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Study of prevalence of leukemia in pediatric age group

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Abstract
Cancer is the third major killer disease in India among children after infection and malnutrition. Leukemia is the most common type of childhood malignancy. During the period of suffering, the child encounters various complications and also sustains several side-effects as unavoidable consequences of the compact treatment. Current therapy for leukemia consists of chemotherapy and radiotherapy or a combination of both and sometimes surgery. The maximum number of malignancies was noticed amongst children aged between 1-4 years. The male and female ratio was 2:1. 36% of all malignant lesions in children are leukemia. The incidence of leukemia is higher in <15 years of aged children. Leukemia is the most common childhood cancer in India. 60-85% of all leukemia reported is Acute Lymphoblastic Leukemia (ALL). Hence based on above findings the present was planned for study of Prevalence of Leukemia in Pediatric Age Group.
The Present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Bihar. The 25 cases of the Leukaemia referred to our hospital were enrolled in the present study. Patients of ALL were treated according to BFM 90 protocol after risk stratification. High risk protocol was given only if good follow up was possible and parents were willing. AML excluding APML was treated with 7+3 regimen and CML was treated with Arsenic or imatinib mesylate. Regular examinations were done during hospital stay & any complications were recorded & treated. Study outcome was noted as discharge or death.
The data generated from the present study concludes that Fever was the most common symptom while Hepatomegaly was most common sign found in Leukemia patients. Most common type of Leukemia was ALL in pediatric age group. Thrombocytopenia was most common complication found in Leukemia patients.

Keywords: leukemia, cancer, paediatric group, etc

Introduction
Childhood leukemia is leukemia that occurs in a child and is a type of childhood cancer. Childhood leukemia is the most common childhood cancer, accounting for 29% of cancers in children aged 0–14 in 2018 [1]. There are multiple forms of leukemia that occur in children, the most common being acute lymphoblastic leukemia (ALL) followed by acute myeloid leukemia (AML) [2]. Survival rates vary depending on the type of leukemia, but may be as high as 90% in ALL [3].

Leukemia is a hematological malignancy or a cancer of the blood. It develops in the bone marrow, the soft inner part of bones where new blood cells are made. When a child has leukemia, the bone marrow produces white blood cells that do not mature correctly. Normal healthy cells only reproduce when there is enough space for them. The body will regulate the production of cells by sending signals of when to stop production. When a child has leukemia, the cells do not respond to the signals telling them when to stop and when to produce cells. The bone marrow becomes crowded resulting in problems producing other blood cells [4, 5].

Common childhood leukemia signs and symptoms include excessive tiredness, easy bruising or bleeding, bone pain and paleness [6].

Leukemia is usually described either as "acute", which grows quickly, or "chronic", which grows slowly. The vast majority of childhood leukemia is acute, and chronic leukemias are more common in adults than in children. Acute leukemias typically develop and worsen quickly (over periods of days to weeks). Chronic leukemias develop over a slower period of time (months), but are more difficult to treat than acute leukemias [2, 5]. The following are some of the main types of leukemia that occur in children.

The most common form childhood leukemia is acute lymphocytic (or lymphoblastic) leukemia (ALL), which makes up 75-80% of childhood leukemia diagnoses [7, 2]. ALL is a form of leukemia that affects lymphocytes, a type of white blood cells which fights infection. When a patient has ALL, the bone marrow makes too many immature white blood cells and they do not mature correctly. These white blood cells also do not work correctly to fight infection. The white blood cells over-produce, crowding the other blood cells in the bone marrow [5, 3].

Another type of acute leukemia is acute myelogenous leukemia (AML). AML accounts for most of the remaining cases of leukemia in children, comprising about 20% of childhood leukemia [7]. AML is cancer of the blood in which too many myeloblasts (immature white blood cells) are produced in the bone marrow. The marrow continues to produce abnormal cells that crowd the other blood cells and do not work properly to fight infection [4].

Acute promyelocytic leukemia (APL) is a specific type of AML. In this leukemia promyelocytes are produced and

build up in the bone marrow. A specific chromosome translocation (a type of genetic change) is found in patients with APL. Genes on chromosome 15 change places with genes on chromosome 17. This genetic change prevents the promyelocytes from maturing properly [4].

