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Epidemiology of childhood acute leukemias

Review

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Abstract

Acute leukemias are the largest group of childhood cancers. According to the latest WHO data 80,491 leukemias were diagnosed in 2020 alone. In the coming years the incidence worldwide will continue at a similar level. The morbidity correlates with biological determinants such age, gender and race. The etiology of leukemia formation is complex and depends on genetic, physiological, environmental and even prior treatment-related factors. Both the incidence and curability are also influenced by age, gender, and race. The peak of incidence of leukemia occurs between the ages of 1-4 years and 9-19. The etiology of leukemia formation is complex and depends on genetic, physiological, environmental and even prior treatment-related factors. Boys suffer from leukemia more often than girls. In 2020 58.2% of diagnoses were for boys. Numerous factors contribute to the development of acute leukemia. In the case of young children, a notable association exists between acute leukemia and infections caused by viruses such as EBV or HHV-6. Furthermore, the risk of leukemia can be elevated by allergies, which involve Th1/Th2 lymphocyte-dependent mechanisms. A familial predisposition to tumorigenesis in children is observed in Li-Fraumeni Syndrome. Also, genetic diseases such as Down syndrome and Fanconi anemia are associated with an increased risk of acute leukemia. Previous exposure to radiation therapy or the use of anti-cancer drugs can also lead to the development of secondary cancers, including leukemia. The analysis of risk factors can be used to support efforts aimed to reduce potentially harmful exposure and to decrease the risk of disease.

Keywords

epidemiology • risk factor • childhood leukemia • ALL • AML

1. Introduction

Leukemia is the most common childhood malignancy, and according to the WHO, it accounts for up to 28.8% of all cancers in children diagnosed by the age of 19. It is also the most common cause of cancer death in children [1]. Acute leukemias constitute a heterogeneous group of cancers derived from precursor cells of the hematopoietic system. In the course of the disease, excessive proliferation of leukemic cells is observed, which leads to quantitative and qualitative changes in the composition of individual blood parameters [2]. Symptoms can include fatigue, easy or spontaneous bruising, infections, hepatomegaly, splenomegaly, and lymphadenopathy [3,4]. Two forms of acute leukemia, namely acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), are commonly diagnosed in children. ALL, the most commonly diagnosed disease that affects approximately 80% of all childhood leukemias is a malignant transformation and proliferation of B or T lymphoid progenitor cells in the bone marrow, blood [4,5]. The classification is based on clinical, molecular, and cytogenetic features (Table 1) [6]. AML is less commonly observed, representing 5-20% of all cases of leukemia in children [5,7,8]. It develops when other than a lymphoid progenitor cell undergoes malignant transformation, leading to the proliferation of AML blasts and their accumulation. AML is categorized by the origin and maturity level of the leukemia cells. AML is separated into two groups: AML with defining genetic abnormalities and AML defined by differentiation (Table 2) [9].

In 2020, there were a total of 80,491 diagnosed cases of childhood leukemia worldwide, with 9,167 cases in Europe and 13,115 cases in the Americas. The global mortality rate for the same year was 32,765 cases, with 6,818 cases in Europe and 4,723 cases in the Americas, according to the latest data from the World Health Organization (WHO) [1,10] (Figure 1). The likelihood of successful treatment is heavily influenced by the quality of medical care provided. Access to advanced diagnostic techniques such as genetics, flow cytometry, and biochemistry plays a crucial role in accurately identifying prognostic factors, and thus significantly impacting the cure rate. The results obtained during the initial screening also allow for personalized treatment approaches, utilizing biological therapies such as receptor-blocking antibodies and cytokines. This enables tailoring the treatment to individual patients based on their specific needs and characteristics. As an illustration, in the United States, a highly developed country, the 5-year event-free survival (EFS) rate for ALL ranges from 89% to 96% [11]. In contrast, in Thailand, an underdeveloped country, the rate is only 67% [12]. In Poland, the cure rate is consistently improving and currently stands

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Table1. The International Consensus Classification of ALL [6]

B-ALL with t(12;21)(p13.2;q22.1)/ETV6::RUNX1
B-ALL. hyperdiploid
B-ALL. low hypodiploid
B-ALL. near haploid
B-ALL with t(5;14)(q31.1;q32.3)/IL3::IGH
B-ALL with t(1;19)(q23.3;p13.3)/TCF3::PBX1
B-ALL. BCR::ABL1–like, ABL-1 class rearranged
B-ALL. BCR::ABL1–like, JAK-STAT activated
B-ALL. BCR::ABL1–like, NOS (undefined)
B-ALL with iAMP21
B-ALL with MYC rearrangement
B-ALL with DUX4 rearrangement
B-ALL with MEF2D rearrangement
B-ALL with ZNF384(362) rearrangement
B-ALL with NUTM1 rearrangement
B-ALL with HLF rearrangement
B-ALL with UBTF::ATXN7L3/PAN3,CDX2 (“CDX2/UBTF”)
B-ALL with mutated IKZF1 N159Y
B-ALLwith mutated PAX5 P80R
Provisional entity: B-ALL. ETV6::RUNX1-like
Provisional entity: B-ALL. with PAX5 alteration
Provisional entity: B-ALL. with mutated ZEB2 (p.H1038R)/IGH::CEBPE
Provisional entity: B-ALL. ZNF384 rearranged-like
Provisional entity: B-ALL. KMT2A rearranged-like
B-ALL, NOS (undefined)
T-ALL
Early T-cell precursor ALLwith BCL11B rearrangement
Early T-cell precursor ALL. NOS
T-ALL. NOS
Provisional entity: natural killer cell ALL

Table 2. The International Consensus Classification of AML [9]

