Review Article

Pathogenesis of Acute Lymphoblastic Leukemia

Farhad Hajializadeh[1, ↑], Ali namjpour[2, ↑], Shahin Aghamiri[3, ↑], Shiva Bayat[4], Soodeh Namjoo[5, *], Farhad Zaker[6, *]

[1]MD College of Veterinary Medicine of Urmia Branch of Islamic Azad University - College of Veterinary Medicine, Urmia Branch, Islamic Azad University, Urmia, Iran.
[2]Virology Division, Department of Pathobiology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of genetic, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[5]Department of Hematology and blood banking of Iran University of Medical Sciences - Allied Medical Sciences - Iran University of Medical Sciences - Tehran – Iran
[6]Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran

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Abstract

Acute lymphoblastic leukemia (ALL) is a hematological malignant disease characterized by an enhanced self-renewal ability of precursor lymphoid cells whose cell division takes more time than their normal counterparts.

ALL occurs most between 2 to 5 years of age and during the sixth decade of life. There is a strong relationship between the time ALL occurrence in children and the genetic abnormalities which are identified by the rate of leukemic concordance between identical twins.

About 90% of ALL cases do not have a clear etiological mechanism. Genetic syndromes, polymorphic variants genes, germline mutations, and some environmental factors are responsible for less than 10% of ALL predisposition but the pathogenesis mechanism of ALL is not identified precisely.

Here we review the recent findings and earlier studies about the pathogenesis of acute lymphoblastic leukemia and its incidence. This article also summarizes the identification of predictive factors for ALL and options available to predict disease recurrence.

Keywords: Acute lymphoblastic leukemia, Genetic abnormalities, Incidence, Pathogenesis.

***Corresponding Author:** Soodeh Namjoo E-mail: nsoodeh@yahoo.com; Farhad Zaker E-mail: farhadz20@yahoo.co.uk.
↑ These authors contributed equally to this work.

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Introduction

Leukemia is one of the most important human challenges worldwide, which causes physical problems. Acute Lymphoblastic Leukemia (ALL) is a malignant disease on B- or T-cell lineage lymphoid progenitor (1, 2). Also, ALL can occur at any age in both children and adults, with the most incidence between the age of 2 to 5 years or in infants (3, 4). Pediatric ALL is an example of successful improvement in chemotherapy regimens and their survival probability has increased from 77% in the three past decades (5), up to 90% (6). The occurrence of relapse in ALL is high in adults (7). Chromosomal abnormalities and imperfect genes are very important factors in the evaluation of leukemia. The four common chromosomal abnormalities in pediatric ALL including t(12;21)(p12;q22)/ETV6-RUNX1, t(1;19)(q23;p13)/TCF3-PBX1, t(9;22)(q34;q11)/BCR-ABL and t(4;11)(q21;q23)/MLL-AF4 (8) along with gene mutation in lymphoid differentiation regulator proteins e.g. Pax5 lead to promotion of ALL. The exact pathogenetic mechanisms in the development of acute

lymphoblastic leukemia are unknown. Only some cases are genetic syndromes, such as Down syndrome, Bloom's syndrome, ataxia-telangiectasia, and Nijmegen breakage syndrome (9). In ALL, extramedullary localizations in the central nervous system (CNS), lymph nodes, gonads, spleen or liver can occur (10).

The aim of this study is to review the pathogenesis, chromosomal abnormalities, and epidemiology of ALL in children and the rate of relapse in adults which can help improve its diagnosis and treatment in patients.

Incidence

ALL is the proliferation and accumulation of lymphoid progenitor cells in the bone marrow and other tissues (11). The number of new cases and deaths in ALL patients diagnosed each year from 2012 to 2015 increased in USA (12, 13). Patients, out of whom 60 %are people younger than 20 years of age, are mostly children. (3, 14-16). The pediatric oncology group has reported survival in 85% to 95% of low-risk ALL patients in 2006 to 2009 (17). The incidence of childhood ALL is about 4–5 cases per 100,000 children (18). In Mexico, the Popular Medical Insurance (PMI) reported an incidence of 62.5 cases per one million/year (19). B-cell acute lymphoblastic leukemia (B-ALL) is observed in 50% of patients (20), Philadelphia chromosome (Ph)–positive ALL in 50% to 60% of patients (21, 22), and T-cell acute lymphoblastic leukemia (T-ALL)in 50% to 60% of patients (23). Acute lymphoblastic leukemia report of osteoporosis was observed in bone marrow more than 25% blasts and leukopenia (24). The two major skeletal complications of leukemia are osteoporosis and avascular necrosis (25). A bone mineral accumulation process happened during the period corresponding to the onset of most childhood ALLs (26). Among the complications, musculoskeletal pain, disturbed gait, fractures, kyphosis, lordosis, and growth failure have been described. Pathological fractures and vertebral collapses secondary to severe osteopenia (leukemic osteopathy) may occur (27). In the childhood cancer study, long-term had an incidence of 73% chronic health conditions and mortality that was 11 times (28-30). Cardiovascular toxicities, including cardiomyopathy, coronary artery disease, and arrhythmias are among the most common serious adverse events (31, 32). According to national cancer institute in Brazil, between 25% to 35% of all cancer types represent leukemia, and acute lymphoblastic leukemia is the most common between 0 to 14 years of age (33). The global estimated incidence of B-ALL is around 1 to 5 per 100,000 persons per year (34).

