PESTICIDE EXPOSURE AND ACUTE LYMPHOCYTIC LEUKEMIA IN CHILDREN: A SCOPE REVIEW

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ABSTRACT

Introduction: Acute Lymphocytic Leukemia (ALL) is a type of cancer that affects the hematopoietic process and is directly related to genetic and environmental factors. Objective: To identify in the literature the existence of an association between exposure to pesticides and the development of Acute Lymphocytic Leukemia in children in the national and international scenario. Methods: A scoping review was carried out in the LILACS, IBECS, MEDLINE, BDENF, CINAHL databases, and Cochrane and Scielo and Google Scholar libraries. Production related to pesticide exposure and the development of Acute Lymphocytic Leukemia in children were included. Results: The review had 22 studies published from 2008 to 2017. The association of pesticide exposure with the development of childhood ALL was due to maternal exposure to domestic pesticides in the pre-conception, gestational period, and the child’s exposure to domestic pesticides in early childhood. Conclusion: The results allowed us to identify publications on the association between the use of pesticides and the development of Acute Lymphocytic Leukemia in children. However, there is a need for further studies on children’s exposure to domestic pesticides, knowledge of their toxicity, and damage to human health, as well as measures to reduce its use.

Keywords: Agrochemicals. Child. Precursor Cell Lymphoblastic Leukemia-Lymphoma.

INTRODUCTION

Chronic Non-Communicable Diseases (CNCDs) are influenced by environmental, genetic, and behavioral factors(1,2). In Brazil, about 70% of deaths from CNCDs are represented by stroke (CVA), acute myocardial infarction (AMI), systemic arterial hypertension (SAH), various types of cancer, diabetes mellitus (DM) and also, chronic respiratory diseases. In this context, children are the most vulnerable to new diseases, as they are in physical, nutritional, and physiological development. Cancer, in particular, proves to be a disease that can develop in different ways, either as a solid tumor or as a neoplasm of blood cells (leukemias)(1,2,3).

Acute Lymphocytic Leukemia is a type of neoplasia that affects the bone marrow, more precisely the hematopoietic process, in its lymphoid lineage, affecting B and T lymphocytes and generating a great impact on the immune system(2). This pathology can affect children, adolescents, and adults with 75% occurring in children aged 2 to 5 years old, and can be fatal when diagnosed at a late stage(3). There is still no determined etiology for ALL; however, its origin is related to genetic and, above all, environmental factors(2,4).

Exposure to pesticides is among the environmental factors. They are chemical products (organochlorines, carbamates, pyrethroids, among others) or classes (acaricides, herbicides, fungicides, among others), to use them in the sectors of production, storage, and processing of agricultural products and urban environments(5). The products used to combat urban pests have the same active principles as agricultural products, causing different...
intoxications, and a home environment is a place with a high risk of accidents. Despite this, they are called household cleaning products or sanitizing products and are sold without any restrictions or controls.

The exposure of children to pesticides occurs in both urban and rural areas. In the urban area, the exhibition takes place through the environment (at home, at school, on lawns and gardens) and food (contaminated water and food). In rural areas, children are exposed due to family farming, through contact with parents after handling pesticides at work. The contamination can even occur through clothing and the fact that their homes and schools are close to crops. Children who have not directly exposed to pesticides are also subject to contamination by different ways such as air, water, and soil.

Studies carried out between 2014 and 2019 highlight the damage caused by the exposure of children to pesticides in rural areas such as the increase in micronuclei, congenital malformations, cytogenetic damage, leukemia, neurological effects, asthma, allergic rhinitis, thyroid disorders, among other injuries. The most common childhood cancer - acute lymphoid leukemia - occurs mainly with the risk factors, which are the genetic polymorphisms in CYP2E1, GSTM1, NQO1, NAT2, MDR1, and XRCC1, increasing the risk of this neoplasm when associated with environmental exposures such as household pesticides and insecticides, smoking, trihalomethanes, alcohol consumption and X-rays. Studies carried out between 2014 and 2019 highlight the damage caused by the exposure of children to pesticides in rural areas such as the increase in micronuclei, congenital malformations, cytogenetic damage, leukemia, neurological effects, asthma, allergic rhinitis, thyroid disorders, among other injuries. The most common childhood cancer - acute lymphoid leukemia - occurs mainly with the risk factors, which are the genetic polymorphisms in CYP2E1, GSTM1, NQO1, NAT2, MDR1, and XRCC1, increasing the risk of this neoplasm when associated with environmental exposures such as household pesticides and insecticides, smoking, trihalomethanes, alcohol consumption and X-rays.

