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Review

Etiology of Acute Leukemia. A Review

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Abstract: Acute leukemias constitute some of the most common malignant disorders. Despite significant progress made in the treatment of these disorders, their etiology remains unknown. A large and diverse group of genetic and environmental variables have been proposed. The role of a variety of factors, including pre-existing and acquired genetic mutations, exposure to radiation and various chemicals during pre-conception, pregnancy and throughout life have been explored. The effects of inherited genetic variations and disorders, pre-existing diseases, infectious agents, hobbies, occupations, prior treatments and a host of other factors have been proposed, but none is universally applicable to all cases. Variation in the incidence and prognosis based on the age, sex, race, type of the disease, geographic area of residence and other factors are intriguing, but remains unexplained. Advances in genomic profiling, including genome-wide gene expression, DNA copy number, and single nucleotide polymorphism [SNP] genotype may shed some light on the role of genetics in these disparities. Separate two-hit hypothesis for the development of acute myeloblastic and lymphoblastic leukemia have been proposed. The latter combines genetics and infection factors resulting in leukemogenesis. A number of pre- and post-natal environmental conditions and exposure to infections, including a mycovirus infected *Aspergillus flavus,* have been suggested. The exact nature, timing, sequence of the events and mechanisms resulting in occurrence of leukemia requires further investigations. This review summarizes some of the above factors and the direction for future research on the etiology of acute leukemias.

Keywords: etiology; leukemia; acute lymphoblastic leukemia; acute myeloblastic leukemia; genetics; causes; occupations; hobbies; genetic; infections; mycovirus; aspergillus

1. Background

Leukemia is one of the most common malignant disorders affecting the world population. Globally, in 2018 leukemia ranked as the fifteenth most common diagnosed cancer with 437,033 cases and 309,006 mortality, amounting to the eleventh cause of death due to malignant disorders [1]. The geographic distribution of leukemia is universal with higher prevalence and mortality in the more developed countries. Based on the Cancer Facts and Figures provided by the American Cancer Society, for the year 2020, It was estimated that 178,520 individuals were to be diagnosed with leukemia, lymphoma and myeloma in the United States. This accounts for 9.9 percent of the estimated 1,806,590 new cancer cases diagnosed in that year. While both sexes are affected, leukemia is more prevalent in males. The age-standardized incidence rates for leukemia in males and females in 2018 in the United States were 6.1 and 4.3 per 100,000, respectively. Likewise, the mortality rate of 4.2 per 100,000 population was higher for males compared to 2.8 per 100,000 in females [1].

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2. Age and Race

Age and race are important factors in the incidence of leukemias. For example, in the United Kingdom, 42.8% of all leukemias occur in the individuals over 65 years [2]. A review of the subject in the United States reports that the overall age-adjusted leukemia incidence is highest in White population at 15 per 100,000, followed by Blacks at 11 per 100,000, and Hispanics 10.6 per 100,000 population [3]. In this report, the incidence among Asian/Pacific Islanders was 7.8 per 100,000 and in American Indian/Alaskan Natives, 8.3 per 100,000 population [3]. Similar racial and ethnic patterns were found for age-adjusted mortality rates per 100,000 population, which were 7 for White population, 5.6 for Blacks, 4.8 in Hispanics, 3.8 in Asian/Pacific Islanders and 3.3 in Indian/Alaskan Natives [3].

While leukemia affects all age groups, its distribution varies based on the type of the disease. The age-adjusted incidence rate of leukemia from 2012-2016 In the United States in children, adolescents and young adults younger than 20 years was estimated to be approximately 4.6 per 100,000**.** Approximately 4.8 percent of all leukemia and lymphoma cases were diagnosed in individuals younger than 20 years of age. As such, it constituted approximately 20-30% of all cancers in this age group. Acute lymphoblastic leukemia (ALL), which is most common in childhood and adolescents, accounts for approximately 75% of all leukemia cases in the individuals under 20 years of age and approximately one quarter of all pediatric cancers. The peak incidence is in children ages 2–5 years. On the contrary, acute myeloblastic leukemia (AML), with the overall incidence of 3–5 cases per 100,000 in general population, is far more prevalent in adults, with an incidence of only 7.7 per million between the ages of 0-14 years. Indeed, the median age at diagnosis for AML is 66 years with 54% of patients being diagnosed after age 65 and 33% over age 75 years. It is of note that the incidence of acute lymphoblastic leukemia has increased over time, at least in the pediatric age group. This, in part, has been attributed to the improved accuracy of the diagnostic techniques and reporting. The incidence for AML appears to have been unchanged [4].

