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A review of risk factors for childhood leukemia

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Abstract. – OBJECTIVE: Leukemia is the most common cancer of childhood, with AML, CML, ALL and CLL being the most common. Environmental and genetic factors have been studied extensively in children with childhood leukemia. Other factors, such as the prenatal parental use of controlled substances, have not been investigated to the same degree. We review what is currently known about environmental and parental factors and the occurrence of leukemia in children.

MATERIALS AND METHODS: Electronic databases were searched for studies correlated pediatric leukemia with (1) ionizing radiation; (2) benzene; (3) parental drug use (4) parental alcohol use; (5) genetic factors.

RESULTS: The two known significant environment risk factors for the occurrence leukemia are ionizing radiation and benzene. However, at least 4 studies have been published over the last century have looked at other environmental factors such as pesticides and drug and alcohol use as well as genetic factors such as gene fusions and translocations.

CONCLUSIONS: We determined the risk of environmental and genetic factors that could be the cause of childhood leukemia in an effort to reduce the incidence of this disease.

Key Words:
Childhood leukemia; environment factors; genetics; effects of ionizing radiation

Introduction

There are over 12 types of leukemia, with the four primary ones being acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL). The differences between the four different types of leukemia are related to the different rates of progressions and the type of blood cells that are affected. The classifications are made under acute vs. chronic and myelogenous vs. lymphocytic. In chronic leukemia, the cancerous cells that are present are mature and retain their normal functions, which lead to a slow progression of the disease. In acute leukemia, abnormal blood cells remain immature and cannot perform proper functions, which causes the number of cancerous cells, and the disease progression, to increase quickly[1,2].

30% of all pediatric cancers is leukemia, and as such, is the most common cancer that is diagnosed in children that are less than 15 years old. In fact, leukemia was the most common cause of cancer-related death in children until the 1980s[3]. ALL is the most common leukemia in the pediatric population; it comprises 75% of all pediatric leukemia cases and is five times more common than AML. After ALL and AML, CML makes up most of the other leukemia cases in children. Pediatric ALL has increased, in the US, over the last three decades. The rate of increase of ALL per 100,000 children is 3 or 4 new cases each year in the US. ALL usually occurs when the child is between 2 and 5 years old and AML most likely presents when the child is 1-year old[4].

Incidences of some types of leukemia vary between the two genders. Females, in general, have a higher chance of developing leukemia in the first year of life. However, the incidence of T-cell ALL is higher in males than females. The rates of AML are similar in both genders. There are also differences in rates of leukemia between ethnicities[5]. For example, rates of ALL in Caucasian children are almost double the rates of ALL in African-American children. Also, in the first three years of life, the rate of AML in Caucasian children is around three times the rate of AML in African American children. However, after three years, African American children develop AML at a higher rate than Caucasian children do[6].

The mortality rate, across all types of leukemia, has decreased by 20% in the last half of the century. The cure rate is fairly high at 90% for ALL but the cure rate for AML is only 40-45%[7].

RIsk Factors

Many studies have examined the role of risk factors in ALL an AML. Ionizing radiation and benzene are the only environment factors that

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have so far been proven to be associated with acute leukemia. Other environmental factors are weakly linked to acute leukemia. Understanding these potential risk factors can help decrease harmful exposure and decrease the incidence of childhood leukemia[8].

Ionizing Radiation

Ionizing radiation is one of the only factors that have been significantly linked to the incidence of pediatric leukemia, especially AML. The degree of risk depends on age, dose of radiation and duration of exposure. Miller et al[10] have investigated and shown that there is a relationship between the amount of exposure to radiation and the incidence of leukemia. A perfect example of this relationship is that the leukemia rates were 20-fold higher in the population of Hiroshima and Nagasaki in Japan after the atomic bomb explosion. This may affect children before they are even conceived, during pregnancy and after birth[9-11].

Some studies have looked at paternal preconception exposure to ionizing radiation at the workplace and found an association with the childhood leukemia. One of the studies found that there was an increase in childhood leukemia in populations that resided near the Sellafield nuclear plant in the UK. In addition, there was also an increase in children with leukemia whose fathers were employed at the plant during conception. It is hypothesized that the radiation of the testes may cause leukemia in the children. However, there were several criticisms behind the study, including the fact that this issue has not been reported for populations residing near other nuclear plants. Therefore, this correlation is not well established[10,12].

Another connection between ionizing radiation and childhood leukemia was investigated. Shu et al[13] demonstrated that there was an increase in childhood leukemia in children whose fathers had to diagnostic X-rays. This was statistically significant for men who had had two or more X-rays in the lower abdomen region. However, preconception exposure of X-rays to the mother did not appear to have a significantly higher risk of childhood leukemia.

