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Impact of Consanguinity, Environment, Socio-Economic and Other Risk Factors on Epidemiology of Leukemia

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Abstract.- The study was aimed to investigate the occurrence and prevalence of leukemia in a hospital population and the impact of consanguinity, surname, birth order, blood group, family history, environment, socio-economic and smoking characteristics on the occurrence of leukemia. A standard questionnaire was used to collect information including different parameters like age, sex, birth order, exact diagnosis, genetic relationships, education, socioeconomic status, smoking, physical activities, allied diseases, locality and family history of patients. Chronic myeloid leukemia (CML) was most commonly occurring malignancy 42.28% followed by Acute lymphoid leukemia (ALL) 26.18%, Acute myeloid leukemia (AML) 16.11% and Chronic lymphoid leukemia (CLL) 15.43%. There was a significant ($P< 0.05$) gender depicted difference in prevalence of leukemia. The patients with blood group O^+ (29.53%) were more affected with Leukemia. 4th Birth order (16.78%) showed the highest affliction of all leukemia conditions. Rural (62.42%) population was significantly influenced than urban (37.58%) population ($P<0.05$). Patients with low level of education were more affected ($P< 0.01$) with leukemia than highly educated patients. In this study outcomes of first cousin marriages resulted in higher leukemia affliction than outcomes of unrelated couples. The inbreeding coefficient was also observed high ($F=0.0267$), which indicates genetic basis of leukemia. Highest percentage of patients among various surnames was observed in Arian (29.53%) and lowest in Mughal (1.35%). Smoking was important risk factor for occurrence of leukemia. It was found that 59.73% patients belonged to the lower class followed by middle class (35.57%) and 4.70% in upper class. The study of the risk factors leading to leukemia is pertinent and would help to identify strategies to develop protective policies and interventions.

Keywords: Cancer, leukemia, consanguinity, hospital population, prevalence.

INTRODUCTION

Leukemia is the 11th most common cancer worldwide and is the cancer of blood forming cells. Occurrence of leukemia is 2.7% of all cancer types and its incidence is 4.7 per 100,000 (Globocan, 2008). American Cancer Society reported that leukemia is a cancer of blood due to abnormal haematopoiesis (ACS, 2012). Major kinds of leukemia are acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). At present an interaction between environmental factors and genetic predisposition is thought to be the reason for the paediatric acute leukemia (Chen *et al*., 2009). Genetic abnormalities driven by environment are major cause of leukemia, which give rise to fusion of oncogenes (Iqbal, 2008). Leukemia is the most common cancer in childhood and adults. According to Karachi cancer registry data, the frequency of cancer in Pakistan is about 1.4 million per year. Enumerated occurrence of leukemia in Pakistani population is 11 per 100,000 per year (www. wrongdiagnosis.com/l/ leukemia/stats-country.htm). As far as the frequency is concerned, leukemia is the second most general form of cancer after breast cancer in Pakistani population. In children, leukemia is the most common type of cancer and prevails up to 36 percent of all childhood cancers (http://www.shaukatkhanum.org.pk/research.htm).

Acute leukemia is mainly casual cancer in adolescence and it might be due to increase of new chemical exposure into the patient's environment comprising of pesticides, parent's smoking, vehicle pollution, domestic chemicals, emulsions and birth

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order (Wiemels, 2012). The most common malignancy in childhood tumors in Pakistan is acute leukemia (34%) (Badar *et al*., 2009). Gender, age and heavy birth weight are risk factors associated with occurrence of leukemia (Caughey and Michels, 2009; Shabbir, 2011). Size of family and order of birth mostly impact the risk of some cancers (Feller *et al*., 2010).

Association between the alcohol consumption of mother during pregnancy and risk of acute leukemia is studied worldwide (Plichart *et al*., 2008). A risk factor in childhood acute lymphoblastic leukemia is the maternal consumption of alcohol during pregnancy (Zhang *et al*., 2010). 60% of children with Down syndrome flourish ALL, and 40% evolved AML (Zwaan *et al*., 2008). Children with Down syndrome had supplemented chance for growing both acute lymphoblastic as well as myeloid leukemia (Zwaan *et al*., 2010). AML is most common leukaemia in the US and integration of several bone marrow-based cancers (Strom *et al*., 2012). In the US and other western countries AML is the most ordinary type of leukemia. The enumerated female-to-male quotient appeared to be 1:1.2 (Jemal *et al*., 2008). An increase of AML had been familiar for over 4 decades (Thomas *et al*., 2012). Wonga *et al*. (2010) reported an increased risk of AML exposed with insecticides, fertilizers, benzene, metals, diesel fuel, adhesives, glue, paints and pigments.

CLL is a malignancy differentiated by the aggregation of small, adult lymphocytes in the lymphoid tissues, bone marrow and blood. The recent WHO classification scheme concedes CLL as a mature B-cell neoplasm (Jaffe *et al*., 2008). The greater exposure of chronic lymphocytic leukemia is greater among the relatives of CLL (Goldin *et al*., 2009). Revelation to high dosage of irradiation slightly but significantly increased the risk of developing CML (Medifocus, 2009). In Arab population consanguinity rate is high and has no after effect on the incidence of cancers overall. Yet, there is an increased incident found for lymphoma and leukemia (Bener *et al*., 2009). Almost 10% of cases with CLL report a family history of CLL or a related lymph proliferative disorder (Brown, 2008).

