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REVIEW

Acute lymphoid leukemia etiopathogenesis

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Abstract

Acute lymphoid leukemia (ALL) is a type of hematological neoplasm that affects the precursor cells of strains B, T and NK, with a higher incidence in the pediatric range. The pathophysiology of ALL is characterized by chromosomal abnormalities and genetic alterations involved in the differentiation and proliferation of lymphoid precursor cells. Despite the lack of information in the literature, it is believed that leukemogenesis originates from a complex interaction between environmental and genetic factors, which combined lead to cellular modifications. Environmental factors have been evaluated as possible predisposing factors in the development of ALL but there are still conflicting results in the world literature. In this context, the aim of the present review is to discuss the major exogenous factors regarding ALL.

Keywords Leukemia · Childhood · Infection · Environment

Introduction

Childhood and juvenile cancer, which affects individuals between 0 and 19 years old, consists of a set of diseases that have their own characteristics in relation to the cells that make up the tumors (histological type) and clinical behavior of the disease [1]. In most populations, childhood and juvenile cancer accounts for 1% to 4% of all malignant tumors and in developing countries, where the child population reaches 50%, this proportion of childhood cancer accounts for 3% to 10% of all cancers. Worldwide, among childhood cancer types, leukemia is common in most populations, corresponding to 25–35% of cases [2].

Leukemias are a group of different hematologic diseases with a different biological concept, clinical presentation, prognosis and treatment response, characterized by the presence of an abnormal cell population suppressing the normal production of cellular components of the hematopoietic system [3].

Leukemias originate from hematopoietic stem cells (HSCs) and precursors in the bone marrow (BM), that promote leukemic cell proliferation and infiltration [4, 5]. In general, hematological malignancies are classified according to lineage, degree of maturation and form of cellular involvement in the BM. Myeloid lineage neoplasms may include granulocytes (neutrophils, eosinophils, basophils), monocytes, erythrocytes, platelets (megakaryocyte derivatives) and mast cells. In contrast, the lymphoid lineage corresponds to B, T and natural killer (NK) cells [6].

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy [7]. The majority of ALL occurs in healthy individuals and predisposing factors, such as hereditary genetic susceptibility or environmental exposure, have been identified in only a few patients. It is characterized by chromosomal abnormalities and genetic changes involved in lymphoid differentiation and proliferation precursor cells [8].

ALL and lymphoblastic lymphoma (LBL) are biologically comparable and treated the same [9], ALL/LBL comprises B-lineage, T-lineage, and uncommon variants (i.e., NK-lineage, early T progenitor ALL [a provisional diagnostic category]) [10].

The ALL pathophysiology involves complex environmental as well as genetic mechanisms at different scales, and

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there must also be a complex relationship between these factors [11]. Along with response to treatment, these abnormalities are important prognostic factors [8].

Epidemiologic studies of acute leukemias in children have examined possible risk factors, including genetic, infectious and environmental, in an attempt to determine their etiology [12]. It is believed that ALL may originate from interactions between exogenous factors. Therefore, this review proposes to clarify the understanding of ALL regarding environmental factors.

Acute lymphoid leukemia

ALL is a malignant disorder that originates from a single haematopoietic precursor affecting the B or T cell line. These cells can acquire a series of genetic alterations that may disrupt normal maturation processes, leading to the blockade of differentiation and transformed cell proliferation [13].

The distribution of ALL categories is B lineage (85%), T lineage (10–15%) and NK lineage (<1%). The incidence of this disease varies worldwide but may be influenced, in part, by diagnostic and reporting differences [14]. The incidence of ALL is higher in Hispanic (43 cases/million) and White (Caucasian) Americans (36 cases/million) than in Black Americans (15 cases/million) and Asians [15]. The peak incidence of ALL occurs between 2 and 5 years of age and it is more common among boys than girls [15, 16].

In the United States, approximately 6000 new ALL cases have been estimated, at a ratio of 1.3 male to 1 female [17]. Most patients are children and 60% cases occur in individuals under 20 years old [7, 18, 19].

ALL, like cancer in general, probably originates from interactions between exogenous and endogenous exposure and genetic susceptibility [20]. ALL pathogenesis occurs from important genetic lesions in genes involved in T or B lymphocyte differentiation [7]. The challenge is to identify exposure elements and relevant inherited genetic variants and also to decipher how and when these factors contribute to the multi-stage natural history of ALL from initiation (usually in the womb) to disease manifestation [21].

The classification for ALL was proposed by the World Health Organization (WHO) (1997) in an attempt to account for the morphology and cytogenetic profile of the leukemic blasts and identified three types of ALL: B lymphoblastic, T lymphoblastic and Burkitt-cell Leukemia [22]. In 2008, Burkitt-cell leukemia was eliminated, and became only Burkitt's lymphoma and B-lymphoblastic leukemia was again divided into two subtypes: B-ALL with recurrent genetic abnormalities and B-ALL without further specification. [6]. In 2016, two new provisional entities were added to the list of recurrent genetic abnormalities and the hypodiploid was redefined as either low hypodiploid or hypodiploid with *TP53* mutations [23].