Risk factors

Genetic Syndromes

The precise pathogenetic events leading to the development of ALL are unknown. Down syndrome, Bloom syndrome, ataxia-telangiectasia mutated (ATM), and Nijmegen breakage syndrome is the genetic syndromes that may occur in ALL (35-38), an estimated frequency of specific genotypes of ALL in children and adults are shown in Table 1 (39). Down

Table1. Estimated Frequency of Specific Genotypes of ALL in Children and Adults

Abnormality	Children (%)	Adults (%)
Hyperdiploidy >50 chromosomes	25	7
Hypodiploidy <45 chromosomes	1	2
t(12;21) TEL-AML1	22	2
t(8;14),t(2;8), t(8;22) MYC	2	4
t(1;19) E2A-PBX1	5	3
t(9;22) BCR-ABL	3	25
t(4;11),t(11;19), t(9;11) MLL rearrangements	8	10
Others	22	23
HOX11L2 5q35*	2.5	1
LYL1 19p13*	1.5	2.5
TAL1 Ip32*	7	12
HOX11 10q24*	0.7	8
MLL-ENL*	0.3	0.5

*Abnormalities T-cell ALL

syndrome is a heterogeneous disorder in ALL patients, including subtypes recognized with identical genetic abnormalities found in people, such as hyperdiploidy greater than 50 and [ETV6-RUNX1]t(12;21) (40, 41). CRLF2 dysregulation is found in approximately 60% of sporadic pediatric DS-ALL patients, which is an indicating factor in the development of DS subtype (42). The study showed that fusion and activation of P2RY8-CRLF2 with JAK mutations are observed in half of ALL patients with Down Syndrome (43, 44). Also, other genetic events including IKZF1 deletion have been found in ALL with Down syndrome (45-47). Patients of ATM (ataxia-telangiectasia mutated) of the specific T-cell phenotype are at greater risk of leukemia than lymphoma (48). Overall, pathogenetic disorders cause acute lymphoblastic leukemia in population.

Environmental factors

The environmental factors that cause ALL include ionizing radiation, utero exposure to ionizing radiation, postnatal exposure to ionizing radiation, nonionizing radiation, alcohol cigarette and illicit drug use.

Ionizing radiation. A case-control study has recognized that 1 percent of leukemia is a result of a slight increase in exposure to ionizing radiation (49, 50). Ionizing radiation is one of the few exposures for which the causal relationship with childhood leukemia has been established (51, 52). Ionizing radiation exposure can cause leukemia during preconception, pregnancy, or the postnatal period.

In Utero exposure to ionizing radiation. In utero exposure to diagnostic x-rays does not decrease the risk of ALL, although there is a positive correlation with the number of exposures(53). A lot of studies have attempted to determine the effect of radiation exposure in utero and development of leukemia related to the atomic bomb exposures at the end of World War two in Japan, the Chernobyl (Russia) accident. Increase in risk of childhood leukemia as a result of the atomic bomb has yet been shown (53, 54).

Postnatal exposure to ionizing radiation. In second world war, atomic bomb blasts increased the risk of childhood leukemia, similar to radiotherapy for benign diseases in postnatal exposure (55). Although to date, children who were exposed to Chernobyl accident have shown no increased risk of leukemia (56, 57). The study found no significant risk of ALL, although three or more were exposed to radiation (58).

Nonionizing radiation. Many epidemiologic studies have been conducted to determine the link between an exposure to nonionizing Electromagnetic Fields (EMFs) and childhood leukemia (59-61). Moreover, research on animals with exposure to higher levels of EMFs than humans haven't shown increased hematopoietic neoplasm (62). Therefore, no significant increased risk of ALL was found based on EMF levels for mother during pregnancy (63).

Alcohol, cigarette, and illicit drug use. Studies have shown an increased risk of childhood leukemia, especially among young children, associated with maternal alcohol consumption during pregnancy (64, 65). Whether smoking before or during pregnancy is a risk factor for childhood leukemia is unknown (66). based on the children's cancer group, maternal use of marijuana before or during pregnancy has been associated with childhood ALL (67).

Conclusion

In conclusion, the review showed the pathogenesis of acute lymphoblastic leukemia and its incidence. Furthermore, important factors such as genetic disorders and environmental factors causing ALL are described. Also, the prevalence of the disease in patients with genetic defects around the world has been mentioned. Thus, important factors in the pathogenesis of acute lymphoblastic leukemia patients were identified to improve health.

Conflicts of interest

The Authors declare that there are no conflicts of interests.

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