As noted above, racial differences in the incidence of, and mortality caused by different types of acute leukemias have been reported. The incidence for some leukemias, such as ALL, is higher in White than Black population. Based on a 2011 report by the American Association for Cancer Research, Hispanic children have the highest incidence of ALL and one of the lowest survival rates among pediatric patients diagnosed in the United States. In this regard, the report indicates that the overall mortality risk for ALL is 45 and 46 percent greater for Blacks and Hispanics than the White population, respectively. The rate of increase death in AML was 12 and 6 percent higher in these two groups than in the White population [5].

Despite documented racial and ethnic differences in the incidence and outcome, the underlying causes for this disparity remains poorly understood [6-10]. While the role of the financial, social structure versus genetic factors in the incidence and outcome in various populations have been considered, the underlying causes are poorly recognized. Advances in genomic profiling, including genome-wide gene expression, DNA copy number, and single nucleotide polymorphism [SNP] genotype may shed some light regarding the roles of genetic in these disparities [11].

3. Genetics

Undoubtedly, genetic plays a major role in the etiology of leukemia. This is most evident in identical twins. If one of the identical twins develops the disease before the age of 7 years, the other has twice as much chance of developing this disease than the general population. The chance of developing leukemia then reduces in time. The twin who reaches age 15 years without developing leukemia, appears not to have higher risk of developing this disease than the average population [12,13].

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While for the majority of leukemia cases there are no obvious known predisposing factor, some genetic and acquired germline mutations and clonal chromosomal abnormalities are associated with increased incidence of leukemia [14]. Increasingly, using genome wide association studies, germline mutations which can cause leukemia prone changes have been identified. Patients with DNA repair disorders and constitutional chromosomal anomalies can be predisposed to developing leukemia. Some inherited mutations have potential to increase the risk of developing leukemia, this in absence of extramedullary phenotypes. Some families have an increased incidence of leukemia with no known inherited mutations [14]. Major inherited and genetic disorders resulting to predisposition to acute leukemia are summarized in Table 1. Identified genes that can be inherited in an autosomal dominant fashion and potentially result in the development of leukemia include CEPBA, RUNX1 and GATA2. The CEBPA, located at chromosome19q13.1, encodes granulocytic differentiation factor C/EBPa, a member of bZIP family of proteins. RUNX1 gene is located at 21q22.12 and is a transcription factor involved in hemopoiesis. GATA2 gene is located on 3q21.3 and is involved in preserving integrity of hematopoietic stem cells and regulation of phagocytosis. Mutation of GATA2 has been associated with congenital neutropenia and MonoMAC syndrome, a disorder which frequently results in myelodysplastic syndrome (MDS), increased rate of infections and AML or chronic myelomonocytic leukemia [14]. Monosomy 7 has been reported in families with multiple members having MDS and AML. Likewise, inherited bone marrow failure syndromes with a variety of genetic abnormalities can lead to the development of leukemia [14].

Individuals with certain genetic disorders are known to have increased rate of developing leukemia [14-22]. Disorders such as Down syndrome, Ataxia-telangiectasia, Bloom syndrome, Klinefelter syndrome and Diamond Blackfan anemia are at higher risk for leukemia [14-22]. Point, missense or nonsense mutations can occur in the tumor suppressor genes, some of which encode for proteins with suppressive effects on regulation of cell cycle and ability to promote apoptosis. Disorders such as Li-Fraumeni syndrome, neurofibromatosis 1, Noonan syndrome and CBL syndrome are associated with high risk of leukemia [14] . Bone marrow failure syndromes such as Thrombocytopenia with absent radius, Shwachman-Diamond syndrome, amegakaryocytic thrombocytopenia, dyskeratosis congenita and severe congenital neutropenia including Kostmann syndrome are also associated with higher risk for the development of leukemia [14]. Myelodysplastic syndrome, myelodysplasia, polycythemia vera, primary thrombocythemia are also found to be associated with the increased rate of this disease [14]. DNA repair defects such as mismatch repair deficiency syndrome which involves sporadic mutations in genes responsible for DNA repair, as seen in some variants of Lynch syndrome, ataxia telangiectasia, Nijmegen breakage syndrome, Bloom syndrome and Fanconi anemia, can be associated with hematological malignancies [14,19]. It is of note that approximately 33% of patients with Fanconi anemia develop a hematological malignancy by age 40. Germline polymorphisms in IKZF1, CDKN2A, CEPBE and ARID5B have been shown to be associated with increased risk of ALL [14].