Pathophysiology of ALL

Leukemia and other cancers share the same biological characteristic which is clonality. Molecular changes are necessary for the development of cancer and they can alter the components of the signaling pathway, that lead to the emission of proliferative signals, even when no more cells are needed, inappropriately activating cell growth, DNA replication and cell division [11].

The development of a malignant hematological disease probably involves a mutation in a critical gene of cell proliferation, differentiation and/or survival in a hematopoietic progenitor [24]. Most leukemia mutations are acquired and occur in a lymphoid cell progenitor; mutated genes are less often inherited (1–5% of leukemias) and this involves a numerical chromosomal abnormality, such as 21 trisomy [25].

When an oncogene is activated by mutation, the encoded protein is structurally modified and generally shows increased transformative activity, remaining in its active state, continuously transmitting its signals through the interaction of tyrosines and/or threonine kinases. These signals induce incessantly continued cell proliferation [11].

There are mutations that suppress gene function and occur in tumor suppressor genes, such as *TP53*. However, less than 3% of childhood patients and an average of 8% of adult ALL patients have mutations in *TP53* [26].

Numeric chromosomal abnormalities as well as structural rearrangements (translocations) commonly occur in ALL. Significant cytogenetic abnormalities in B cell precursors are associated with poor ALL prognosis, including t(9; 22) or Philadelphia chromosome, with frequency directly proportional to age [27]; t (4; 11), related to the mixed lineage leukemia (MLL) gene, common in childhood and also associated with myeloid leukemia [28, 29]; hypodiploidy [30]; and chromosome 8 trisomy in adults diagnosed with ALL [31].

In addition, the genetic alterations associated with ALL are mainly localized at sites where oncogenes exist, for example: the MLL oncogene MLL related to ALL in children [32]; t (8; 14) translocation associated with gene dysregulation of the C-MYC oncogene [33]; *TP53* tumor suppressor gene mutations [34]; and deletions and inversions, such as the transcription factor *PAX5* deletions, present in at least 30% of B cell precursor ALL [35].

Aberrant methylation of CpG islands in gene promoter regions has been identified in ALL cell lines and is considered important since methylation of CpG dinucleotides near transcription initiation sites may silence gene expression

[36]. Thus, hypermethylation of tumor suppressor genes and hypomethylation of oncogenes can trigger leukemias.

Another important mechanisms of ALL development are the modification of angiogenesis [37], signal transduction in interaction with tyrosine kinase receptors and apoptosis regulatory molecules [38], as is the case of the *BCL2* gene, which encodes a cytoplasmic protein located in the mitochondria and increases cell survival by inhibiting apoptosis.

There are cases of complications from long-term treatment observed in cancer patients, which is the increased risk of developing hematological malignancies [39]. They usually manifest as acute leukemias or myelodysplastic syndromes and are frequently high, possibly due to increased use of genotoxic agents in antitumor therapies and increased survival in other cancers [40].

Increasing evidence supports a multi-step process in leukemogenesis, with sequential steps and a series of changes in oncogenes, tumor suppressor genes and microRNA genes in tumor cells [24, 41]. Unlike genes involved in cancer development, genes for microRNAs do not encode proteins; their products are small RNA molecules (single stranded 21–23 nucleotides) that recognize and bind to messenger RNA (mRNA) nucleotide sequences, blocking protein translation and thereby regulating gene expression [41, 42].

Several microRNAs have been implicated in ALL pathogenesis [43–45]. In this context, Li, Li [46] identified an increase in miR-708, miR-210 and miR-181b microRNA expression in B-line precursor ALL cells (common ALL). Moreover, they demonstrated that miR-708 expression is related to the high-risk ALL group, when compared to low-risk groups, by regulating the expression of the ciliary neurotropic factor receptor (*CNFTR*), neuronatin (*NNAT*) and guanine nucleotide-binding protein subunit gamma *(GNG12)* genes.

Molecular changes required for leukemia development are rare phenomena when considering the large number of target cells susceptible to genetic modification [24]. It is important to mention that when referring to the origin of cancer, in the case of ALL, two terms must be referenced: the original cell and the leukemic stem cell.

Environmental factors

Although little is known about the etiology of ALL, the multifactorial behavior of the disease suggests that risk factors contribute to its development, such as environmental and/or genetic risk factors [47]. On the other hand, there are three highlighted hypotheses: population mix [48], late infection [49] and hygienic-sanitary [50], suggesting the involvement of the immune system in the ALL etiology.

Studies have reported an increased incidence of ALL in association with advanced paternal age and maternal fetal loss (hazard ratios ≤1.1 for either) [11–13]. Studies of the relationship between childhood leukemia and urban/rural status, population density and other possible etiologic factors (eg, environmental exposures, abnormal immune response to common infections) have yielded inconsistent results [50–56].

In most cases, childhood ALL is not considered to be a familial disease [57]. Importantly, because ALL is a disease with a low incidence in the general population, even a large increase in the relative risk among siblings does not translate into a high likelihood of developing leukemia. Certain genetic syndromes (eg, Down syndrome, neurofibromatosis type 1, Bloom syndrome, ataxia-telangiectasia) [58, 59], rare germline mutations in *PAX5*, *ETV6*, and *TP53* and polymorphic variants of *ARD5B*, *CDKN2A* and *IKZF1* (the gene encoding Ikaros) are associated with an increased risk of leukemia [60–64].