AML with defining genetic abnormalities
AML with RUNX1::RUNX1T1 Fusion
AML with CBFB::MYH11 Fusion
Acute promyelocytic leukaemia with PML::RARA Fusion
AML with KMT2A rearrangement
AML with DEK::NUP214 Fusion
AML with MECOM rearrangement
AML with RBM15::MRTFA Fusion
AML with NUP98 rearrangement
AML with other (rare) defined genetic alterations
AML with NPM1 mutation
AML with CEBPA mutation
AML defined by differentiation
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia

at approximately 86.6% for EFS [13]. The outcomes of treating AML are less favorable in comparison to the lymphoblastic form [7,14]. Remission of the disease is typically achieved in up to 63% of patients within a 5-year period and it depends on the AML subtype. As an example, the remission rate is lowest in M5, reaching 43%, while it is highest in M0, reaching 66% [15]. The 5-year event-free survival rate typically ranges from 60% to 64.3% on average [7,14]. Projections indicate that over the next decade, global morbidity and mortality rates are expected to remain relatively stable, with a slight downward trend. However, regions such as Africa and the East Mediterranean are projected

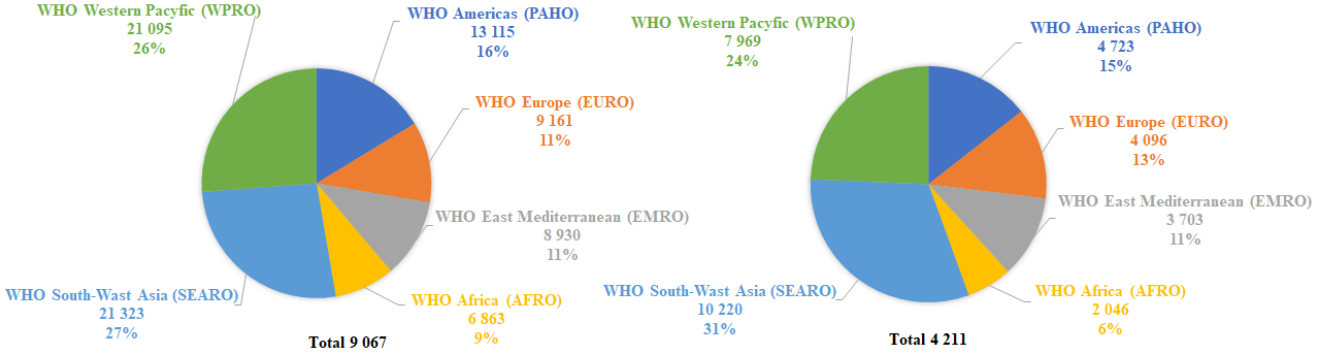

Figure 1. Incidence statistics of childhood acute leukemias in 2020 in WHO regions. a. Number of new cases; b. Number of new deaths [1,10]

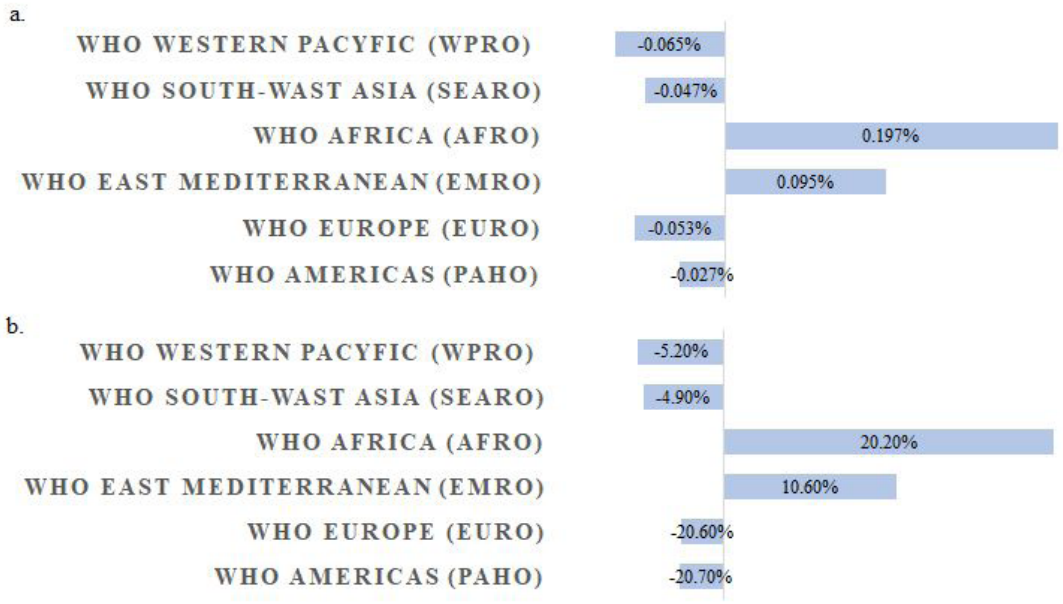

Figure 2. Incidence trends of pediatric leukenia in 2020-2030. a. Percent of new cases; b. Percent of new deaths [16]

to experience a significant increase in morbidity and mortality. Conversely, Europe, both Americas, South-East Asia, and the Western Pacific are expected to see a decrease in morbidity and mortality rates [16] (Figure 2). The statistics mentioned above underscore the critical importance of conducting comprehensive epidemiological studies. While it's clear that acute leukemia risk in children is primarily influenced by inherited and acquired genetic disorders, often with sporadic or unknown origins, it remains essential to investigate environmental factors as well, especially when comparing this scenario to the adult population. This review explores various risk factors to help us better understand why leukemia is becoming more common in children. Although ALL and AML represent distinct types of leukemia, there exist shared and distinct etiological factors between them. Consequently, we have undertaken a comprehensive discussion of both pathologies. Notably, this review presents a novel contribution in the form of a comparative summary of these two leukemia types.

2. Biological factors determining the occurrence of leukemias and response to treatment

As previously stated, biological factors such as age, gender, and race have an impact on both the occurrence and treatability of leukemia. However, variations in these associations can be observed between the two types of leukemia.