Patients with various primary inherited immunodeficiency syndromes are predisposed to the development of malignant disorders including leukemia [14]. These include Wiskott-Aldrich syndrome, a X-linked disorder with the triad of thrombocytopenia, immune deficiency and eczema and Bruton agammaglobulinemia which is due to Bruton tyrosine kinase gene located at chromosome Xq21.3-22 location.

As is discussed in the AML and ALL sections of this review, two-hit theories involving genetics for the development of leukemias have been proposed.

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Table 1. Inherited predisposing syndromes to hematologic malignancy

Predisposing disorder	Gene	Inheritance	Type of leukemia
CEBPA	*CEBPA*	AD	MDS/AML
Monosomy 7	*7p/q*	AD	MDS/AML/ALL
Familial platelet disorder/AML	*RUNX1*	AD	MDS/AML/T-cell ALL
MonoMAC Syndrome	*GATA2*	AD	MDS/AML
Familial AML with mutated DDX41	*DDX41*	AD	MDS/AML/CMML
Thrombocytopenia 2	*ANKRD26*	AD	MDS/AML
Thrombocytopenia 5	*ETV6*	AD	MDS/AM/CMML, B-cell ALL
Familial MDS/AML with mutated GATA2	*GATA2*	AD	MDS/AML/CMML
Li-Fraumeni syndrome	*TP53*	AD	ALL
Neurofibromatosis type 1	*NF1*	AD	JMML/MDS/AML
Noonan syndrome	*PTPN11*	AD	JMML/MDS/AML
CBL syndrome	*CBL*	AD	JMML
Familial aplastic anemia with mutated SRP72	*SRP72*	AD	MDS
Familial B- cell ALL with mutated PAX5	*PAX5*	AD	ALL
Germline SH2B3	*SH2B3*	AR	ALL
Telomere syndromes (dyskeratosis congenita)	*TERC, TERT, CTC1, DKC1, NHP2, NOP10, RTEL1, TINF2, WRAP53, ACD, PARN*	AD, AR	MDS/AML
Diamond Blackfan anemia	*RPS19, RPL5, RPL11*	Sporadic, AD, AR,	MDS/AML/ALL
Shwachman-Diamond syndrome	*SBDS*	AR	MDS/AML/ ALL
Amegakaryocytic thrombocytopenia	*c-MPL*	AR	MDS/AML
Thrombocytopenia with absent radii syndrome	*RBM8A*	AR, Sporadic	ALL/AML
Severe congenital neutropenia	*ELA2, HAX1, G6PC3, WASP*	AD, AR, X-linked	MDS/AML
Fanconi anemia	*FANCA, FANCB, FANCC, BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4*	AR	ALL/AML
Mismatch repair Cancer syndrome	*PMS2, MSH6, MLH1, MSH2*	AR	ALL
Ataxia telangiectasia	*ATM*	AR	ALL
Nijmegen breakage syndrome	*NBS1*	AR	ALL
Bloom Syndrome	*BLM*	AR	ALL
Werner Syndrome	*WRN (RECQL2)*	AR	MDS/AML
Rothmund-Thomson	*RECQL4*	AR	AML
Wiskott-Aldrich Syndrome	*WASP*	X-linked	ALL
Burton's agammaglobulinemia	*BTK*	X-linked	ALL
Trisomy 21 (Down Syndrome)	*21q*	Sporadic	ALL/AML

AD=autosomal dominant, AR=autosomal recessive, MDS=myelodysplastic syndrome, ALL=acute lymphoblastic leukemia, AML=acute myeloblastic leukemia, JMML=juvenile myelo-monocytic leukemia, CMML=chronic myelomonocytic leukemia.

4. Environment and Occupations

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A large number of environmental causes for the development of leukemia have been suggested. These mostly involves exposure to cancer-causing agents, including chemicals, infectious agents and radiation during various stages of life [23-32]. Certain exposures, occupations, industrial hazards, and hobbies have been implicated in a higher risk of leukemia [29-32] (Table 2). Occupations described to be associated with increased risk for leukemias include, but are not limited to, agricultural and forestry work and crop production [33-40] with exposure to pesticides and fertilizers [41-43], construction [33], animal slaughtering and poultry work [33,44,45], vocations in the oil/gas industries with exposure to benzene [35,43,46-52], oil refining and petrochemicals [53-59], automobile mechanic works [37,60], electrical utility careers, jobs with exposure to magnetic fields [61-66], works in the nuclear power industry/exposures to ionizing radiation [50,51,67-71], furniture manufacturing and repair [72] and nursing and health care positions with exposures to infectious agents/viruses [37,39,73-75]. Other occupations with increased risk of leukemia include hairdressing and hair dying [50,76], Painting [77-80], Laundry work, dry cleaning with exposure to dry cleaning chemicals [37,81,82], teachers [35,37], workers in shoe and boot manufacturing industry, [83], taxi, bus, truck, railway drivers and conductors [50,53,66,84,85]. Occupations with exposure to alkylating agents and formaldehyde [73,86,87], textile workers and manufacturers [50,88], semiconductor workers etc. [50,89] are also found to have higher risk of leukemia. With a few exceptions, such a diverse range of occupations, without a unifying element, lack specificity.