Chronic myelogenous leukemia (CML) is a chronic leukemia that develops slowly, over months to years. CML is rare in children, but does occur [7]. CML patients have too many immature white blood cells being produced, and the cells crowd the other healthy blood cells. A chromosome translocation occurs in patients with CML. Part of chromosome 9 breaks off and attaches itself to chromosome 22, facilitating exchange of genetic material between chromosomes 9 and 22. The rearrangement of the chromosomes changes the positions and functions of certain genes, which causes uncontrolled cell growth [4].

Chronic lymphocytic leukemia (CLL) is another form of chronic leukemia, but is extremely rare in children [2].

Juvenile myelomonocytic leukemia (JMML) is a form of leukemia in which myelomonocytic cells are overproduced. It is sometimes considered a myeloproliferative neoplasm. It is rare and most commonly occurs in children under the age of four. In JMML, the myelomonocytic cells produced by the bone marrow and invade the spleen, lungs, and intestines [8, 9].

The exact cause of most cases of childhood leukemia is not known [10]. Most children with leukemia do not have any known risk factors [10].

One hypothesis is that childhood acute lymphoblastic leukemia (ALL) is caused by a two-step process, starting with a prenatal genetic mutation and then exposure to infections [11] while this theory is possible, there is not enough evidence in patients currently to either support or refute the relationship between infections and developing ALL [12]

There is evidence linking maternal alcohol consumption to AML development in children [13]. Indoor insecticide exposure has also been linked to the development of childhood leukemias [14]. High levels of coffee consumption during pregnancy (2-3 cups/day or greater) have been linked to childhood leukemia as well [15].

It has also been suggested that allergies are linked to the development of childhood leukemia but this is not supported by current evidence [16].

Childhood leukemia is diagnosed in a variety of ways. The diagnostic procedures confirm if there is leukemia present, the extent of the leukemia (how far it has spread), and the type of leukemia. The diagnostic procedures are similar for the different types of leukemias:

A bone-marrow aspiration and biopsy to look for and collect leukemia cells. In aspiration, a fluid sample is removed from the marrow. In biopsy, bone marrow cells are removed. Usually both procedures are performed at the same time and used together to help with diagnosis.

Tests called immunophenotyping and cytogenetic analysis are performed on the cells to further determine the type and subtype of leukemia.

A complete blood count, which is a measurement of size, number, and maturity of different blood cells in blood. Blood tests may include blood chemistry, evaluation of liver and kidney functions, and genetic studies. A spinal tap: a special needle is placed into the lower back into the spinal canal, which is the area around the spinal cord. Cerebral spinal fluid is fluid that bathes the child's brain and spinal cord. A small amount of cerebral spinal fluid is sent for testing to determine if leukemia cells are present [5, 17].

Treatment for childhood leukemia is based on a number of factors, including the type of leukemia, characteristics of the leukemia, prognostic characteristics (children with worse prognostic characteristics receive more aggressive therapy, see Prognosis section), response to therapy, and extent of the disease at diagnosis. Treatment is typically managed by a team of health care professionals, consisting of pediatric oncologists, social workers, pediatric nurse specialists, and pediatricians among others [5, 4].

While the exact treatment plan is determined by the type of leukemia and factors listed above, there are five types of therapies that are generally used to treat all childhood leukemias. Four of these are standard treatment and one is in clinical trials. The four specific types of treatments that are traditionally used are Chemotherapy, Stem cell transplant, Radiation therapy and Targeted therapy [3, 4, 5, 18]. Immunotherapy is another type of therapy that is currently in clinical trials [3, 5, 4].

Chemotherapy is a treatment that uses chemicals to interfere with the cancer cells ability to grow and reproduce. Chemotherapy can be used alone or in combination with other therapies. Chemotherapy can be given either as a pill to swallow orally, an injection into the fat or muscle, through an IV directly into the bloodstream or directly into the spinal column [5, 4, 19, 20].