2.1. Age

The incidence of ALL and AML varies depending on age (Figure 3). The peak of ALL incidence occurs between the ages of 1–4 years, and in children aged 5–9 years a significant downward trend is observed., During the developmental period, i.e. children aged between 10–19, the incidence decreases only slightly. AML is most commonly diagnosed in children under 1 year of age. Similar to the case of ALL, the incidence decreases between the ages of 5–9 years, while in older children aged 10–14 years, it slightly increases [17]. Long-term event-free survival is significantly affected by the type of acute leukemia. The poorest long-term survival rates in children with ALL are observed in both infants and older children aged 15–19 years, while slightly higher chances of long-term survival are observed in children aged 1–9 years. [18,19]. In children with AML the lowest survival rate is observed in infants and young children aged 1–4 years [19].

2.2. Gender

Boys suffer from both leukemias ALL and AML more often than girls and regardless of region of residence, e.g. in 2020, 57.9% of diagnoses were for boys and 42.1% were of females. Boys also have a lower chance of survival than girls; in 2020 the rate was 58.5% for girls and 41.5% for boys (Table 3) [20,21]. Lower chances of a long-term cure in boys are associated with the more frequent incidence T subtype of ALL. In addition, boys are more likely to have an unfavorable negative CD10 immunophenotype [22,23]. Recent studies suggest that the increased incidence of ALL in boys is related to single nucleotide polymorphisms [24].

2.3. Race

Hispanic children are most likely to develop ALL. In contrast, children of Black ethnicity have the lowest likelihood of developing ALL [25,26]. AML cases are observed the most often in

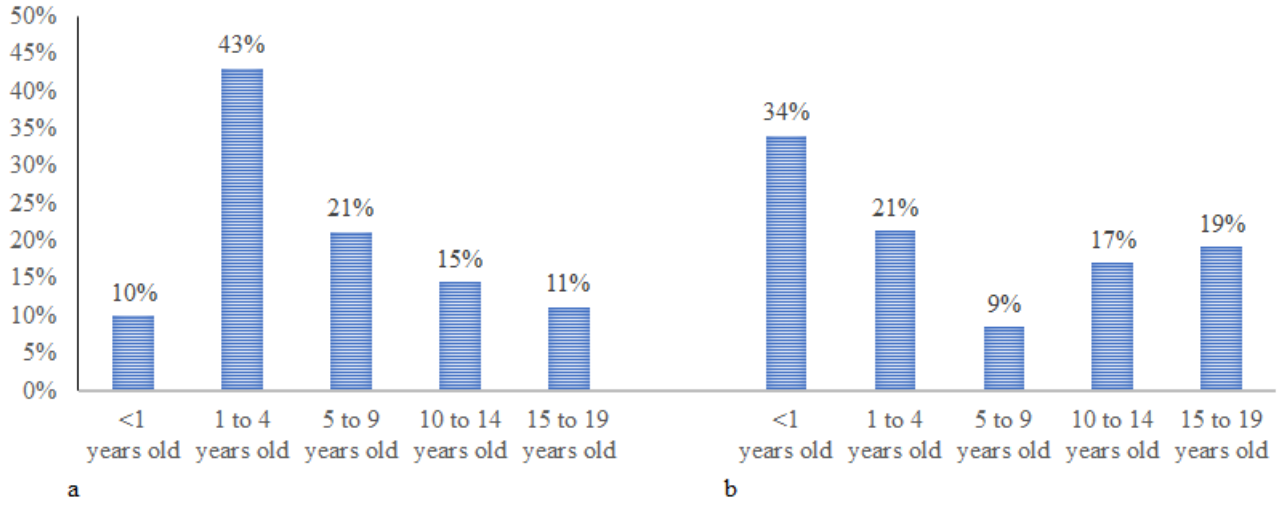

Figure 3. a. Incidence percantage of childhood ALL by age; b. Incidence percantageof childood AML by age [17,18,19]

Table.3 Estimated number of new cases and mortality in 2020 for childhood leukemia [20,21]

Population	New incident		Mortality	
	Females	Male	Females	Male
WHO South-East Asia	40.8 %	59.2 %	38.3 %	61.7 %
WHO Western Pacific	40.6 %	59.4 %	43.1 %	56.9 %
WHO Americas	44 %	56 %	41.5 %	58.5 %
WHO East Mediterranean	43.5 %	56.5 %	40.1 %	59.9 %
WHO Europe	41.7 %	58.3 %	42.1 %	57.9 %
WHO Africa	42.3 %	57.7 %	43.9 %	56.1 %
all WHO regions	42.1 %	57.9 %	41.5 %	58.5 %

Asian children. Moreover, similar to ALL, Hispanic children suffer from AML quite often [25,26]. Children of Hispanic and Black ethnicity have a lower probability of achieving long-term event-free survival (EFS) [26,27]. Preliminary screening studies suggest the involvement of certain genetic factors in the development of childhood leukemia among Hispanic and Black children [26,28]. These genetic factors associated with race may influence disease characteristics and treatment response, although the precise mechanisms are not fully understood. It is observed that Hispanic and Black children with AML tend to have worse outcomes, possibly due to a higher prevalence of cytogenetic translocation t(8;21), as well as deletions of chromosome 5q or 7q [26]. A recent genome-wide association study conducted in Hispanic children with ALL revealed the discovery of a previously unidentified susceptibility locus within the *ERG* gene [28]. The higher incidence of leukemia among Hispanic children is also associated with a somatic mutation in the *ARID5B* gene [29].

3. Etiological hypotheses

Extensive research has been conducted to understand the etiology of leukemias over the years. Numerous factors have been identified thus far that can initiate or contribute to the development of leukemia, including infections, allergies, genetic disorders, dietary factors, chemical exposures, UV radiation, and medication usage [30-34].

3.1. Infections

The age group most commonly affected by leukemia is children between the ages of 1 and 5, particularly in ALL as mentioned earlier. This coincides with a critical period of intense immune system development and learning to effectively respond to bacterial and viral threats. Researchers have extensively studied this association for many years [35,36]. Throughout this time, several hypotheses have been proposed, with three main hypotheses currently prevailing. These hypotheses share the

common belief that leukemia may be triggered by an abnormal immune response to infections.