In this sense, this study aims to synthesize the research related to the occurrence of Acute Lymphocytic Leukemia in children and its relationship with pesticides since environmental aspects can be related to the emergence of diseases and conditions such as cancers, for example. Brazil is one of the countries that leads the consumption of pesticides in the world and such evidence may strengthen stricter measures regarding the release and commercialization of pesticides, many of them banned in their countries of origin. Thus, this study aimed to identify evidence in the literature on the relationship between exposure to pesticides and the development of Acute Lymphocytic Leukemia in children in the national and international scenario.

METHODS

This is a systematic review study of the scope review type. We adopted Arksey and O'Malley's structure. This form of knowledge synthesis is ideal when the objective is to research, map, and identify productions on a given subject in a comprehensive way. We followed the following methodological stages: 1) identification of the research question; 2) identification of relevant studies; 3) selection of studies; 4) data extraction; 5) summarization and reporting of results. Arksey and O'Malley also recommend a sixth stage considered optional in which specialists are consulted, but we did not use it in this study.

In this study, we used the PCC mnemonic strategy (population, concept, and context) to elaborate the guiding question, in which (P) Population: children; (C) Concept: exposure to pesticides and the development of Acute Lymphocytic Leukemia; and (C) context: the national and international scenario. Thus, the research question for this study was: “What is the evidence about the relationship between exposure to pesticides and the development of Acute Lymphocytic Leukemia in children in the national and international scenario?” One of the strengths of a Scoping review is the search area for evidence on a topic. We consulted several sources to ensure the identification of the most relevant studies on the topic, including the VHL (Virtual Health Library), EBSCO (EBSCoHost Online Research Databases) and Web of Science platforms, which cover the bases: LILACS (Latin Literature) American and Caribbean Health Sciences), IBECS (Spanish Bibliographic Index of Health Sciences), MEDLINE (Medical Literature Analysis and Retrieval System Online), Cochrane Library, SciELO (Scientific Electronic Library Online), BDENF (Nursing Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature) and the Google Scholar tool. Also, we checked the references of the included studies for additional data sources.

We used the following Decs (Health Descriptors), Mesh (Medical Subject Headings), and/or keywords: Pesticides; Pesticides; Child; Precursor Cell Lymphoblastic Leukemia-Lymphoma; Lymphoblastic leukemia; Acute Lymphocytic Leukemia; Acute lymphoid leukemia. All of these terms were searched for in Portuguese.
and Spanish. The search strategy used followed the definition of each corresponding database. We used the Boolean AND operator with the following combinations: Pesticide AND Leukemia-Lymphoid Lymphoma, Precursor Cell AND Child; Pesticide AND Lymphoblastic Leukemia AND Child; Pesticide AND Acute Lymphocytic Leukemia AND Child; Pesticide AND Acute Lymphoid Leukemia AND Child. Pesticides AND Leukemia—Lymphoid Lymphoma, Precursor Cell AND Child; Pesticides AND Lymphoblastic Leukemia AND Child; Pesticides AND Acute Lymphocytic Leukemia AND Child; Pesticides AND Acute Lymphoid Leukemia AND Child. We adopted these search strategies in their equivalence in Spanish and Portuguese.

The inclusion criteria were completely original and theoretical articles, literature extracted from governmental organizations, associations, and university collections in Portuguese, English, and Spanish. The review included studies with children up to 9 years old\(^{14}\) and/or family members (mother/father) in their sample. We used the time frame between 2008 and 2017, allowing an analysis of the last 10 years. We excluded editorials, experience reports, case studies, publications, and other populations in their sample and studies that did not answer the research question. We carried out the searches from November 2017 to May 2018. Figure 1 shows the search, exclusion, and selection process of the studies found, based on the PRISMA recommendation\(^{15}\).