Direct and indirect exposures to chemical and pesticides, in a variety of occupations, as a cause for the development of leukemia has been suggested [91-93]. Contact with hydrocarbons compounds such as benzene, gasoline and trichloroethylene has been implicated in the development of leukemia [59,94]. Likewise, in children, a multiplicity of factors including parental occupations, has been proposed to increase risk of acute leukemia. A review of the subject is available [90].

5. Effects of Radiation

The effects of Ionizing radiation in the development of leukemia at various phases of life, including preconception, in utero, and postnatal exposures has been proposed and various examples have been published. A correlation between the dose of irradiation and occurrence of leukemia has been reported [95,96]. Following the bombing of Hiroshima and Nagasaki, Japan, the rate of occurrence of leukemia among survivors who were within 1000 m of the explosions was 20-fold higher than the general population [96]. More recently, consequences of Chernobyl nuclear power plant accident have been studied [97-99].

There are conflicting data regarding the risk of the development of leukemia and exposure to diagnostic x-rays (100-103). Some studies have shown an increased risk for childhood leukemia related to paternal diagnostic x-rays. An increased risk was found if two or more X rays of the lower abdomen were done. However, no increased risk was noted if the data were restricted to lower abdominal X rays [100,101]. In one study, no increased risk of leukemia was noted with maternal abdominal x-rays. Some evidence of increased risk in offspring was noted if the father had more than one abdominal x-ray done before conception or had a prior intravenous pyelogram [103]. some reports reveal only a slight elevation in risk, but no evidence of a dose-response relationship, when x-ray procedures near the time of diagnosis are excluded. In general, correlation between diagnostic X-rays and development of leukemia is inconsistent, inconclusive and subject to a number of variables, including time and reason for the procedure and statistical errors. Some studies have reported increased rate of leukemia in individuals who have had diagnostic X-ray. For example, in one study, children having one or more computed tomography scans had an increased ratio of developing leukemia, indicating that even with low doses of ionizing radiation there is an increased risk of this disease [104].

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However, others find no correlations between diagnostic X-ray tests and increased risk, especially if tests done close to the time of diagnosis of leukemia are subtracted[103].

Inconsistent results regarding exposure to nonionizing radiation as an etiological factor for the development of leukemia have been reported, and generally the effects of such an exposure in the development of this disease has been disputed [105-110].

Table 2.

Industries with increased rate of acute leukemia
Agriculture/Crop production and related ventures
Forestry
Fishing and hunting
Construction and related services
bAnimal slaughtering/poultry processing
oil refining and petrochemicals
Industries with decreased rate of acute leukemia
Professional, legal and technical services
Computer system and related services
Business support, management and administrative services
Public administration

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Table 3.

Occupations associated with increased risk of acute leukemia

Farmers, foresters, agriculture workers and related occupations

Fishing and related works

Construction, painting, maintenance and related occupations

Carpet, tile and floor installers

Building and ground cleaning, janitorial and maintenance workers

Healthcare workers

Workers exposed to solvents, chemicals and benzene

Electricians/electrical utility workers

Workers exposed to high doses of radiation/ nuclear power industry

Automobile mechanics /drivers/rail conductors and pilots

Furniture manufacturers and repair personnel

Laundry workers, dry cleaners

Textile workers and manufacturers

Hairdressers

Teachers

Occupations associated with decreased risk of acute leukemia

Attorneys and legal workers

Moving

6. Prior Immunosuppressive and Chemotherapy

Individuals who have received chemotherapy for the treatment of cancer, with or without radiation, have an increased risk of leukemia. A variety of immunosuppressive therapies can also increase risk of developing acute leukemias. Certain chemotherapy agents such as alkylating agents, platinum derivates and topoisomerase II inhibitors are associated with higher risk for the development of this disease. Addition of radiation therapy to the chemotherapy increase the risk involved [111,112]. In a study of 82,700 women with invasive breast cancer, the risk of acute nonlymphocytic leukemia was significantly higher after regional radiotherapy alone, alkylating agents alone, and combination of chemotherapy and radiation. The relative risk was 2.4 for radiotherapy, 10 for alkylating

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agents and 17.4 for the combination. The observed risk for the development of leukemia was dose and treatment dependent, with melphalan having ten times more leukemogenic effect than cyclophosphamide. With total cyclophosphamide doses of less than 20,000 mg, only small increase in risk of secondary leukemia was observed [113].