The extensive body of evidence on this topic has been primarily gathered by Greaves.

According to this researcher, the development of ALL involves two distinct stages, each driven by separate genetic events. The initial event involves the spontaneous occurrence of gene fusion or hyperdiploidy in utero during the proliferation of B-cell precursors, leading to the formation of a pre-leukemic clone. The second event takes place early in life within the same mutated pre-leukemic clone, triggered by antigenic challenge. [37-39]. According to Greaves, the second event affects only infants and children who live in isolation from infectious agents in the first years of life. If exposure to infectious agents is delayed, the immune system does not develop properly, and these children may experience greater cell proliferation following the first infections. Thus, the risk of a second mutation leading to the development of ALL is increased. For this reason, Graves called his hypothesis delayed infection hypothesis [37-39]. The hypothesis put forth by Greaves is supported by research findings that demonstrate a lower incidence of leukemia among children who, irrespective of their race, had early-life exposure to other children, siblings, or attended kindergarten [40-43].

The second hypothesis described by Smith suggests that the development of childhood leukemia could be caused by an infection during pregnancy. Exposure of the fetus to an infectious agent can impact genetic stability, potentially initiating the development of leukemia, particularly in young children up to the age of 5 years [44]. Several independent studies have confirmed this hypothesis, but no single specific maternal infectious agent has been identified. They are concerned about a variety of infections, including viruses such as EBV (Epstein-Barr virus), influenza, pneumonia, or even sexually transmitted diseases such as chlamydia, genital herpes, and human papillomavirus [45,46]. Contradictory findings have been reported in other studies regarding the association between maternal infection and leukemia in the child [47,48]. Thus, the results remain inconclusive.

Another hypothesis, proposed by Kinlen, is the population mixing hypothesis, which primarily applies to developing countries. This hypothesis suggests that the increased incidence of leukemia is linked to the migration of individuals from urban to rural areas, where children live in relatively isolated communities. According to this hypothesis, the introduction of a new infection, possibly viral, into the local population could play a role in triggering leukemia. Therefore, leukemia could be a consequence of an immune response to an unrecognized and novel infection [49]. Independent research has provided supporting evidence for Kinlen's hypothesis, particularly in relation to children between the ages of 1 and 4 years, with a specific focus on ALL [50,51].

Regardless of the above hypotheses, it is believed that some viruses may be oncogenic and lead to the development of leukemia. Such viruses include EBV and HHV-6. A higher incidence of a specific subtype of acute large B-cell leukemia has been noted in patients with an Epstein-Barr virus (EBV) infection [45,52]. Additionally, it was observed that children diagnosed with leukemia who had detectable EBV DNA in their bone marrow exhibited a higher rate of relapse compared to those without the virus detected [53]. This suggests the oncogenic nature of EBV and involvement in the promotion of leukemia. The HHV-6 virus has the ability to integrate its genome into the telomeres of host chromosomes during latent infection in cells. This integration within the telomere region can potentially have adverse effects on the host cell by disrupting its protective mechanisms against chromosome shortening or causing misidentification of the chromosome end as a double-strand break. As a result, it is believed that HHV-6 has oncogenic potential [54]. Indirect evidence comes from tests indicating the detection of HHV-6 DNA in the bone marrow of children diagnosed with acute T-cell and B-cell leukemias [55,56]. Additionally, children with leukemia were found to have higher levels of anti-HHV-6 antibodies in their serum, indicating a potential oncogenic potential of this virus [57].

3.2. Allergies

Over the past few decades, there has been a notable rise in the incidence of cancer and allergies among patients, prompting researchers to investigate the potential connections between these two conditions. Currently, two hypotheses have been proposed to explain this relationship. One hypothesis suggests that allergies may decrease the risk of cancer, while the other hypothesis proposes that allergies may increase the risk [58]. The first hypothesis, based on enhanced immune surveillance, suggests that immune hyperresponsiveness to external antigens may play a role in inhibiting or protecting against the development of cancer [58]. Limited data suggest that children diagnosed with allergies may have a reduced risk of leukemic hyperplasia [30]. This mainly concerns children diagnosed with atopy, who are less likely to suffer from ALL. There was no association between atopy and AML [59]. However, the majority of data regarding the association between leukemia development and allergic diseases tend to support the second, opposing hypothesis. According to it, the reduction of tolerance to environmental allergens leads to a shift in the balance between Th1 / Th2 lymphocytes in favor of Th2. Consequently, the weakened reactions related to the Th1 anticancer response and the increased reactions associated with the Th2 immunotolerant response result in an augmentation of tolerance mechanisms towards malignant cells. This effectively facilitates or sustains the formation of cancer [58]. For instance, a significant correlation has been demonstrated between the diagnosis of an allergy at least one year prior to the onset of ALL [60].

It has been observed that an imbalance between Th1 and Th2 lymphocytes may be attributed to a congenital defect in tolerance mechanisms. Infants with ALL exhibit lower levels of IL-10, an important regulator of response timing and duration, compared to healthy children. IL-10 is primarily secreted by immunoregulatory Tregs, which play a crucial role in maintaining the balance between Th1 and Th2 lymphocytes [61]. Furthermore, the dysregulation of immune function in the early stages of life implies that maternal factors may have an impact on the development of leukemia and allergic diseases. A modest positive correlation was found between increased levels of maternal serum immunoglobulins, a key indicator of allergies, and the risk of lymphoblastic leukemia. This association is particularly noticeable in the Hispanic population. Since IgE antibodies play a role in initiating several mechanisms involving cytokines and inflammatory mediators, they may be linked to the development of ALL in children [62]. Furthermore, Schaub et al. observed reduced expression of Foxp3, as well as decreased levels of interleukin-10 and IFN-γ, in children born to atopic mothers. These findings indicate a potential dysfunction in the regulatory functions of Treg cells in newborns with atopic mothers [63]. Reduced activity of Treg cells may result in dysregulation of Th1 and Th2 functions and may explain the simultaneous increase in the incidence of allergic and cancer diseases. Individuals with allergies are known to be more susceptible to infections. Similarly, it has been observed that children born to mothers with allergies may also exhibit compromised anti-infective immunity. This weakened response to infections can potentially contribute to the development of leukemia, as discussed earlier [64]. It is also hypothesized that chronic immune system stimulation by allergens could elevate the risk of cancer development. The increased presence of proliferating cells raises the probability of genetic errors, including pre-cancerous mutations that may go uncorrected during subsequent cell divisions [65]. The relationship between leukemias and allergies is intricate and necessitates additional comprehensive research. Conducting a thorough analysis of the underlying mechanisms in both conditions could contribute to the development of biological medications.