For the data extraction stage, we used a structured instrument to identify and describe the items, such as year of publication, title, country, objectives, and results. This instrument allowed for the synthesis, interpretation of data, and basic numerical analysis of the extension, nature, and distribution of studies incorporated in the review. Then, we compiled and communicated the results, presenting an overview of all the material through a thematic construction. We presented the extracted results in a table and discussed narratively based on classifications of conceptual categories.

**RESULTS**

We selected 22 studies published between 2008 and 2017 and analyzed according to information related to the year of publication, country of study, objectives, and main results (Chart 1).
| Author/Year/Country | Study objectives | Study method | Study participants | Main results |
|---------------------|-----------------|--------------|--------------------|--------------|
| Mellodasilva CA, Fruchtengarten L, 2005 Brazil | To review the recent medical literature available information on the risks of exposing children to chemical agents in the environment. | Review | - | It has associated children's exposure to chemical agents (including pesticides) with diseases such as cancer. |
| Lira SVG et al., 2009 Brazil | To analyze the interactions by pesticides in children, adolescents, and young people seen at an emergency hospital in the city of Fortaleza, from 2000 to 2004. | Documentary research | 1,569 records related to pesticide poisoning. | The data showed that the most toxic agent is rodenticide (pesticide), which causes poisoning in 68.2% of the cases. It associated the exposure of children to pesticides with various intoxications. |
| Wemmel JL et al., 2011 USA | To identify the association of maternal age (at birth) and high hyperdiploidy with pre-pregnancy paternal smoking; to explore the moment of origin of both IGH rearrangements and RAS mutations; to assess the value of RAS mutation due to parental smoking. | Population-based epidemiological study | The patient population consisted of 517 consecutive leukemia patients enrolled in the 9 hospitals that participated in the Northern California Childhood Leukemia Study from 1995 to 2002. | There was no evidence of mutations in the pretranslational KRAS KRAS mutations have been associated with childhood chemical exposures and adult leukemias. Mutated RAS was not associated with parental smoking. |
| Chokkalingam AP et al., 2012 USA | To evaluate the role of genes involved in the transport and metabolism of xenobiotics in the risk of ALL in childhood, either alone or in conjunction with domestic chemical exposures, previously associated with the risk of childhood ALL. | Population-based epidemiological study | 377 cases and 448 controls, using a haplotype-based approach to evaluate 62 xenobiotic transport and metabolism genes together with data on self-reported exposures to household chemicals. | Associations between home exposure to pesticides and some childhood ALL haplotypes have been identified. |
| Radant J et al., 2016 France | To investigate the possible interactions between ALL risk alleles and unexpected non-genetic risk factors that had a sufficient prevalence in the French ESCALE study. | Case-control | 434 ALL cases and 442 controls of European origin taken from the ESCALE population-based case-control study. | Statistical interactions between the allele of risk for ALL and the use of maternal insecticides with pregnancy. |
| Metayer C et al., 2016 USA | To discuss the association versus causation arguments in perspective, and to discuss the benefits versus risks of immediate and long-term preventive actions. | Review | - | The available published data, which relate early environmental exposures to childhood leukemia, are more comprehensive than most other cancers, whether adult or childhood. It associated ALL in childhood with domestic use of pesticides before and after birth. |
| Hernández AF, Martínez P, 2017 Spain | To review available experimental and epidemiological evidence, relating pesticide exposure to childhood leukemia, and to provide a mechanistic basis to support the association, focusing on early molecular events. | Review | - | There was an unexpected epidemiological evidence to suggest a risk of leukemia from intrauterine exposure or after birth to pesticides. It associated ALL with intrauterine and postnatal exposure to pesticides. |
| Ruff RP et al., 2009 USA | To examine whether residential proximity to agricultural pesticide applications is related to acute lymphoblastic leukemia, the most common subtype of childhood cancer. | Case-control | Residential histories were collected from families of 213 cases of acute lymphoblastic leukemia and 268 corresponding controls. | The study found a modest increase in the risk of ALL with residential proximity to moderate levels of agricultural use of different types of pesticides, but not at very high levels of use. It associated LLA with lifelong exposure to pesticides. |
| Bailey HD et al., 2016 France | To investigate whether home exposure to pesticides in the period before conception, during pregnancy, or after the child's birth, increased the risk of ALL or AML in childhood. | Review | - | Any exposure to pesticides in the few months before conception, during pregnancy, or after birth, was associated with an increased risk of childhood ALL. It attributed a varying time in the period, type of pesticide, or between subgroups. It associated ALL with any exposure to pesticides shortly before conception, during pregnancy, or after birth. |
| Whitehead TP et al., 2016 USA | To provide a concise perspective on the epidemiology of childhood leukemia for the benefit of doctors and policymakers. | Reflection | - | It supported the role of folate supplementation during the preconception period, pregnancy and/or breastfeeding, alone or with other vitamins, in reducing the risk of childhood leukemia. It was associated with pesticide exposure to ALL. |
| Soldin OP et al., 2013 USA | To investigate the association of household pesticide exposure to ALL risk in children in the Washington DC metropolitan area. | Case-control | Children newly diagnosed with ALL and their mothers (n = 41 mother-child pairs) | Pesticide levels were higher in cases than in controls. Statistically significant differences were found between children with ALL and controls for organophosphate metabolites in urine. It was associated with prenatal exposure to pesticides with childhood ALL. |

