INTRODUCTION

Leukemia represents about 30%of childhood cancers, Acute lymphoblastic leukemia (ALL) is the dominant type accounts for approximately 80-85% of childdhood leukemia, acute myeloblastic leukemia (AML) represents approximately 15-20% and chronic myelogenous leukemia (CML) represents about 2-3%. Human Parvovirus B19 is associated with a wide range of disease manifestations. It is linked with a broad spectrum of hemolytic disorders including anemia, neutropenia, thrombocytopenia and heamophagocytic syndrome ***(Mucclain, 1999).***

In patients with underlying hemolytic disorders, infection is the primary cause of transient aplastic crises. Persistent infection may develop presenting with pure red cell aplasia and chronic anemia ***(Graves, 2002).***

Pancytopenia may develop during therapy of childhood leukemia and in many cases it is recorded to be secondary to parvovirus B19 infection ***(Mehal, 2005).***

In immuno compromised host who is unable to produce neutralizing antibodies an infection with parvovirus B19 can persist and cause bone marrow failure ***(Cullen,2002).***

Evidence of parvovirus replication in neutrophils in the peripheral blood might provide an explanation for neutropenia that was sometimes observed, megakaryoblasts and lymphoblasts could be affected ***(Kratzman 2000)***.

AIM OF THE WORK

The aim of work is to study the frequency and clinical importance of parvovirus B19 in children with hematological malignancies developing cytopenias during chemo/radiotherapy by searching for antibodies to parvovirus B19 in their blood for proper follow up and modulation of therapy. Detection of psychological consequences of hematological malignancies with parvovirus B19 infection is also considered.

EPIDEMIOLOGY

Leukemia could be defined as a group of malignant diseases in which genetic abnormalities in hemopoietic cells giving rise to colonal proliferation in those cells, the progeny of these cells had a growth advantage over normal cellular elements which owed to an increase rate of proliferation, a decreased rate of spontaneous apoptosis or both. The result was disturbance of normal marrow function and ultimately marrow failure ***(Fisher, 2001).***

Leukemias are the most common cancers affecting children accounting for 31% of all occurrences of cancer among children younger than 15 years of age and 25% of occurrences of cancers among children younger than 25 years of age ***(Gayon, 2000).***

In the United States, leukemia was diagnosed in approximately 3250 children each year with incidence of 3-4 cases per 100,000 white children ***(Gurney et al., 2000).***

In National Cancer Institute in Egypt ALL represents 23.3% of all pediatric malignancies and 75% of pediatric leukemias ***(Gadalla, 1996).***

In childhood AML was a rare disease with an incidence of 1-3 per 100,000 child each year in most countries it accounted for 15-20% of childhood leukemias although there were exceptions such as in Japan and some

parts of Africa, where AML seemed to be more common than ALL during childhood ***(Paul, 2000).***

There was a gradual increase in incidence of Leukemia with non significant seasonal variation at presentation ***(Khalifa et al., 1988).***

Age

There was significant peak of incidence between 3 and 5 years of age but this peak might increase in many developing countries leading to theories that certain exposure e.g. to infection associated with modern life style might lead to Leukemia ***(Gurney et al., 2000).***

In developed countries the age incidence curve for ALL was characterized by an age peak between 1 and 4 years (Fig. 1), thus a sharp peak in ALL incidences was seen among 2-3 years of age (>80 per million) which decreased to a rate of 20 per million for 8 to 10 years of age.

The incidence of ALL among 2-3 years of age was approximately four folds greater than that for infants and was nearly ten folds greater than that for 19 years old patients ***(Gurney et al., 2000).***