Stem cell transplant is a process in which the blood-forming cells that are abnormal (like leukemia cells) or that were destroyed by chemotherapy are replaced with healthy new blood-forming cells. A stem-cell transplant can help the human body produce more healthy white blood cells, red blood cells, or platelets. It also reduces the risk of life-threatening conditions such as anemia, or hemorrhage. Stem cell transplants can be done by obtaining cells from the bone-marrow, blood or umbilical-cord blood. Stem cell transplants can use the cells from one's self, called an autologous stem cell transplant or they can use cells from another person, known as an allogenic stem cell transplant. The type used in childhood leukemia is typically allogenic. The donors used must be a match to the child getting the transplant by a marker called HLA [18, 21]

Radiation therapy uses various types of radiation to kill cancer cells.

Targeted therapy is the use of medication to specifically kill the cancerous cells. The medication is able to leave healthy normal cells alone while it targets the cancer [18]. These include tyrosine kinase inhibitors (TKIs), monoclonal antibodies, and proteasome inhibitors [4, 5].

Immunotherapy is a type of therapy that uses the child's own immune system to fight the cancer. This therapy is currently in clinical trials [3, 22].

Leukemia is the most common cancer in children, accounting for 25-30% of all cancers in children and adolescents. It most commonly is diagnosed in children when they are 1–4 years old. The median age of diagnosis is 6 years old. Childhood leukemia is more common in boys than girls. It is also more frequently diagnosed in white and Hispanic children. The incidence of childhood leukemia has been increasing over time. However, this may be because of increased ability to detect, diagnose, and report the disease, rather than an actual increase in children who are affected.

ALL is the most common type of childhood leukemia, accounting for 75-80% of diagnoses. AML is most

commonly is diagnosed in 3-5-year-old children. As with childhood leukemia in general, it is more common in boys than girls and more common in white and Hispanic children [23].

AML is the second most common type of childhood leukemia, making up most of the remaining diagnoses. It is most commonly diagnosed in children less than 1 year old. Unlike ALL, it occurs equally in boys and girls and occurs equally across racial/ethnic groups.

There are a number of risk factors that have been studied for childhood leukemia. Genetic risk factors include: Down syndrome, Fanconi anemia, familial monosomy 7, Shwachman–Diamond syndrome, Bloom Syndrome, as well as mutations in specific gene mutations [3, 39]. Besides genetic risk factors, exposure to ionizing radiation is a known risk factor for childhood leukemia. Other factors that may be linked to development of childhood leukemia include: family history of blood cancers, maternal alcohol abuse, parental cigarette use, prior loss of pregnancy in the mother, older age of the mother, high birth weight, low birth weight, exposure to benzene, exposure to pesticides, and infections. However, whether or how much these factors actually contribute to the development of leukemia has yet to be determined and is unclear [23].

Cancer is the third major killer disease in India among children after infection and malnutrition. Leukemia is the most common type of childhood malignancy. During the period of suffering, the child encounters various complications and also sustains several side-effects as unavoidable consequences of the compact treatment. Current therapy for leukemia consists of chemotherapy and radiotherapy or a combination of both and sometimes surgery. The maximum number of malignancies was noticed amongst children aged between 1-4 years. The male and female ratio was 2:1. 36% of all malignant lesions in children are leukemia. The incidence of leukemia is higher in <15 years of aged children. Leukemia is the most common childhood cancer in India. 60-85% of all leukemia reported is Acute Lymphoblastic Leukemia (ALL). Hence based on above findings the present was planned for study of Prevalence of Leukemia in Pediatric Age Group.

Methodology

The Present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Bihar. The 25 cases of the Leukaemia referred to our hospital were enrolled in the present study. Patients of ALL were treated according to BFM 90 protocol after risk stratification. High risk protocol was given only if good follow up was possible and parents were willing. AML excluding APML was treated with 7+3 regimen and CML was treated with Arsenic or imatinib mesylate. Regular examinations were done during hospital stay & any complications were recorded & treated. Study outcome was noted as discharge or death.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Results & Discussion

Of all cancers in childhood (by WHO definition: O-14 year age group), leukemias constitute one of the most important groups of tumors. Our understanding of the biologic features of the childhood leukemias has increased greatly over the past decade. The ability to discern cytogenetic and molecular differences among morphologically and immunologically similar populations of leukemic cells has helped to establish the basis for a revised classification of the leukemias. This advance, in turn, has led to new approaches to clinical management.