7. Parental and residential factors

In the pediatric age group, paternal hobbies and occupations such as work involving contact with gasoline, paint, pigments, solvents, pesticide and plastics, jobs in metal, textile, pharmaceutical industries and professions requiring engine repair, have been investigated for the development of leukemia in children. Direct and indirect effects of chemical agents on children, including via breast feeding, exposure to contaminated clothing or environment have been implicated [59,91-93,107,113-119]. Likewise, household exposure to insecticides has been found to be associated with higher risk of leukemia in the pediatric age group [120]. Proximity of place of birth and industrial sites with release of volatile organic compounds has been reported [121].

Parental alcohol consumption and smoking during prenatal and neonatal periods and childhood have been suggested to contribute to the development of leukemia in their offspring. The risk may be related to the severity, frequency, duration and extent of the exposure [122-129]. Maternal use of marijuana during and after pregnancy has been reported to increase risk of ALL and AML by 10 folds [130]. Effects of the Chemico-Biological Interactions have been explored.

Several studies regarding the etiology of leukemia in childhood have examined the relation of the parent's age, maternal history of fetal loss, birth characteristics and higher birth weight. A positive trend associating maternal and paternal age greater than 35 and 40, respectively, and the occurrence of ALL in the offspring was found. Maternal and paternal age exceeding 40 years has been reported to be associated with an increased odd ratio of 1.95 and 1.45 for the development of childhood leukemia [131]. Maternal history of fetal loss and the risk of the development of ALL and AML is conflicting. This may reflect genetic predisposition or the effects of the environment [132-134]. Higher birth weight is presumed to reflect increased ability for cell proliferation [135].

8. Infections

Infections, including bacterial, viral and fungal agents alone, and in conjunction with genetic mutations, have been implied in leukemogenesis. Infections have been suspected and reported to be associated with the development of cancer in general, and acute leukemias in particular, save for some recent reports, generally an assumption without availability of a consistent agent [136-139]. The impact of a variety of infectious organisms including Epstein-Barr virus, herpesvirus, human immunodeficiency virus (HIV), SARS, COVD-19, Human T-lymphotropic virus (HTLV-1) and others in the development of leukemia in certain patients have been hypothesized and explored [90,136,140-150]. Associations, such as that of EBV and Burkett's lymphoma in the endemic area of Eastern Africa is well known. Despite existence of a relatively strong association, lack of universal application of the finding, characteristic 8;14 chromosomal translocation resulting in constitutive activation of c-Myc oncogene, variation in viral gene expression in subgroups of patients, effects of EBV oncoproteins, p53 mutations and a number of other factors complicate this connection. Exposure to EBV in the first two years of life, resulting in serological response, and the development of Burkett's lymphoma has been reported [136,146,151].

Human T-cell leukemia virus type I, also known as human T-lymphotropic virus (HTLV-1) has been linked to adult T-cell leukemia/lymphoma (ATL), presumably by insertion of their DNA or RNA into the host cell. HTLV-I is proposed to cause ATL in approximately 5% of carriers after a long latent period. Post infection, it is proposed that HTLV-I promotes the clonal proliferation of HTLV-I infected cells *in vivo* by actions of encoded

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viral proteins, including Tax [152]. Mice with monoallelic loss of the B-cell transcription factor PAX5, are genetically predisposed to B-cell ALL, if exposed to pathogens [144,153].

Carcinogenic effects of fungal agents and aflatoxin are well established, but the mechanisms resulting in this phenomenon are not entirely clear. Few reports of fungal isolation from residences of patients with leukemias, including ALL, are available [154-157] and generally, their carcinogenic impacts are attributed to immunosuppression [155,156]. Mycotoxin-producing fungi from a residence associated with four patients with leukemia from three families has been reported and the leukemogenesis attributed to the immune depressive effects of mycotoxins [155]. Study of fungal agents isolated from a house where a husband and wife had developed acute myelomonocytic and undifferentiated leukemia, respectively, have been reported. The extract of the fungal isolates was found to have a depressive effect on phytohemagglutinin skin test in guinea pigs as compared to control [156]. In a published article, sera from 36 patients with cancer, 15 of whom had leukemia or lymphoid malignancy, using a modified microimmunodiffiusion technique, supernatant of the culture of *Aspergillus* had produced 30% precipitation in cancer patients and only 6% in controls. This effect was attributed to reaction to the aflatoxin produced by the fungi [155].