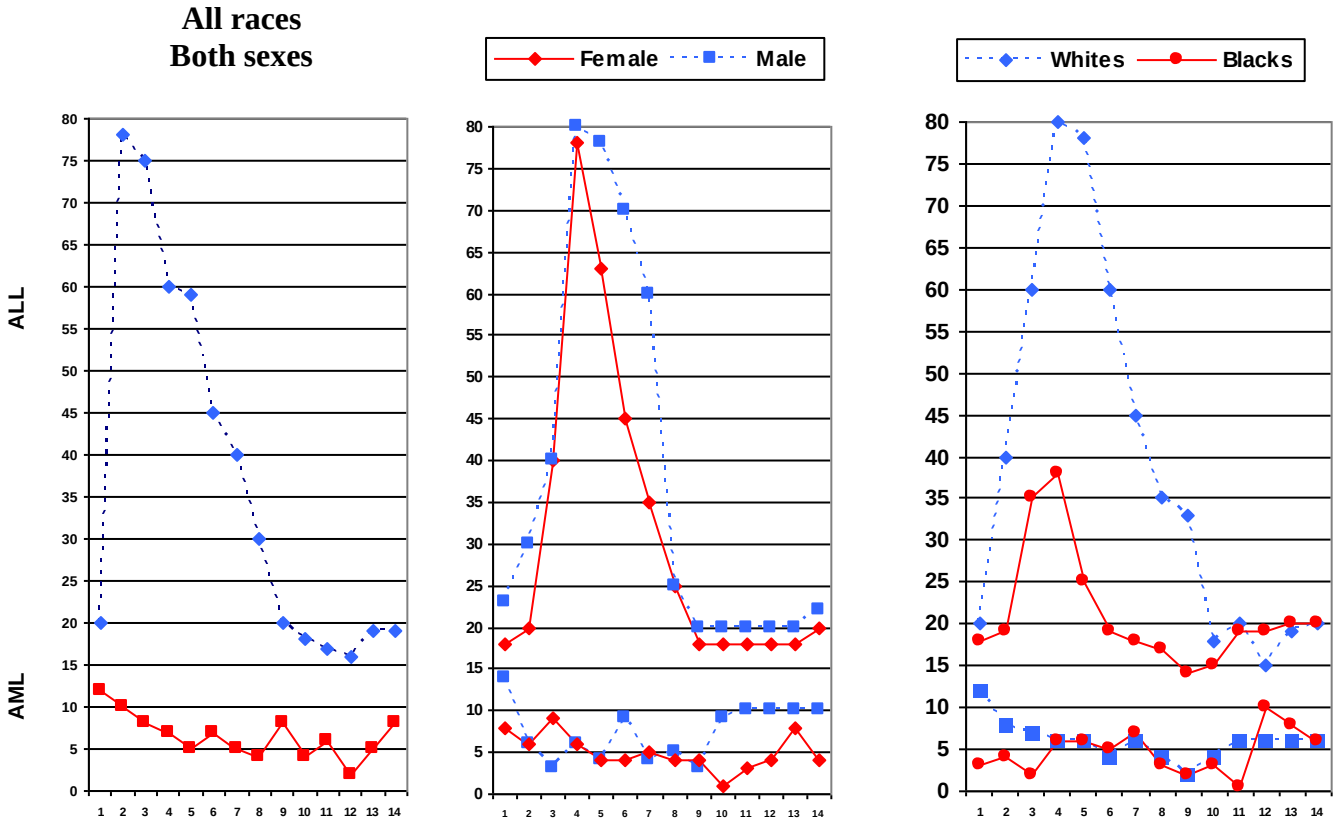

Fig. (1): Age, sex and race-specific annual incidences rates (per million population) for children in the USA ***(Gurney et al., 2000).***

Unlike ALL, the incidence of AML was relatively unique form throughout pediatric age groups ***(Mehal, 2005)***.

AML constituted minority in childhood period with a relative increase of incidence 10-20% in the first decade of life rising to approximately double that by the age of 1.5 years. In the 1st four weeks of life by contrast AML did predominate over ALL ***(Jaffe et al., 2001).***

The incidence rates of AML in United Sates during 1986-1995 during the age of 1-4 years old group was 10.3 per million and during the age of 5-9 years old it was 50.0 per million and 10-14 years old group it was 6.2 per million. Comparable rates had been reported else where in Europe and in England (Fig. 2) ***(Severson, 2000).***