To be continued...
Pesticide Exposure And Acute Lymphocytic Leukemia In Children: A Scope Review

| Author/Year/Country | Study objectives | Study method | Study participants | Main results |
|---------------------|------------------|--------------|--------------------|--------------|
| Brison GD et al., 2015(29) Brazil | To understand the association between genetic polymorphisms and the risk of childhood leukemia. | Review | - | The evidence collected suggests that genetic polymorphisms, in some specific genes, can modulate the risk of leukemia, especially when associated with environmental exposures, such as household pesticides and insecticides, smoking, thalidomide, alcohol consumption, and X-rays. It associated ALL with prenatal, gestational, and postnatal exposure to pesticides. |
| Castro AA et al., 2017(31) Brazil | To search for new methods of remediation for poisoning caused by organophosphates. | Review | - | Many studies have described some possibilities, such as the use of degrading enzymes (bioremediation), which is highly promising. Unfortunately, to date, no antigen has been found capable of reacting with the AChE inhibited by all the more potent organophosphates. |
| Mangas IE et al., 2009(35) Brazil | To highlight the current uses of organophosphates that are producing several neurotoxic effects. | Review | - | Recent data prove that other molecular targets, in addition to AChE, could be the target of organophosphates, triggering these effects. |
| Camponogara S et al., 2017(36) Brazil | To know the perceptions of family members of children with active neoplasms, such as rural workers, about the disease process and implications of the use of pesticides. | Qualitative | 10 family members of children with cancer | The results showed that the perceptions refer to the use of pesticides as dangerous, but necessary, being recognized as the only way to achieve agricultural production. It has associated pesticide exposure to cancer. |
| Almeida, MD et al., 2017(37) Brazil | To contribute to a reflection on the topic of pesticides based on the Brazilian legal reference, from the perspective of protecting human health and the environment. | Reflection | - | It was observed that the PL 3,200/2015 values economic issues in the pesticide-producing market and contributes to maintaining the social, environmental, and short, medium, and long-term impacts generated by the indiscriminate use of pesticides paid for throughout the population. |
| Nicolopoulos-Stamatopoulos ET et al., 2016(38) Greece | To highlight the urgent need for a new concept in agriculture, involving a drastic reduction in the use of chemical pesticides. | Review | - | The urgent need for a more sustainable and ecological approach has produced many innovative ideas: agricultural reforms and food production, implementing sustainable practices that evolve toward food sovereignty. |
| Siqueira SL, Khayr MK, 2008(39) Brazil | To know, gather, and present the contribution of health professionals, especially nurses, to the topic of pesticides and human health, published in Brazilian magazines. | Review | - | The analysis of the articles highlights that the contribution of health professionals is focused on human health—especially on worker health and food quality. |
| Santos CV, 2013(40) Brazil | To investigate, through a literature review, the relationship between exposure to pesticides and the development of acute childhood lymphocytic leukemia (ALL), and to define the level and nature of this association. | Review | - | The results suggest that the main route of exposure to pesticides occurs through maternal exposure during pregnancy or by children in childhood. |

Chart 1. Synthesis of the articles included in the review. Porto Alegre, RS, Brazil, 2018.

Source: Developed by the authors based on the analysis of the selected studies, 2018.