3.3. Genetic predispositions

Our research, summarized in Table 4, underscores the genetic underpinnings of leukemia, which typically arises from de-novo mutations but can also manifest as a secondary genetic disorder. While hereditary leukemia predominantly affects adults, children, although less commonly, can also be afflicted, thus contributing to the increased incidence of leukemia in this population. For example, individuals with Down syndrome (DS) exhibit a 10-20 times higher likelihood of developing acute leukemia, with the most prevalent subtype being AML constituting 10% of all cases of AML. Only 2% of all childhood ALL cases concern children with DS. A total of 20% of children with DS ALL have a somatic mutation in the *JAK2* gene [1]. There are 5-10% of children with DS, less than 1-year-old, who may have a transient myeloproliferative syndrome characterized by the presence of young immature hematopoietic cells in the peripheral blood that infiltrate extramedullary hematopoiesis. In 13-33% of these children, AML develops as a result of the myeloproliferative syndrome. In myeloproliferative syndrome and in AML blasts, *GATA1* mutations are almost always detected [66]. The development of acute leukemias in patients with DS is mainly associated with an extra chromosome 21 and rearrangement of the *AML-1* gene located on chromosome 21q22 [66].

DNA repair gene syndromes and chromosomal instability syndromes are a group of diseases that may be predisposed to leukemia. Fanconi anemia (FA) is a recessively inherited disorder associated with developmental abnormalities, progressive bone marrow failure, and aplastic anemia. The consequence of this type of anemia is most often AML, but there are cases of ALL as well [67,68]. AML likely begins due to deletions or point mutations in the FANCA gene, a characteristic feature of Fanconi anemia. In both conditions, chromosome abnormalities such as 1, 3q, 5, and 7 are commonly observed [69]. Bloom's syndrome (BS) is an autosomal recessive disease, caused by mutations in the *BLM* gene. BLM protein, which functions as a DNA helicase, is essential for DNA replication and repair processes. [70]. Bloom's syndrome leads to inflammatory skin alterations as a result of heightened sensitivity to UV light, along with the presence of telangiectatic features, as well as both hypo- and hyperpigmented skin spots. It also predisposes individuals to malignancies, including an increased risk of developing ALL and AML. [66,71]. Ataxia-telangiectasia (AT) is an autosomal recessive disorder involving chromosome breakage, resulting from mutations in the *ATM* gene. This condition is marked by the progressive development of cerebellar ataxia, the presence of telangiectasia, immunodeficiency, and an increased susceptibility to cancer, particularly lymphoid malignancies and ALL [72-74]. Constitutional Mismatch Repair Deficiency (CMMRD) is a condition that is inherited by 50% of affected patients. CMMRD results from mutations in repair genes such as *MSH2*, *MSH6*, *MLH1*, and *PMS2*. The correction of replication errors is vital to preventing the buildup of mutations in dividing cells. Replication correction and repair are managed by the exonuclease domains of DNA polymerases and the mismatch repair system. Mutations in these genes can lead to DNA repair disorders and an increased risk of cancer, including ALL. [75,76]. Robertsonian translocation (RT) is a genetic event where a chromosome from one pair becomes nearly fully fused with a chromosome from another pair, resulting in the loss of a small number of genes that are also found on other chromosomes. This translocation specifically involves chromosomes 15 and 21 and typically doesn't manifest any distinctive external features, however, children with Robertsonian translocation have an increased likelihood of developing ALL [77,78]. Beckwith-

Table.4. Genetic predisposition to childhood leukemia

Acquired syndromes/ Genetic disorders	Type of leukemia	Mutation
Down Syndrome		
Down Syndrome (DS)	ALL/AML	*JAK2* *GATA1*
DNA repair gene syndromes and chromosomal instability syndromes		
Fanconi anemia (FA)	MDS/AML	*FANCA*
Bloom's syndrome (BS)	ALL AML	*BLM*
Ataxia-telangiectasia (AT)	ALL	*ATM*
Constitutional Mismatch Repair Deficiency (CMMRD)	ALL	*MSH2* *MSH6* *MLH1* *PMS2*
Robertson translocation(RT)	ALL	
Tumor suppressor gene syndromes		
Li-Fraumeni syndrome(LFS)	ALL	*TP53*
Neurofibromatosis (NF1)	ALL AML (JMML)	*NF1*
Beckwith-Wiedemann syndrome (BWS)	ALL	*CDKN1C*
Pure familial leukemia		
Acquired monosomy 7	MDS/AML	*Unknown*
Hereditary platelet disorders (HPDs)	MDS/AML	*RUNX1* *ETV6* *RD26*
Bone marrow failure syndromes		
Shwachman-Diamond syndrome (SDS)	AML	*SDS*
Diamond Blackfan anemia (DBA)	MDS/AML	*DBA*
Congenital amegakaryocytic thrombocytopenia (CAMT)	MDS/AML	*c-Mpl*
Cyclic neutropenia (CyN)	MDS/AML	*ELANE*
Severe congenital neutropenia (SCN)	AML	*ELANE HAX1*
Amegakaryocytic thrombocytopenia (AMT)	MDS/AML	*c-MPL*
Hereditary platelet disorders (HPDs)	MDS/AML	*RUNX1* *ETV6* *RD26*
Aplastic anemia (AA)	MDS/AML	*SLIT1* *SETBP1* *ASXL1* *MYBL2* *TET2*

Wiedemann syndrome (BWS) is a syndrome characterized by neonatal hypoglycemia, abdominal wall defects, macroglossia, organomegaly, and birthweight. Children with BWS have an increased risk of malignancy and ALL. BWS is caused by genetic or epigenetic defects in the chromosome 11p15.5 region, and *CDKN1C* mutation [79].