In recent reports, a *Aspergillus Flavus* species, isolated from the home of a patient with ALL, by electron microscopy examination was found to contain mycovirus within the body of the organism and its culture supernatant [138,139]. In chemical analysis, this organism was found not to produce any aflatoxin. The latter was attributed to the known fact that fungi, as virus hosts, provide a unique platform for virus/virus and virus/host interactions that can block the production of aflatoxin [158-160]. Using culture of this mycovirus containing *Aspergillus flavus* with ELISA technique, plasma of patients with ALL in full remission and long-term survivors were found to have antibody to this organism. By this test, it was found possible to distinguish patients with ALL in remission from normal controls as well as those with sickle cell disease and solid tumors [138]. In a related study, exposure of peripheral blood mononuclear cells (PMBC) from patients with ALL in complete remission to the products of the culture of the above mycovirus containing *Aspergillus flavus* had reproduced cell surface phenotypes and genetic markers characteristic of ALL. Controls were found to be negative. Serial timeline evaluation of the cell surface phenotypes, using flow cytometry, had revealed that the reported conversion from normal to leukemic cell surface markers had started shortly after incubation with the supernatant of the mycovirus containing *Aspergillus Flavus* and completed in 24 hours. Addition of EBV to the mixture had not change the results. In the experiments described, aflatoxin, used as a positive control, had indiscriminately induced abnormal cell surface phenotypes in both, PBMC from normal controls and ALL patients in remission. This study may indicate that mycovirus containing *Aspergillus Flavus* has a direct effect on ALL cells in remission and is well capable of altering and transforming cellular and genetic makeup of the genetically vulnerable cells. The report also indicates that in limited studies, when cultures with and without EBV were irradiated, this significantly had increased co-expression of CD10/CD19, which is one of the characteristic cell surface phenotypes in the ALL [139]. Considering the two-hit theory for the development of acute lymphoblastic leukemia, it is postulated that the mycovirus containing Aspergillus Flavus may provide a consistent organism in the mechanism of leukemogenesis in acute lymphoblastic leukemia [138].

These experiments may give credence to the idea that a combination of genetics and epigenetic and environmental factors have a role in the development of leukemias [139].

Mycotoxins produced by fungal agents, including aflatoxins, ochratoxin A, fumonisins, certain trichothecenes, and zearalenone, are known to be carcinogenic [161]. Some mycotoxins, such as Patulin and Gliotoxin, a toxic epipolythiodioxopiperazine metabolite with significant immunosuppressive activity, are capable of causing apoptosis in

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PBMC and have selective in vitro cytotoxicity, while others have suppressive effects on the immune response [162,163]. Gliotoxin, in vivo, is reported to inhibit transcription of NF-κB in response to a variety of stimuli in T and B cells. In high concentrations, this agent was reported to prevent NF- κB DNA binding in vitro [164]. Presence of NF- κB p65 (Rel A) is required for protection from TNA-α. It is of interest that constitutively activated NF- κB complexes have been previously reported in the majority (39/42) of ALL patients without subtype restriction [165].

The correlation between exposure to infections, including fungal organism, and occupations with increased rate of leukemia, such as agricultural work, which potentially exposes the individuals to fungal and other agents is not clear and require future investigation.

As noted before, in recent years, two-hit hypothesis, indicating multi factorial causation for the development of acute leukemias have been proposed [166,167]. The specifics for two major acute forms of the disease, i.e., acute lymphoblastic and myeloblastic leukemia are described in the following sections.

9. Acute Myeloblastic Leukemia

Acute myeloblastic leukemia (AML) has two peaks in occurrence, early childhood and later in adults. The median age for the newly diagnosed patients with AML is 66 years. While the disease can occur at any age, the diagnosis is relatively rare before 40 years of age. Based on the US statistics obtained from 2000 to 2004 , the incidence in individuals under the age 65 is 1.7 per 100000, with the rate increasing to 16.8 per 100,000 in those ages 65 or older. The incidence of AML varies with gender and race. Overall, in the SEER data base for children aged 1–4 years there is an incidence rate of 0.9 per 100,000 for boys and 0.8 for girls [168].