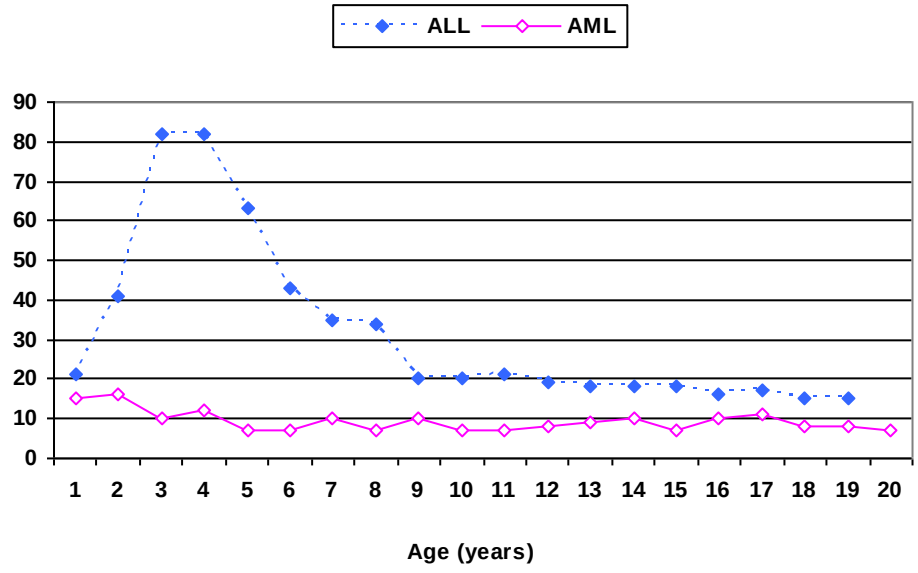

Fig. (2): Age-specific incidence rates for acute lymphoblastic and acute myeloid leukemias (ALL and AML) in childhood ***(Severson, 2000).***

Sex

In childhood ALL males were over affected than females with the notable exception of female predominance in infancy. The male predominance was particularly evident in cases of T- Cell ALL as shown in Fig. (1) ***(Davis et al., 2000).***

In Egypt, ***Gad El-Mawla (1984)*** had found that the incidence of ALL was higher in males than in females with ratio of 1.7:1 while ***Khalifa et al. (1988)*** found a ratio of 2.1:1.

Gurney(2000) found in his study that male to female in ALL was 1.1:1 while in AML it was 1.3:1 as regards CML there were 1.2 per million for infants and 1.6,0.5 and 0.7 for children aged 1-4, 5-9 and 10-14 years respectively. The male to female sex ratio is 1.6:1 ***(Gurney et al .,2000).***

Race

A striking difference in the incidence of ALL existed between white and black children with a higher incidence among white children in most age groups ***(Smita et al., 1999).***

All was more common among whites than blacks, with the incidence in whites for younger ages was approximately 2 folder higher than in blacks as shown in (Fig 1) ***(Gurney et al., 2000).***

This might reflect a difference in susceptibility or in exposure to what ever environmental influences might be responsible for the early age peak in whites ***(Mehal, 2005).***

Despite early reports that the outcome from black children with ALL was worse than white children, later reports proved equivalent treatment results ***(Pui et al., 2000).***

Geographic Variation

Significant international variation existed in the incidence of childhood ALL with rates ranging from 7-47 per million for males and from 7-43 per million for females ***(Parkin et al., 2002)***.

Fig (3) showed the incidence rates of ALL for selected countries notably incidence rates were higher in USA among white and in Australia (new south Wales), Costa Rica and Federal republic of Germany. Intermediate rates existed in most European countries, while the lowest rates of ALL occured in American blacks, India (Bombay) and Kuwait. For most countries of ALL was higher in males however some notable exceptions include Kuwait where the ratio of female: male was 2:1 and American blacks ratio approximately 1:0 ***(Parkin et al., 2002).***

This geography variation might practically reflect the distribution of different immunologic ALL subtypes. There appeared to be a lower incidence of common ALL and a

higher incidence of T cell ALL in developing countries than in the more industrialized countries. Although this might reflect an under diagnosis of common ALL in developing countries, it was also possible that children in industrialized countries are exposed to leukomogens that cause common ALL (CALL) ***(Magrath, 2002).***