One of the most related environmental factors associated with an increased risk for ALL is the involvement of ionizing radiation, which is more prevalent in pediatric leukemias, especially in ALL and acute myeloid leukemia (AML) [12, 65]. Potential exposure of children to ionizing radiation may occur during the gestational phase or in the postnatal period [12]. Other risk factors already accepted include prenatal x-ray exposure and postnatal exposure to high doses of radiation [66].

In a study associating haplotypes with patients that were exposed to radiation, Chokkalingam, Bartley [67] observed that, when analyzing 32 genes responsible for cell cycle repair pathways, 4 haplotypes from *APEX1*, *BRCA2*, *RAD51* and *ERCC2* genes demonstrated a risk association. They also showed that 3 genes (*NBN*, *XRCC4* and *CDKN2A)* were associated with structural and numerical genetic alterations in ALL patients, showing genetic susceptibility regarding ionizing radiation.

The hypotheses of population mixture and late infection suggest that a poor immune system in the early stages of human development may cause abnormal immune responses against infections, allowing an altered cell to develop. Both hypotheses are similar to the sanitary hygienic hypothesis, which explains the emergence of the original cell due to increased allergy frequency during the first years of life. Many studies support the hypothesis of infections and the immune system as ALL etiological factors [47, 50, 54, 68, 69]. However, little is known about the role of genes in this etiology.

Although there are studies with conflicting results, environmental factors have been investigated as predisposing to the development of ALL. Moreover, adult leukemia risk factors differ from those of children. For adult-onset leukemia, the most established environmental risk factor is exposure to ionizing radiation. Benzene, agricultural exposures, smoking and the consumption of alcohol, cigarettes

and illicit drugs during pregnancy have been described as predisposing factors for childhood ALL [70–75].

A common type of DNA change that can lead to leukemia is known as a chromosome translocation, for example, a translocation seen in some cases of childhood ALL is a swap of DNA between chromosomes 9 and 22, which leads to what is known as the Philadelphia [76], and the review by Quiroz, Aldoss [77] describes chromosomal abnormalities and specific genomic landscape in Latinos with ALL and their association with unfavorable prognosis, focusing on Philadelphia chromosome-positive (Ph^+) ALL. These authors compared ALL distribution throughout the various countries in Latin America in an attempt to shed some epidemiological light on the genetic ancestry of ALL.

Growing evidence from epidemiological studies suggests that the increased leukemia rate is probably related to an abnormal immune response to infections early in life and viruses have been suggested to play a role in the ALL pathogenesis [49, 78]. Some biological agents, such as viruses, as the Epstein Barr virus (EBV) and the human T cell lymphotropic virus 1 (HTLV-1), also remain as risk factors for ALL. The data suggest that a dysfunctional immune response to a common childhood pathogen(s), such as bacterial or viral infection, is a final step leading to leukemia [20, 50].

Many epidemiological studies have attempted to identify risk factors in the etiopathogenesis of ALL. Belson, Kingsley [12] presented an elegant review that discusses the environmental risk factors including some of the most researched and also controversial topics such as hydrocarbons and pesticides, alcohol, ionizing and non-ionizing radiation, smoking and use of illicit drugs. In addition, they also reviewed genetic and infectious risk factors and others. Studies of environmental exposures and childhood cancer do not depend only on the records of the maternal address at birth or at the time of diagnosis, but on whether there is residential mobility to assess exposures in early childhood [79, 80].

The relationship between the immune system and ALL is a complex process that involves the interaction of many components such as epithelial barriers, cells, proteins, cytokines and variations in the genes of these cells can affect the development and function of immune responses, and thus increase susceptibility to ALL [68, 81].

There is evidence that advanced parental age is associated with increased childhood ALL risk and this association was most marked among children aged 1–5 years. Employing datasets with cytogenetic information may further elucidate the involvement of each parental component and clarify underlying mechanisms [82].

A study by Orsi et al. [83] included 7847 ALL cases and 11,667 controls aged 1–14 years old and investigated the associations between childhood ALL) and several factors related to early stimulation of the immune system, that is, farm residence and regular contacts with farm animals (livestock, poultry) or pets in early childhood. However, there was no evidence of significant association with agricultural residence and regular contact with animals in the first year.

In this context, there is a concern in the developing countries, with a broad heterogeneous territorial population exposed to different infectious agents and hygiene levels, and also a concern with children, that, in addition to being exposed to common infectious diseases in this age group, are prone to the development of regional diseases, such as parasitic diseases, mainly due to climatic and sanitation differences.

Although the recognition of leukemia among childhood diseases is well established, as well as the role of treatment groups for this disease, very little is known about the involvement of the environment in the development of the disease. As pointed out in this review, the true biological profile of childhood leukemia is unknown and in-depth studies should be made regarding different geographical regions, exposure to risk factors, such as exposure to ionizing rays, xenobiotics and chemicals, in addition to the presence of infectious microorganisms.

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