In the first few years of life, the incidence of AML in Whites is three-fold higher than in blacks; however, black children after this age have slightly higher rates of this disease. In the US between 2000 and 2004, with the rate of 3.7 per 100,000 population, AML was more common in Whites than Blacks who had a rate of 3.2 per 100,000 [168]. The increased incidence with age is partially suspected to be due to the progression of myelodysplastic syndromes (MDS) to AML. The so called MDS-related AML is characterized by common cytogenetic abnormalities shared with MDS and has a higher frequency of unfavorable prognosis. In children, the incidence of acute myeloblastic leukemia during 2005-2009 was estimated to be 7.7 cases per million for ages 0-14 years. In this age group, the peak incidence rate occurs in the first year of life and then decreases steadily up to the age of 4 years. In infants less than one year of age the incidence is 18.4 per million [2,169]. The incidence of AML has remained relatively constant in children and adults with the exception of slight increase in the oldest age group [170].

Other than MDS, etiology for most cases of AML is unclear. A growing knowledge concerning leukemogenenic agents, specially chemotherapy regimens used for the treatment of a variety of malignant disorders, have been recognized [111,112]. Associations of certain molecular pathogenesis such as (8;21) translocation and inversion of chromosome 16 in AML have been reported. In addition to these genetic alterations, epigenetic changes such as promoter silencing by hypermethylation of the p15/INK4b and other genes in the pathogenesis of AML, have been recognized. The association of certain genetic factors, including genetic defects and AML, especially in children, is suggested. As noted above, patients with a variety of genetic disorders such as Down's syndrome, have substantially higher potential for the development of malignant disorders, including AML. For example, children with Trisomy 21 have a 10- to 20- fold increased potential of developing acute leukemia, mostly AML [10,14,16,21,171,172].

Acquired genetic and clonal chromosomal abnormalities are found in 50–80% of AML patients, especially in older individuals and those with secondary leukemia. These

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abnormalities include loss or deletion of chromosome 5, 7, Y, and 9. Chromosome translocations, including those of t(8;21) (q22;q22); t(15;17) (q22;q11), trisomy 8 and 21, and abnormalities in the chromosomes 16, 9, and 11 have been reported [2,173-181]. Cases of tetraploid acute leukemia have been documented. In one case report, a pseudodiploid clone characterized by t(8;21) and a hypotetraploid clone with two t(8;21) and a loss of two Y chromosomes was documented [182].Specific associations of the most frequent balanced translocations in AML, such as AML with the (8;21) translocation and inversion of chromosome 16, and acute promyelocytic leukemia with the (15;17) translocation have been reported. In addition to these genetic alterations, epigenetic lesions such as promoter silencing by hypermethylation of the p15/INK4b and other genes, in the pathogenesis of AML have been recorded.

A "two-hit-hypothesis" for the development of AML phenotype by class I and II mutations has been proposed. This two-hit hypothesis is different from that proposed for ALL. Among candidates for class I are mutations in FLT3, N-RAS or K-RAS. Class II mutations are exemplified by AML1/ETO, CBF/ SMMHC, PML/RAR, and MLL-related fusion genes. An example for this hypothesis is activating mutations in FLT3, which is seen in all subtypes of AML and can confer a proliferative advantage to the hematopoietic progenitors, (class I) and gene rearrangements affecting one of the hematopoietic transcription factors (class II). A combination of class I and class II mutations are necessary for the proposed theory to result in the development of AML [166,183]. This theory is in line with increased rate in the development of AML in individuals treated for other malignant disorders [111,112].

Risk factors for the development of AML, as outlined before, include exposure to radiation, chemicals and engagement in various occupations and hobbies.

In some forms of acute promyelocytic leukemia (APML), a distinct chromosomal and gene-rearrangement aberrations have been recognized. These may be different in various areas of the world. For example, while increased incidence of APML in adult patients originating from Latin America and in children in Southern Europe has been reported, genetic rearrangement in these two localities are different. This may indicate that a particular breakpoint site may be responsible in various locations. It is known that certain polymorphisms in the genes metabolizing carcinogens are associated with an increased risk of AML. For example, NAD(P)H:quinone oxidoreductase 1 (NQO1), is a carcinogen-metabolizing enzyme that detoxifies quinones and reduces oxidative stress. A polymorphism at nucleotide 609 of the NQO1 complementary DNA decreases the activity of these enzymes and can result in therapy-related AML [166,184,185].

10. Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children, representing one quarter of all pediatric cancers. The annual incidence of acute lymphoblastic leukemia within the United States is approximately 4.6 cases per 100,000 children age 0-14 years, with a peak incidence at aged 2-5 years. During the first year of life, the incidence of ALL is slightly higher in females than males [186].