Studies have also looked at in utero exposure to ionizing radiation. Researchers investigated whether the nuclear spill in Chernobyl led to higher leukemia risk in children when the children were in utero and living in areas close to Chernobyl. While some studies have shown that there was an increased risk in childhood leukemia, others have not confirmed a risk. In fact, many researchers in Europe showed no correlation between childhood leukemia and in utero exposure to nuclear spill[8,14]. However, authorities have said that a small risk should not be ruled out. In a different study, pregnant mothers living in a highly contaminated area in Sweden were found to have an increased risk of their children developing ALL. Studies have also looked at the risk of in utero exposure to diagnostic X-rays and the development of leukemia. The risk of leukemia in children that were exposed to X-rays in utero was increased by 40%. However, several studies have not found any association between X-ray exposure and childhood leukemia, which once again, leads to ambiguous results in determining whether the two are related[15].

Ionizing radiation that was exposed to children post-birth showed that there was an increase in the risk of childhood leukemia. This data was mostly gathered from the atomic bomb blasts in World War II in Japan as well as those that received radiotherapy for other diseases. However, contrary to other reports, radiation exposure to children during Chernobyl accident did not show an increase in the risk of leukemia. When looking at X-ray exposure to the children, it was found the risk for children to develop pre-B cell ALL increases when exposed to three or more X-rays in children older than five years old. Post-birth X-rays have shown some, but not significant increase in childhood leukemia risk[16].

Chemicals

Hydrocarbons and pesticides are a common class of chemicals that are normally associated with childhood leukemia. These studies have looked at both direct exposures to the chemicals as well as secondary exposure.

Hydrocarbons

These are organic compounds that are composed of carbon and hydrogen, which include things like gasoline. Hydrocarbons are widely used as household and industrial products such as in paint removers and thinners. Benzene is a chemical that is used in things like paint; it is also formed in the combustion of fossil fuels. Benzene is also a known carcinogen. It has a positive correlation with the development of leukemia at exposures that not much higher than the standard limit for workers. A research was conducted to determine whether parental hobbies and projects were correlated with increased childhood leukemia. There

was a statistically significant increase in ALL levels when there was prenatal exposure to newly painted homes and artwork with solvents[17,18].

Many studies were looked at to determine if there was a significant correlation between jobs of parents and children with leukemia. Jobs that included exposure to paints and pigments had the most positive results regarding correlating with the development of childhood leukemia. The paternal jobs that most correlated with an increased risk of childhood leukemia were painter, machinist or factory worker. Paternal hydrocarbon exposure seems to be related to an increase in both AML and ALL in children less than 1 years old. In a separate study, a paternal exposure to plastics was the only characteristic that correlated with an increased risk of childhood leukemia. The pathology behind the paternal risk of leukemia may be due to a genetic alteration of the father's sperm, which causes the child to be more susceptible to cancer[17,19].

For jobs of mothers, the occupations that led to higher chances of childhood leukemia were metal manufacturing, textiles and pharmacists. Some studies have looked at whether indirect exposure through breast milk could increase the risk of childhood leukemia. However, in general, breast milk decreases the overall risk of ALL, especially when a baby drink breast milk for a longer duration. Maternal exposure to solvents and paints before conception and during gestation also increased the risk of the child developing leukemia[20,21].

It was discovered that children living in areas with high levels of carcinogenic hazardous air pollutants such as benzene and trichloroethylene in California are at an increased risk of developing leukemia[22]. Similarly, a study in United Kingdom showed a positive correlation between birthplace of children with leukemia and closeness to industrial sites that release components like dioxins, volatile organic compounds and benzopyrene[23].

Pesticides

Studies have suggested a potential link between exposure to pesticides and an increase in the risk of childhood leukemia. However, these studies are limited because the amount of children that are exposed to pesticides is small. The most exposure of the children to the pesticides is caused by their use at home and in the garden, by local agricultural applications, by the contaminated food and by pet products. Some researches have linked exposure of pregnant women to pesticides and the risk of the child developing leukemia. A child in utero or a newborn child is more susceptible to developing leukemia than an adult[24].

An analysis looked at whether residential or occupational exposure to pesticides indirectly by parents or directly to the children leads to an increased risk of leukemia. It was found that exposure to pesticides to children through work or home was associated with increased childhood leukemia. The risk is associated with garden insecticide use during childhood. In addition, children that are exposed to professional pest control services between the ages of one and three demonstrated an increased risk of childhood leukemia. Some works have also shown that maternal exposure to constant prenatal or pregnancy pesticide exposure led to an increased risk as well[7]. However, other studies[8,25] found no association between exposure of pesticide to parents and the risk of childhood leukemia.