Regarding the language of the selected studies, 11 were written in English (19,28,31,34) and 10 in Portuguese(16,18,29-35). As for data collection, 10 studies used searches through the literature (16, 18,29-35), three were based on official documents (such as notification forms and service reports)(17,18,22) and 10 had interviews or questionnaires with the children’s parents(20,28,32).

Regarding the design of the studies, 13 articles were quantitative (17,23,25,29,31,34,35) and eight were qualitative (16,24,27,30,31,32,33,35). As for the countries, 10 were carried out in Brazil (16, 18,29-32,34,35), six in the United States (20,21,23,25,27,28) and a study carried out in each country: Canada (19), France (22), Spain (24) and Greece (34).

Regarding the theme of each study: six addressed pesticides, citing their definitions, characteristics, classifications, uses, and effects(19,23,25,29,31-34); one elucidated the general concepts about ALL (20); two associated the exposure of children to pesticides with childhood cancer (16,31); two others made an association between children's exposure to pesticides and the emergence of various intoxications (17,18), and 11 studies associated exposure to pesticides with the development of childhood ALL (19-29,35).

Within the group that directly associated pesticide exposure to childhood ALL, we identified different forms of exposure, which may be: maternal exposure to domestic pesticides in the pre-conception period (19,26,29,36), maternal exposure to domestic pesticides during pregnancy (19,22,23,24,26,28,29,36), and the early
childhood exposure to domestic pesticides(21, 27,29,36).

DISCUSSION

About 50% of the studies related the exposure to pesticides to the development of childhood ALL. In general, studies that mentioned the damage caused by pesticides refer to household pesticides, mainly insecticides, and fungicides. Such substances are used indiscriminately in homes(7) since people are usually unaware of the insecurity of their use.

A study indicated that there is a specific association with childhood ALL, with the toxicity of such substances evidenced since the preconception period. The studies showed that the toxicological effects remain in the female organism, which can cause damage in a future pregnancy. This alerts to the subsistence time of the pesticides in the human body, which is much longer than the exposure period, allowing us to assume the occurrence of damage long before the clinical manifestation of any disease(35).

Although this study shows all types of pesticides, organophosphates were cited as the most common class of insecticides used in homes and gardens(28), and, for this reason, they were found in both adults, children, and fetuses. Maternal exposure to pesticides before conception often occurred at home due to the use of insecticides(37). However, such products were not perceived as potential health risks, and are often used as a protective measure against mosquitoes and other vectors. Indiscriminate use has been associated with pre-conception paternal exposure and damage to germ cells(29). However, due to the non-specificity of the exposure period, none of the studies showed a specific measurement of how long after exposure the pregnancy occurred.

The use of pesticides during pregnancy was also imprecisely described in the investigated articles. Thus, we observed, in addition to the development of ALL, other gestational signs or symptoms that could be directly linked to exposures to pesticides. However, maternal and paternal exposure to pesticides corroborates the appearance of this disease in children(36). Also, the selected sample enabled to identify the pregnant women’s lack of knowledge regarding the toxic effects of pesticides, which they believed were harmless because they are water-based. However, these articles have shown that maternal exposure during pregnancy may result in fetal exposure since pesticide residues have been identified in umbilical cord blood, meconium, and the newborn.

Intoxications from the exposure of pesticides continuously are classified as chronic or subacute since agricultural workers generally do not relate the signs and symptoms with the use of the products. This is identified by the high number of reported cases, and one of the main age groups was from zero to ten years old, with 151 cases of poisoning in the period from 2003 to 2011, at the Poison Control Center of the Hospital Universitário Regional de Maringá (CCI/HUM) (40). The most common sources associated with exposure to pesticides for children are dietary, dermal, inhalation sources, and direct and frequent contact with pets treated with pesticides (mainly fungicides and ticks)(25).

The accentuated vulnerability of children to such products is because they have more permeable skin, have lower levels of intoxication enzymes in their livers, and exhibit hand-mouth behavior, facilitating the ingestion of pesticides. The child becomes more susceptible to external exposures since there are greater ignorance and detachment from precautions(25).

The results of the studies need to be interpreted with care since the limits of the search used by the researchers may have favored the inclusion of studies in Portuguese. Therefore, the authors acknowledge that important research published in another language may have been omitted using this search strategy.