In acute myeloid Leukemia rates were higher (greater than 10 per million) among the New Zealand, Mabry, China and Japan and lowest (less than 4 per million) in Canadian Atlantic provinces, (Fig 3) ***(Parkin et al., 2002).***

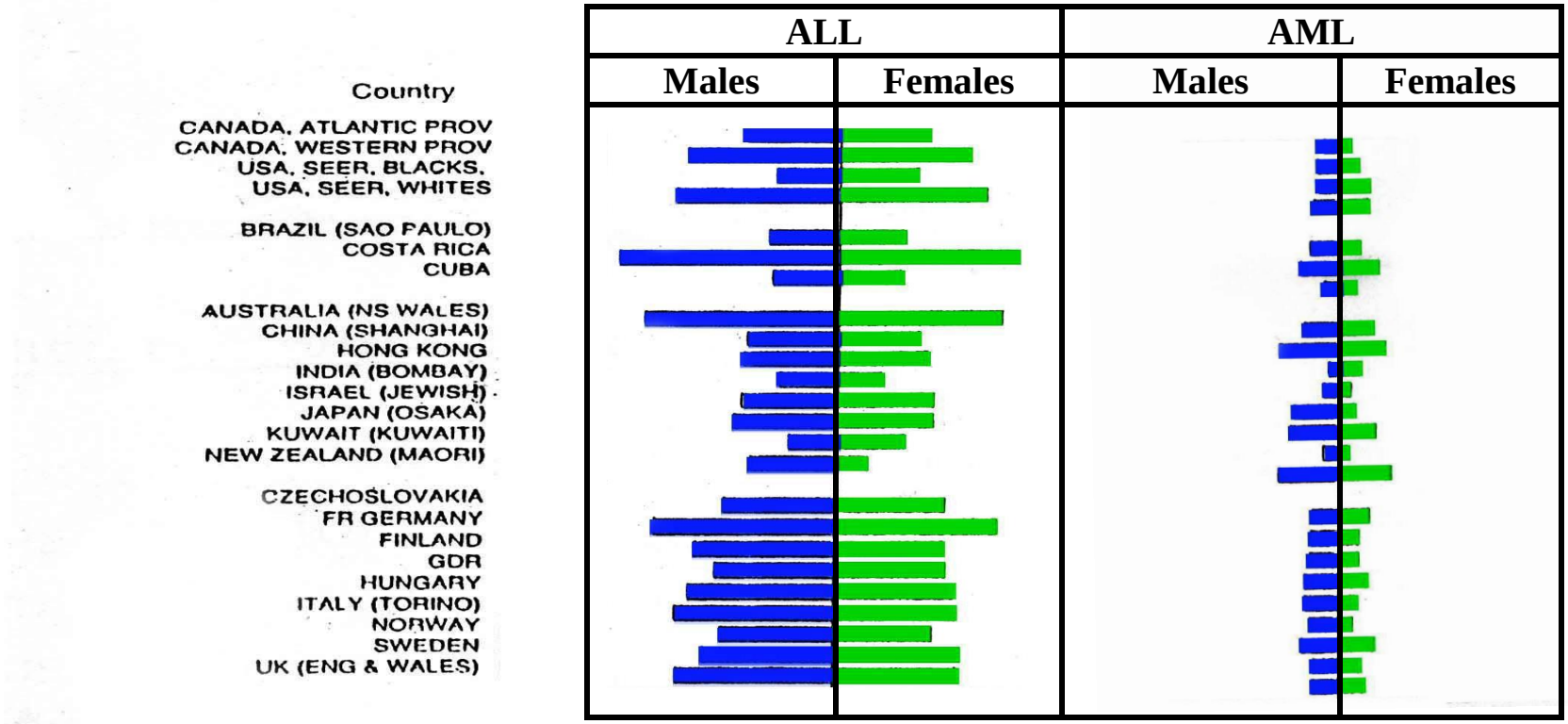

Fig. (3): Annual incidence rates (per million population). In selected international sites for childhood ALL and AML ***(Parkin et al., 2002).***