Tumor suppressor gene syndromes, which exert a suppressive influence on cell cycle regulation and encourage apoptosis, constitute another category of diseases that increase the predisposition to leukemia. Li-Fraumeni syndrome (LFS) typically affects older children, with a median age of 15.5 years [80]. LFS, a rare autosomal dominant syndrome, is marked by an elevated vulnerability to multiple primary tumors. The syndrome results from mutations in the tumor suppressor gene TP53. Mutations in the TP53 gene result in the impairment of the transcription factor p53, leading to irregularities in the cell cycle and apoptosis. Among children carrying this mutation, the most prevalent diagnosis is ALL leukemia with a hypodiploid karyotype. [80] [81]. Neurofibromatosis (NF1) is an autosomal dominant genetic disorder classified within the group of neurocutaneous dysplasias (phakomatoses). This condition is attributed to a mutation in the *NF1* gene located on chromosome 17, responsible for encoding neurofibromin—a tumor suppressor protein [82]. Patients with NF1 also have a higher risk of ALL and AML. The *NF1* tumor suppressor gene encodes neurofibromin that regulates the growth of immature myeloid cells by accelerating guanosine triphosphate hydrolysis on Ras proteins [74]. The 15% of children with juvenile myelomonocytic leukemia (JMML) have a mutation in the *NF1* gene. The JMML is a unique, aggressive hematopoietic disorder of infancy and early childhood [83,84].

Certain inherited mutations can increase the susceptibility to familial leukemia. Acquired monosomy 7 predisposition syndromes typically exhibit the following characteristics: a heightened risk of bone marrow insufficiency, severe cytopenia, varying degrees of adaptive immune deficiency, bone marrow aplasia, and myelodysplastic syndrome (MDS) [85]. Monosomy 7 is identified in peripheral blood and/or bone marrow cells and is an acquired clonal cytogenetic alteration. Children with monosomy 7 don't have other predisposing medical conditions [85,86]. Monosomy 7 (–7) is found in about 40% of children with AML [86]. Hereditary platelet disorders (HPDs) impact the quantity and/or functionality of platelets, leading to hemostatic defects in patients that can range from mild to severe. One common complication in affected children is bleeding. Additionally, there is an elevated risk of other complications, such as kidney diseases, deafness, immune deficiencies, and malignancies [87]. This condition is primarily attributed to mutations in up to 40 genes, with the most frequent mutations occurring in three specific genes: *RUNX1*, *ETV6*, and *ANKRD26* [87,88]. Mutations in these three genes predispose individuals to MDS and AML [89].

Hereditary bone marrow failure syndromes are a heterogeneous group of disorders that lead to anemia and bone marrow failure and are characterized by an increased incidence of malignancies. For example, Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder that is the second most common cause of exocrine pancreatic insufficiency after cystic fibrosis. There are 90% of children with SDS are found to have a mutation in the Shwachman-Bodian-Diamond syndrome (*SBDS*) gene on chromosome 7 [90]. Children with SDS most commonly

experience neutropenia along with cytopenia in other blood cell lineages. They may also exhibit characteristics such as red blood cell macrocytosis, high hemoglobin F, and varying degrees of marrow hypoplasia. Approximately 15–20% of children with SDS develop MDS, and they are at a heightened risk of progressing to AML [91,92]. Diamond-Blackfan anemia (DBA) is a rare bone marrow failure syndrome, occurring in approximately 6–7 cases per million live births. In DBA, patients have haploinsufficient mutations in one of several ribosomal genes, categorizing DBA as a "ribosomopathy" [93]. Children with DBA suffer from hypoplastic anemia, congenital anomalies, and are at an increased risk of hematologic AML and MDS [92,93]. Congenital amegakaryocytic thrombocytopenia (CAMT) disorder is characterized by thrombocytopenia presenting at birth in a child and reduced or absent bone marrow megakaryocytes. The megakaryocytes that are present may look small or immature. Infants have petechiae and other signs of bleeding [94]. It has been shown that children with CAMT have homozygous or heterozygous mutations in the thrombopoietin receptor c-Mpl [95]. CAMT, an autosomal recessive disease, can evolve into MDS or AML [94,95]. Neutropenia is defined by a reduction in circulating neutrophil levels. In cyclic neutropenia (CyN), neutrophil counts oscillate between nearly normal levels and close to zero in a 21-day cycle. CyN, which is an autosomal dominant disorder, is associated with heterozygous mutations in the *ELANE* gene, responsible for encoding neutrophil elastase [96]. Sometimes these patients require granulocytic growth factor (G-CSF) [97]. They are also at increased risk of developing MDS, and about 11% of patients develop AML [96,98]**.** Severe congenital neutropenia (SCN) is a congenital immunodeficiency characterized by impaired maturation of neutrophil granulocytes. Children are prone to recurrent and often life-threatening infections that begin in their first months of life [98]. The disease is caused by the *ELANE* gene and mutation of the *HAX1* mitochondrial gene with an anti-apoptotic function. Therefore, neutrophils affected by the mutation undergo premature apoptosis [97]. They are also at an increased risk of developing MDS; about 12.7% of patients develop AML [96,98]. Amegakaryocytic thrombocytopenia (AMT) is a severe condition characterized by a significant reduction or absence of megakaryocytes in the bone marrow, leading to low platelet counts. This condition exists in two primary forms: congenital and acquired. [99,100]. CAMT is a rare, severe form of thrombocytopenia with reduced or absent megakaryocytes in the bone marrow since birth, especially seen in the neonatal period. CAMT is caused by mutations in the thrombopoietin *c-MPL* receptor gene [100]. Acquired amegakaryocytic thrombocytopenia (AAMT) is seen in later years of life and is also characterized by reduced or absent megakaryopoiesis. The megakaryocyte maturation suppression is caused by autoimmune diseases, viruses such as EBV or parvovirus B19, and chromosome aberrations such as the Philadelphia chromosome or and 5q deletion [99,101]. It has been shown that both forms of AMT can evolve into MDS or AML [99-101]. Hereditary platelet disorders (HPDs) are a group of conditions characterized by a decreased platelet count and impaired platelet function, often resulting in bleeding as a typical symptom. As a consequence of HPD, kidney diseases, deafness, immunodeficiencies, and cancer are observed. As the disease progresses, mutations can arise in more than 40 genes, with the most frequent ones being *RUNX1*, *ETV6*, and *ANKRD26*. Mutations in these three genes also increase the susceptibility to MDS and AML [87-89]. Aplastic anemia (AA) is a clinical condition characterized by a deficiency of blood cells in the peripheral blood and a bone marrow with reduced cellularity. AA can follow various courses, including acute, subacute, or chronic forms with intermittent periods of temporary remission. One significant long-term complication is the development of secondary myeloid malignancies [102]. Somatic mutations in genes such as *SLIT1*, *SETBP1*, *ASXL1*, *MYBL2*, and *TET2* are identified in about 5.3% of AA patients [103]. Over a 10-year period, AA can progress to MDS or AML with a cumulative incidence ranging from 3.1% to 9.6% [103,104]. Dyskeratosis congenita (DC) is a condition characterized by the presence of shortened telomeres and mutations in genes associated with telomere biology. These mutations result in abnormal cell division within the bone marrow and accelerated cell death. DC manifests as keratinization of mucous membranes, nail abnormalities, unusual skin pigmentation, and aplastic anemia. Furthermore, DC heightens the likelihood of developing malignancies, with AML and MDS being the most frequently observed [105,106].