Table 1: Demographic Details

Parameters	No. of Cases
Age	
1 – 3 Years	4
3 – 5 years	4
5 – 8 years	7
8 – 12 years	10
Sex	
Male	13
Female	12
Total Cases	25

Table 2: Immunophenotype of Leukemia

Immunophenotype of leukemia	Total
B cell All (Acute lymphoblastic leukemia)	19
T All (Acute lymphoblastic leukemia)	3
AML (Acute myeloid leukemia)	1
CML (Chronic myeloidleukemia)	2
Total	25

Table 3: Presenting Symptoms

Finding	No of patients
Fever	8
Abdominal pain	12
Abdominal distention	10
Lymphadenopathy	9
Easy fatigability	7
Cough	6
Bony pain	5
Loss of appetite	4
Anorexia	4
Bleeding spot	4

Table 4: Clinical findings

Sign	No of patients
Hepatomegaly	20
Splenomegaly	17
Pallor	16
Lymphadenopathy	10
Bleeding spots	4
Bone tenderness	4
Parotid enlargement	2
CNS manifestation	2

Table 5: Duration of Hospital Stay

Days	No of patients
1-4 weeks	16
4-6 weeks	5
>6 weeks	4
Total	25

Numerous factors have been linked to an increased risk of leukemia in children. The higher frequency of acute leukemia in children with constitutional genetic defects (e.g., trisomy 21, Fanconi'sanemia, and germ-line p53 mutations) is evidence of a hereditary influence [24]. The

megakaryoblastic subtype of AML predominates in children with Correspondence to: Prof. Vinod Kochupillai, Chief, IRCH Department of Medical Oncology, Institute Rotary Cancer Hospital All India Institute of Medical Sciences, New Delhi 110029 Down's syndrome who are three years of age or younger, whereas ALL is the characteristic leukemia in older children with Down's syndrome [25, 26]. The high rate of concordance for leukemia in monozygous twins, especially during the first year of life, may reflect a common prezygotic or intrauterine genetic event or perhaps metastasis through shared placental circulation. The latter mechanism was recently confirmed in three pairs of monozygous twins, each pair having unique (clonal) genetic rearrangements in their blast cells?. That the leukemic cells in these twins had llq23 chromosomal rearrangements - a common feature of secondary AML induced by epipodophyllotoxin therapy and the most common clonal abnormality in infants with leukemias, suggests that intrauterine exposure to carcinogens is responsible for at least some cases of leukemia in very young children.

Leukemia, first identified by researchers Virchow and Bennet in 1845 [27], is a malignant disease that starts in the blood-forming tissues such as the bone marrow and causes a large number of blood cells to be produced and enter the blood stream.

Acute lymphoblastic leukemia (ALL) accounts for 1/4th of all childhood cancer and 3/4th of all malignant leukemias. Peak age of its occurrence in children is between 3 and 5 years, and is slightly more frequent in boys than in girls [28].

Although a few cases are associated with inherited genetic syndromes (i.e., Down syndrome, Fanconi anemia), the cause remains largely unknown. Some of the risk factors which are important in the pathogenesis of leukemia are ionizing radiation, chemicals (e.g., benzene, heavy metals, pesticides, petroleum distillates), drugs (chemotherapeutic drugs agents, alkylating agents, and etoposide, especially when used with radiotherapy), viral infections, and genetics [28].

Advances in the treatment regimens, including multiagent chemotherapy and radiation therapy, have greatly increased the chances of survival [29]. The treatment modalities widely accepted for ALL are chemotherapy and a combination of chemotherapy with radiation. Radiotherapy to or near the oral cavity may cause mucositis, infection, trismus or xerostomia which further interrupts radiotherapy, inducing malnutrition or systemic infection. Combination of chemotherapy and radiotherapy may have an additive if not a synergistic effect on the afore mentioned complications [30].

Conclusion

The data generated from the present study concludes that Fever was the most common symptom while Hepatomegaly was most common sign found in Leukemia patients. Most common type of Leukemia was ALL in pediatric age group. Thrombocytopenia was most common complication found in Leukemia patients.

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