Environmental and Risk Factors

1. Socioeconomic Factors:

Socioeconomic factors had been proposed as an explanation for the age peak in childhood Leukemia ***(David, 2003).***

Thus it had been hypothesized that the economic development, poor communities moved from a situation in which Leukemia was rare (T cell ALL is the predominant type of ALL) through an intermediate stage in which CALL began to appear, to a state of high socioeconomic status that was associated with a high incidence of ALL and CALL ***(Ginsburg, 2003).***

In contrast several investigators had examined the relationship between AML and socioeconomic status and had failed to show an association between both of them ***(Miller, 1999).***

2. Ionizing Radiation:

The leukomogenic potential of ionizing radiation had been well documented in studies of survivors of the atomic bombing of Japan in 1945 ***(Tomonaga et al., 2004)*** and as regards type of Leukemia it was related to the age at exposure.

Acute lymphoblastic leukemia was seen more frequently in children while Acute non lymphoblastic leukemia was more in adults ***(Dolls, 2005).***

In children, exposure in utero to diagnostic X ray was associated with an increased risk of both ALL and AML with risks of 1.5 : 1.7 for ALL ***(Linet, 1999).*** According to National Academy Of Science exposure during the 1st trimester was five folds increased risk of all childhood cancer that was found, for children exposed to diagnostic radiation than those occurred in the 2nd and 3rd trimesters the risk was 1.5 times normal ***(Ross et al., 2000).***

Leukemia comprised approximately one half of the cancer in that study. The increased risk for Leukemia extended through 12 years of age ***(National Research Council, 1999).***

Non ionizing radiation

The possibility of exposure to electromagnetic fields (EMF) might be considered as to be related to the development of childhood ALL. It was also the subject of controversy as a two folds to three folds higher incidence of childhood cancers including ALL were discovered among children living in proximity to high voltage power lines ***(Savitz et al., 2002).***

Laboratory Studies suggesting that (EMF) exposure might cause cancer by increasing cellular levels of the myconcogene (***Draper, 2003).***

3- Exposure to Chemicals:

There was a considerable interest in association between pesticides including insecticides, fungi, herbicides and childhood Leukemia, primarily because of the observed higher incidence of Leukemia in rural areas and because of the biologic activity of these chemical ***(Shut et al., 2000).***

A positive association between maternal exposure during pregnancy, lactation and paternal exposure during the time mother was pregnant to house hold pesticides and garden pesticides or herbicides was reported ***(Turkeretal, 2003).***

4. Cigarette Smoking

The association with maternal cigarette smoking had been inconsistent. Some of the studies had found an increased risk of Leukemia in the children of women who smoked during pregnancy ***(Styernleledt et al., 2003),*** where as others had reported no increasing risk of either ALL ***(Pershagen et al., 2002)*** or AML ***(Shu et al., 2000)***.

Two recent studies had suggested an association between paternal cigarette smoking and the risk of childhood Leukemia in offspring ***(Sorhan et al., 2001).***

5. Lactation (Breast – Feeding):

Breast feeding was well known to have a protective effect against infection in infants ***(Schuz, 2000).***

A report of a large case-control study from the children cancer group revealed that breast-feeding was associated with a reduced risk of childhood acute Leukemia ***(Davis, 2003).***

6. Feta loss

Several studies had reported an increase risk of childhood Leukemia (Both AML and ALL) with a maternal history of feat loss ***(Yeazel et al., 2004).***

A history of fetal loss might indicate some common environmental exposure and/or an inherited genetic defect with varying effects on the fetus ***(Ross et al., 2004).***

7. Infection

The Epstein Barr Virus (EBV) had been implicated as a causative factor in B-cell lymphomas, while the Human. T-cell Leukemia Lymphoma Viruses (HTLV-1 and HTLV-2) had been isolated from adult with T-cell Leukemia ***(Judith 1996)***. Cases of childhood