An interesting association was also found between the incidence of leukemia in both monozygotic twins. When one of the twins was diagnosed in the first months of life, the other was diagnosed within a few months [107,108]. Moreover, twins suffering from leukemia shared a common aberration in the *MLL* 11q23 gene, which is a factor of poor prognosis and is a characteristic genetic alteration for infantile ALL. This suggests that this mutation, which is the cause of leukemia initiation, appears in utero [109]. There are studies suggesting that childhood leukemias may have a genetic foundation and could potentially originate during prenatal development. One piece of indirect evidence supporting this idea is the connection between elevated birth weight and an increased risk of developing ALL. Additionally, there is an elevated risk of AML in both underweight and overweight newborns. However, it's important to note that this evidence remains indirect, as researchers have not yet identified a specific genetic factor to account for this relationship. [110].

3.4. Diet, stimulants, chemical factors

The data presented above highlight the strong correlation between fetal development and the risk of leukemia, underscoring the critical significance of the prenatal period in ensuring optimal

child development in the future. An inappropriate diet, excessive consumption of stimulants, or exposure to diverse chemical compounds during pregnancy can potentially disrupt this crucial developmental process. Over the last decade, numerous studies have been conducted to investigate the potential link between these factors and the development of leukemia. Furthermore, researchers have explored whether exposure to these same factors during childhood also impacts the initiation of the leukemia process. Studies have demonstrated that the dietary choices of women before and during pregnancy can significantly influence the likelihood of their child developing leukemia. Consuming a diet abundant in vegetables, fruits, and diverse sources of protein has been found to be inversely associated with the risk of ALL [33,111]. Eating a lot of protein from meat is moderately linked to the risk of leukemia in a baby. It is likely that fetal exposure to bioactive compounds found in vegetables, fruits, and protein products, such as vitamins and minerals, fiber, peptides, amino acids, and other factors, may contribute to reducing the risk of cancer [111]. Additionally, folic acid supplementation is important. WHO recommends taking folic acid to women planning pregnancy before and during pregnancy to reduce the risk of neural tube defects, low birth weight, and anemias in offspring [112]. Nowadays, it is known that the supplementation of folic acid during pregnancy, to a small extent can also prevent the development of ALL and AML [113-115]. Another highly advisable practice is breastfeeding, as it exerts a regulatory influence on the immune system of the newborn due to the presence of components in breast milk, including vitamins, maternal antibodies, microorganisms like Lactobacilli or Bifidobacteria spp., cytokines/chemokines, lipids, and oligosaccharides that nourish the infant's intestinal microbiome. Breastfeeding is also associated with a low risk of infectious diseases, asthma, autoimmune diseases, and obesity in childhood [116,117]. It has been shown that breastfeeding also reduces the risk of ALL and AML in childhood, but only if the newborn has been breastfed for at least six months [118,119]. The presence of pesticides, including insecticides and herbicides, in the residential environment during pregnancy has been positively linked to the occurrence of childhood leukemia. Similarly, there is a smaller yet still positive association between childhood exposure to pesticides and morbidity [120]. These findings support the concepts proposed by Geraves' two-stage model of leukemia, indicating that the initial mutations occur during prenatal development, followed by additional mutations occurring after birth. While the traditional view suggests infectious agents as the causative agents, these results suggest that pesticides can also play a role in the development of leukemia. Interestingly, no elevated occurrence of leukemia was observed even in cases of children's exposure to passive tobacco smoke inhalation, both during pregnancy and in early childhood [121]. Some studies suggest that smoking by fathers one month before pregnancy may increase the risk of leukemia initiation in a child [122]. In the case of alcohol consumption by pregnant mothers, the situation is different. There is a notable association between a higher frequency of myeloid leukemia in children, particularly in infants and those up to 18 months old. The most frequently diagnosed subtypes in these cases are M1 (acute myeloblastic leukemia without maturation) and M2 (acute myeloblastic leukemia with maturation) [122]. The use of non-aspirin and non-steroidal anti-inflammatory drugs during pregnancy is not found to be significantly linked to the risk of infant leukemia[123]. Likewise, research indicates that the use of antidepressants during pregnancy does not affect the child's leukemia risk [124].