Similar to other leukemias, the role and possible effects of a number of factors, as outlined above, for the development of ALL have been proposed. The effects of various environmental factors including parental preconception, in utero and postnatal exposure to ionizing radiation have been explored. Likewise, the risks of nonionizing radiation, chemicals, infections, hydrocarbons and pesticides have been evaluated. The effects of parental alcohol, cigarette, and illicit drug use in development of ALL in offspring have been examined.

Genetics play a major role in the development of leukemia in general and acute lymphoblastic leukemia in particular. The importance of the genetics is most evident based on the concordance studies on identical twins with leukemia [12,187,188].

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The concept that some cases of leukemia originate in utero by leukomogenic translocations or clonotypic gene fusion sequences is intriguing. Siblings of children with leukemia have a higher risk than others to develop this disease, albeit the risk in relatively minimal [189,190].

It is well recognized that some genetic disorders including Down syndrome [15,16] Shwachman syndrome [17], neurofibromatosis [18], Fanconi anemia [19,20], Bloom syndrome [20,21], and ataxia telangiectasia [22] are associated with the increased rate of leukemia. Some of these syndromes such as Down and Bloom syndromes and Fanconi anemia have a higher incidence of AML than ALL. While genetic syndromes resulting in the development of ALL only accounts for a very small portion of the cases, the fact that they are associated with the increased rate of this disease points to the importance of genetics in the process of leukemogenesis. In B-cell ALL, genetic alterations, which are specific to each ALL immunophenotype, include hyperdiploidy, hypodiploidy, *BCR-ABL1*, *ETV6-RUNX1*, or *TCF3-PBX1* fusions; *PAX5* or *ETV6* mutations, MLL rearrangements, or intrachromosomal amplification of chromosome 21 (iAMP21) specific for B-ALL. Alterations in *LMO2*, *TAL1*, *TAL2*, *TLX1*, *TLX2*, or *HOXA* are characteristics of T-cell ALL [183,191].

A revised taxonomy of B-ALL highlights the genetic heterogeneity of this disease by incorporating 23 subtypes, defined by chromosomal rearrangements, sequence mutations or heterogeneous genomic changes. Most of these molecular changes are acquired and not inherited [192]. Epigenetic priming in pediatric ALL has been suggested [193].

A recent two-hit theory combines genetic mutation and exposure to one or more infections for the development of ALL. The revised two-hit model for the occurrence of precursor B cell acute lymphoblastic leukemia suggests that this disease arises through a two-step process. The proposed first step is a predisposing genetic mutation. The second step involves exposure to one or more infections [167]. This proposal therefore suggests that the process of ALL development is initiated in utero by fusion gene formation or hyperdiploidy, and production of pre-leukemic clone. The step one is estimated to occur in approximately 5% of newborns, but only one in a 100 of the predisposed proceeds to develop ALL. It is postulated that exposure to infections early in life are protective. In absence of such an exposure in a small fraction of the population, later exposure to infection triggers the critical secondary cellular mutations.

In Western industrialized countries, approximately 80% of the cases of B-lineage ALL have either an *ETV6*/*RUNX1* translocation or a high-hyperdiploid leukemic clone. These are proposed to have been initiated in utero. Only one percent of healthy newborns have translocation t(12;21)[*ETV6*/*RUNX1*]-positive cord blood cells. In the industrialized countries, a lower chance of exposure to infections in early life is proposed to be reason for a relatively higher rate of ALL in children. In contrast, in the developing countries, a higher rate of exposure to infections and possibly malnutrition are proposed to contribute to a reduced rate of childhood ALL. These factors are proposed to increase the cortisol secretion during infections and the cellular response to cortisol [194].

Although the exact sequence of the events cannot be ascertained and multiple alternatives can exist, genetic predisposition with random exposure to an infection can be plausible. While a number of genetic mutations are proposed, no infectious agent or category has been suggested. Recent reports suggest a mycovirus containing Aspergillus flavus as one of the possible candidates for the infection [138,139].

11. Conclusion:

Acute leukemias account for a significant portion of malignant disorders. These malignancies occur universally, albeit with different rates in various areas of the world and affect all age groups, including children. While association of significant causative factors for acute leukemias have been reported, the etiology of these disorders remains unclear.

Recent advances in genetic and epigenetics provide indications for their involvement in leukemogenesis in acute leukemias. Likewise, effects of the environmental factors including infections have been explored. Recent finding of antibody to a mycovirus containing Aspergillus flavus in patients with ALL in remission and re-development of cell surface phenotypes and genetics, characteristic of ALL upon exposure on PBMN cells to the products of this organism, may provide a new venue for research in leukemogenesis. More research to fulfill the required tenants of theories regarding the development of acute leukemias based on the combining genetics and environment are needed.

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