Clinical and laboratory finding in children with leukemia: A systematic review. International Journal of Research Studies in Science, Engineering and Technology. 2018;5(10):1-6.

2. Callahan K-J. Residential Exposure to Electromagnetic Fields and Childhood Leukemias: A Meta-analysis: The University of Texas School of Public Health; 2018.

3. Nikbakht Dastjerdi M. Investigation of p53 codon 72 polymorphism in patients with acute myeloid leukemia in Iran. Scientific Journal of Iran Blood Transfus Organ. 2015;12(1):23-13.

4. Eghbalian M, Amiri S, Roshanaei G, Esfahani H, Ahmadi M, Assadi Sajadi N. Common malignancies in children (under 18 years) and its affected factors in Hamedan Province during 1386 to 1395. SSU_Journals. 2018;25(11):897-906.

5. Zhao L, Liu X, Wang C, Yan K, Lin X, Li S, et al. Magnetic fields exposure and childhood leukemia risk: a meta-analysis

based on 11,699 cases and 13,194 controls. Leukemia research. 2014;38(3):269-74.

6. Hjalgrim LL, Westergaard T, Rostgaard K, Schmiegelow K, Melbye M, Hjalgrim H, et al. Birth weight as a risk factorfor childhood leukemia: a meta-analysis of 18 epidemiologic studies. American journal of epidemiology. 2003;158(8):724-35.

7. Van Maele-Fabry G, Gamet-Payrastre L, Lison D. Household exposure to pesticides and risk of leukemia in children and adolescents: Updated systematic review and meta-analysis. International journal of hygiene and environmental health. 2019;222(1):49-67.

8. Latino-Martel P, Chan DS, Druesne-Pecollo N, Barrandon E, Hercberg S, Norat T. Maternal alcohol consumption during pregnancy and risk of childhood leukemia: systematic review and meta-analysis. Cancer Epidemiology and Prevention Biomarkers. 2010;19(5):1238-60.

9. Liu R, Zhang L, McHale CM, Hammond SK. Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. Journal of oncology. 2011. https://doi.org/10.1155/2011/854584.

10. Filippini T, Heck JE, Malagoli C, Giovane CD, Vinceti M. A review and meta-analysis of outdoor air pollution and risk of childhood leukemia. Journal of Environmental Science and Health, Part C. 2015;33(1):36-66.

11. Amitay EL, Keinan-Boker L. Breastfeeding and childhood leukemia incidence: a meta-analysis and systematic review. JAMA pediatrics. 2015;169(6):e151025-e.

12. He JR, Ramakrishnan R, Hirst JE, Bonaventure A, Francis SS, Paltiel O, et al. Maternal Infection in Pregnancy and Childhood Leukemia: A Systematic Review and Meta-analysis. The Journal of pediatrics. 2020;217:98-109.e8.

13. Van Maele-Fabry G, Gamet-Payrastre L, Lison D. Household exposure to pesticides and risk of leukemia in children and adolescents: Updated systematic review and meta-analysis. International journal of hygiene and environmental health. 2019;222(1):49-67.

14. Latino-Martel P, Chan DS, Druesne-Pecollo N, Barrandon E, Hercberg S, Norat T. Maternal alcohol consumption during pregnancy and risk of childhood leukemia: systematic review and meta-analysis. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010;19(5):1238-60.

15. Ha M, Im H, Lee M, Kim HJ, Kim B-C, Gimm Y-M, et al. Radio-frequency radiation exposure from AM radio transmitters and childhood leukemia and brain cancer. American journal of epidemiology. 2007;166(3):270-9.

16. Zhao JLX, Wang C, Yan K, Lin X, et al. . Magnetic fields exposure and childhood leukemia risk: A meta-analysis based on 11,699 cases and 13,194 controls. Leukemia Research. 2014;38(3):269–74.

17. Merzenich H, Schmiedel S, Bennack S, Brüggemeyer H, Philipp J, Blettner M, et al. Childhood leukemia in relation to radio frequency electromagnetic fields in the vicinity of TV and radio broadcast transmitters. American journal of epidemiology. 2008;168(10):1169-78.

18. Feychting M. Mobile phones, radiofrequency fields, and health effects in children–epidemiological studies. Progress in biophysics and molecular biology. 2011;107(3):343-8.

19. Filippini T, Heck JE, Malagoli C, Del Giovane C, Vinceti M. A review and meta-analysis of outdoor air pollution and risk of childhood leukemia. Journal of environmental science and health Part C, Environmental carcinogenesis and ecotoxicology reviews. 2015;33(1):36-66.