3.5. Ionizing radiation and electromagnetic fields

Ionizing radiation is a form of high-energy radiation that directly impacts the DNA structure, causing various forms of damage. This includes single base alterations, single-strand breaks, as well as double-strand breaks occurring at multiple locations. [125]. This type of damage increases the frequency of mutations, which leads to cancer formation. Evidence of this association was observed in the late 1940s, when after the explosion of atomic bombs, doctors from Hiroshima and Nagasaki noticed a significant increase in the incidence of leukemia, especially among children. The first reports on this subject started to appear several years after the bomb explosion [32]. Since then, the influence of ionizing radiation on the formation of childhood leukemias has become the subject of many studies. Among others, exposure to low dose radiation in radiological studies and even small doses of radiation generated by CT have been shown to result in a small but detectable increase in the risk of developing leukemia. There are no significant disparities across age groups or leukemia subtypes, although there is a slightly higher risk of B-cell precursor ALL [126]. Similarly, X-ray examination of the abdominal cavity of women, especially in the last trimester of pregnancy, is associated with a slight positive effect on the subsequent formation of leukemia in children [127]. Moreover, therapeutic radiation like radiotherapy used in cancer treatment slightly increases the risk of secondary cancers, including leukemia. AML is slightly more common than ALL [34,128]. Leukemias as a result of childhood oncological treatment are usually diagnosed about 10-15 years after the first cancer diagnosis. For this reason, they mainly affect adults, less often children [34,128]. According to one hypothesis, the suppressor genes undergo several changes. Therefore, the longer time and additional environmental factors may be involved to initiate the growth of the leukemic clone [129]. Observations have indicated that the administration of therapeutic bone marrow irradiation, particularly at average doses ranging from 3 to 6.6 Gy, is correlated with the subsequent development of secondary cancers, including leukemia. The relationship between radiation and the risk of developing

leukemia is intricate, involving cell killing, transformation, and DNA repair processes. When administered at very high doses and high rates, cell destruction is more likely to prevail, and as a result, high doses do not contribute to an increased risk of developing leukemia [34]. Also, radiotherapy used in the treatment of non-oncological diseases is slightly associated with the detection of leukemia. For example, children who received radiation therapy for the treatment of mycosis skin or treatment of hemangiomas were more frequently observed to have leukoplakia diseases [130,131]. It is suggested that exposure to the electromagnetic field emitted by mobile phones or radios is carcinogenic and may cause leukemia [132,133]. So far, there is no direct evidence that a carcinogenic effect of those magnetic fields might cause leukemia in children, as most studies are based on epidemiological data or animal experiments [134].

3.6. Anticancer drugs and secondary leukemias

In addition to radiotherapy, the risk of developing leukemia can also be influenced by the administration of anticancer drugs. Secondary cancers, including leukemias, can arise as a result of such drug treatments, with AML being the most commonly observed type. The risk is influenced by the administration of specific drugs used in therapy, namely alkylating cytostatics and inhibitors of topoisomerase II (such as epipodophyllotoxins and anthracyclines) [128,135]. Both groups of these drugs are widely used in anti-cancer treatment and they are to kill the cancer cell by damaging the DNA structure [128,135,136]. The risk of developing secondary AML increases with epipodophyllotoxin dose and is greater in patients who had a high dose (6g/m2). Children who took moderate doses of epipodophyllotoxin (between 1.2 and 6g/m2) showed a similar risk to children who took moderate or high doses of anthracyclines (170 mg/m2) [137]. It has been shown that AML occurs as a consequence of the treatment of solid tumors in up to 0.5% of children, and after treatment of non-Hodgkin's lymphomas in 1.4% within 5 years [136].

4. Conclusion

Due to the rare occurrence of childhood leukemia, most of the available information on the etiological risk factors for leukemia in children comes from case-control studies. Epidemiological data may not be accurate, especially from low-income countries. These studies employ diverse methodologies, and there is variation in the criteria used to assess different factors related to children and parents. Consequently, some of the findings are contradictory. It is essential to establish protocols for future epidemiological studies and report it in order to minimize potential errors found in existing research. By doing so, we can enhance the quality of results and provide further clarification on the current divergent findings. Although there may be disparities in certain results, the aforementioned factors undoubtedly have an impact on the risk of leukemia development. Their influence varies depending on the different stages of a child's life. The analysis of the available data strongly suggests the need for the development of new guidelines for cancer prevention in all children, particularly those belonging to the high-risk group, such as children with genetic disorders. Currently, periodic cancer screenings are only conducted for children with a history of cancer and children with known genetic predisposition, such as Beckwith-Wiedemann syndrome, NF1, etc. However, in many cases, such screenings could help identify initial abnormalities, such as altered proportions of specific blood cell populations or enlarged internal organs. Therefore, there is a pressing need to implement regular cancer screenings that can detect these early signs and ensure timely intervention. Raising public awareness about prevention is equally crucial, emphasizing the measures that can be adopted to minimize exposure to chemical risk factors associated with childhood leukemia. Promoting information on adopting a healthy lifestyle, minimizing exposure to pesticides and tobacco smoke, as well as following a nutritious diet, can significantly contribute to reducing the incidence of the disease, or at the very least, mitigating its escalating trend.

Authors' contribution

Marzena Ciesielska- Research concept and design, Supervising the project, Carrying out the experiments, Acquisition of data, Data analysis and interpretation, Writing, Visualization, Literature review, Final proofreading and approval of the version for publication; Beata Orzechowska - Final proofreading and approval of the version for publication; Andrzej Gamian - Final proofreading and approval of the version for publication; Bernarda Kazanowska - Final proofreading and approval of the version for publication

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Conflict of interest

The authors have no potential conflicts of interest to declare.

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