Alcohol, Drug and Cigarettes

Maternal consumption of alcohol during pregnancy showed an increased risk for AML during childhood. Alcohol consumption for mothers, starting at month 1 of gestation and going through till birth, greatly increased the chance of childhood AML. The risk for AML was two times the risk for ALL. On the other hand, paternal alcohol consumption before birth did not increase the risk of leukemia[26]. Reports also looked at the effect of smoking on pregnancy and found that maternal smoking preconception increased the risk of childhood leukemia. Paternal smoking, at any time, did not appear to correlate with the disease[27]. Finally, the medical use of marijuana during the pre-pregnancy and during the gestation is correlated to childhood AML and ALL. Even though it was a small sample size, the risk of childhood AML showed a ten-fold increase due to maternal use of marijuana before or during pregnancy. The pathology behind marijuana contribution to leukemia is that this drug is a teratogen in animals and due to that it may be leukemogenic in humans as well[28].

Genetics

In utero genetic events have been suspected to contribute to the development of childhood leukemia as twins are two-fold as likely to develop leukemia as the rest of the population if one the twin has developed it by the age of 7. Once twins reach the age of 15, there is no increased risk of developing leukemia. In addition, siblings of children with leukemia are more likely to develop

leukemia and a family history of hematopoietic malignancies among relatives has been associated with a small increase in childhood leukemia risk[29]. More evidence that shows that childhood leukemia may originate in utero is that leukemogenic translocations and gene fusions have been found that correlate to some cases of childhood ALL. In fact, babies with acute leukemia have been found to have gene fusions with the MLL gene. DNAt2 inhibitors, which are found in both chemotherapy as well as in some foods and beverages, cause this gene fusion and contribute to leukemia[30].

The risk of childhood leukemia has come to be correlated with genetic polymorphisms that affect the ability of the patient to metabolize xenobiotic exposures. Polymorphic genes that encode carcinogen and drug-metabolizing enzymes both increase the risk of ALL as well as increase the risk of a relapse. As an example, patients with cytochrome P450 1A1 and NADPH quinine oxidoreductase 1 variants were found to have a worse prognosis than other patients. Some genetic diseases, such as Bloom syndrome, Down syndrome and Shwachman syndrome, are associated with an increased risk of childhood leukemia. These genetic disorders are characterized by faulty DNA repair, chromosome aneuploidy or chromosome abnormalities, which increase the pathology of leukemia. Children with Fanconi anemia, Blood syndrome and Down syndrome have a higher incidence of developing AML than ALL[31].

Transmissible Agents

There is a lot of evidence that leads scientists to believe that a transmissible agent may be responsible for childhood leukemia. First of all, the incidence of childhood leukemia and the incidence of most infections are between the ages of 2 and 5. The infections are higher because the immune system is not mature enough. In addition, some viruses have been shown to be oncogenic for other cancers. Finally, there has been evidence that children living in rural areas tend to have higher rates of leukemia. This one may be due to the immunologically active environment rural environment. Another theory that may be possible is that an abnormal response to a virus may lead to a "delayed infection" which causes a response that leads to the pathology of leukemia. It has been shown that children with ALL are less likely to have experienced normal infections, due to potential immunologic isolation. The mechanism might relate to the ability of the virus to infect and transform B-cells or the ability to activate abnormal cell growth[3,8,32].

Other Characteristics

One of the most important characteristics that lead to an increased risk of childhood leukemia is parental age. For mothers older than 35 years old and fathers greater than 40 years old, the risk for ALL is considerably increased. Another characteristic that was observed was the association of higher birth weight and childhood ALL. It was found that birth weight did correlate with an increased rate of cell proliferation, and therefore, an increase in cells that are at a risk for transformation. In addition, higher birth weight correlated with an increase in the age of the mother, which is a known factor for the development of ALL in children[20].

Conclusions

Despite the advances in the pathology of childhood leukemia, it is still unclear exactly what leads to this disease. If we can recognize the risk factors of childhood leukemia then perhaps we can reduce the occurrence of the disease in children. The two most important factors that are known for childhood leukemia are exposure to hydrocarbons and ionizing radiation. However, there have been many works that have looked at other factors such as pesticides, alcohol, drugs, cigarettes, genetics, viral agents and parental age.

Conflicts of interest
The authors declare no conflicts of interest.

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