CONCLUSION

The study sought to identify publications on the association between the use of pesticides and the development of ALL in children. In this study, we concluded that 11 studies strongly correlated the use of pesticides with the development of ALL in children. Such an association was identified in all types of exposure (pre-conception, prenatal, or early childhood) and without variation in the time of exposure or the type of pesticide exposure.
The implications of this study can be seen in the sense of strengthening awareness for the study of the topic of pesticide use and the development of ALL in children by health professionals, patients, managers, policymakers, educators, and researchers. A gap that remains little explored in studies is the contribution of health professionals to the prevention of children's exposure to pesticides. The need for continuous and specific studies on the subject is emphasized, updating knowledge about the toxicity of pesticides and future damage, to implement measures to reduce the use of these pesticides that are harmful to health, especially children. We recommend further studies on the use of pesticides and their relationship with the development of ALL in children enter the priority agenda of Brazilian health policy.

EXPOSIÇÃO A AGROTÓXICOS E A LEUCEMIA LINFOCÍTICA AGUDA EM CRIANÇA: UMA REVISÃO DE ESCOPO

RESUMO

Introdução: A Leucemia Linfócita Aguda (LLA) é um tipo de câncer que acomete o processo hematopoético e está diretamente relacionada a fatores genéticos e ambientais. Objetivo: Identificar na literatura a existência de associação entre a exposição a agrotóxicos e o desenvolvimento de Leucemia Linfócita Aguda em crianças no cenário nacional e internacional. Métodos: Realizou-se uma revisão de escopo nas bases de dados LILACS, IBECS, MEDLINE, BDENF, CINAHL e bibliotecas Cochrane e Scielo e Google Scholar. Incluíram-se produções relacionadas à exposição por agrotóxicos e o desenvolvimento de Leucemia Linfócita Aguda em crianças. Resultados: A revisão abrangeu 22 estudos publicados de 2008 a 2017. A associação da exposição a pesticidas com o desenvolvimento de LLA infantil deu-se na exposição materna aos pesticidas domésticos no período pré-concepção, gestacional e exposição da própria criança a pesticidas domésticos na primeira infância. Conclusão: Os resultados permitiram identificar as publicações sobre a associação entre o uso de agrotóxicos e o desenvolvimento de Leucemia Linfócita Aguda em crianças. Entretanto, há a necessidade de novos estudos sobre a exposição de crianças à pesticidas domésticos, conhecimento sobre sua toxicidade e danos à saúde humana, assim como medidas para redução do uso.

Palavras-chave: Agroquímicos, Criança, Leucemia-Linfoma Linfoblástico de Células Precursoras.

EXPOSIÇÃO A PESTICIDAS Y LEUCEMIA LINFOCÍTICA AGUDA EN NIÑOS: UNA REVISIÓN DEL ALCANCE

RESUMEN

Introducción: La Leucemia Linfócita Aguda (LLA) es un tipo de cáncer que acomete el proceso hematopoyético y está directamente relacionada a factores genéticos y ambientales. Objetivo: identificar en la literatura la existencia de asociación entre la exposición a pesticidas y el desarrollo de Leucemia Linfócita Aguda en niños en ese escenario nacional e internacional. Métodos: se realizó una revisión del alcance en las bases de datos LILACS, IBECS, MEDLINE, BDENF, CINAHL y bibliotecas Cochrane y Scielo y Google Scholar. Se incluyeron producciones relacionadas a la exposición por pesticidas y el desarrollo de Leucemia Linfócita Aguda en niños. Resultados: la revisión abarcó 22 estudios publicados de 2008 a 2017. La asociación de la exposición a pesticidas con el desarrollo de LLA infantil ocurrieron la exposición materna a los pesticidas domésticos en el período preconcepción, gestacional y exposición del propio niño a pesticidas domésticos en la primera infancia. Conclusión: los resultados permitieron identificar las publicaciones sobre la asociación entre el uso de pesticidas y el desarrollo de Leucemia Linfócita Aguda en niños. Pero, hay la necesidad de nuevos estudios sobre la exposición de niños a pesticidas domésticos, conocimiento sobre su toxicidad y daños a la salud humana, así como medidas para la reducción del uso.

Palabras clave: Agroquímicos, Niño, Leucemia-Linfoma Linfoblástico de Células Precursoras.

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