Data on the occurrence of leukemia in South Asia, including Pakistan is scarce. In a hospital population blood cancer is quite prevalent in Pakistan but due to lack of knowledge and awareness less work is done on this issue. In our society, inbreeding is very common due to cousin marriages. Due to lack of education, people are unaware that these diseases are inheritable. Keeping in view above facts the study was designed to investigate the occurrence and prevalence of leukemia in a hospital population and the influence of consanguinity, surname, birth order, blood group, family history, environment, and smoking characteristics on the occurrence of leukemia. The study about the risk factors leading to leukemia would be helpful to identify strategies to develop protective policies and interventions.

SUBJECTS AND METHODS

The study was carried out at Allied Hospital Faisalabad, Punjab Institute of Nuclear Medicine Faisalabad, Sahil Hospital Faisalabad, District Head Quarter Hospital Sargodha and Combined Military Hospital (CMH) Sargodha from December 2013 to June 2014. A prior consent of patients and respective Heads of the Oncology Institute was sought before the start of study and after approval by the local ethics committee of GC University Faisalabad information was collected by interviewing patients or their close relatives. A standard questionnaire was used to collect information including different parameters like age, sex, birth order, exact diagnosis, blood group, surname, genetic relationships, education, socioeconomic status, smoking, physical activities, allied diseases, clinical findings, locality and family history of patients.

Data analysis

The data was analysed in two ways. Firstly, the cases were examined as a whole to accomplish facts of the hospital and institution's population. Secondly, the patients were analysed in relation to consanguinity. Hereditary relationships in marriages were classified into first cousin (1C), first cousin once removed (1½ C), second cousin (2C), distant relatives (DR), bradri/clan (B) and unrelated (U) (Shami and Iqbal, 1983).

Statistical analysis

The data was statistically analysed which included percentages, mean, standard error and chi-square test ($p<0.05$). Coefficient of inbreeding was calculated by Wright's method (Wright, 1992).

Table I.- Percentage distribution of leukemia in male and female patients in a hospital population.

Blood cancer type	Male (M) %	Female (F) %	Sexes combined (M+F) %	Sex ratio/100 female
ALL	16.78	9.39	26.17	178.57
AML	11.41	4.70	16.11	242.86
CLL	14.10	1.34	15.44	1050
CML	24.83	17.45	42.28	142.31

ALL, Acute lymphocytic leukemia; AML, Acute myeloid leukemia; CLL, Chronic lymphocytic leukemia; CML, Chronic myeloid leukemia.

RESULTS AND DISCUSSION

During this study, 149 patients were studied. They were examined for various types of Leukemia. The percentage distribution of various types of Leukemia has been shown in Table I. Subtypes of leukemia observed in this study were CML (42.28%), ALL (26.17%), AML (16.11%) and CLL (15.44%). In this study, 100 males (67.1%) and 49 females (32.9%) were affected with blood cancer (n=149). There were significant differences between male and female in the affliction of disease ($P<0.05$). Present investigations are in good agreement with previous studies where different types of Leukemia were more widespread in males than females (Modak *et al*., 2011). They focused on parameters like age, sex, race, blood group and lifestyle habits and found that compared to female patients, Hindu males had greater risk of occurrence of leukemia ($P=0.0333$). These findings are also in agreement with findings of leukemia and lymphoma society survey (2012) that incidence rates for all types of leukemia are higher among males than among females.

Table II represents the percentage distribution of patients according to their age groups, blood groups and education. Maximum number of patients was recorded in 46-60 years age group followed by 0-15 and 16-30 years age groups. The maximum percentage of patients was seen in O^+ (29.53%) and A^+ (25.51%) blood groups and lowest in A^- and AB^- blood groups and these findings are in accordance with the findings of Samin *et al*. (2006) who reported the existence of blood type A in patients with leukemia was higher than in normal population. In this study highest percentage of Leukemia was reported in patients having primary level of education. Education of parents also had significant effects ($p<0.01$) on the occurrence of disease in the children. Similar arguments were reported by Kong *et al*. (2010), who found that significant cancer deaths were linked with academic career of maternal and paternal at middle school or below rather than college graduates.

In this study different birth orders of 149 patients were recorded up to 12^{th} birth order. Percentage distribution of both sexes in different birth orders showed that 3^{rd} (15.44%) and 4^{th} (16.78%) birth order had the highest contribution and 12^{th} (1.34%) birth order had the lowest representation (Table III). These findings are in harmony with the investigations of Westergaard *et al*. (1997), who reported that children born second and later in the birth order had greater exposure of AML and ALL compared with first born. Bevier *et al*. (2011) determined that size of family and order of birth mostly impacts the risk of some cancers. Von *et al*. (2011) explored contemplated extended risks with increasing order of birth for AML. In this study out of 149 patients, 62.42% belonged to rural areas and 37.58% belonged to urban areas. These findings are in agreement with Kong *et al*. (2010) who reported that children born in rural areas showed significantly increased risk of death from cancer.

Patients were explored on the parental consanguinity basis and showed following categories of first cousin (38%), second cousin (21%), first cousin once removed (2%), bradri (19%), distant relations (11%), and unrelated spouses (9%), respectively. These findings are in accordance with those of Yasmeen and Ashraf (2009) who reported that acute lymphoblastic leukemia comprising of 32% of all cancers in their

Table II.- Percentage distribution of leukemia among different age and blood groups and in patient's education level in a hospital population.

Age Groups	Percentage (n)	Blood Groups	Percentage (n)	Education	Percentage (n)
0 – 15	15.44 (23)	A^+	25.51 (38)	Nil	14.09 (21)
16 – 30	13.42 (20)	A^-	0 (0)	Primary	39.59 (59)
31 – 45	10.74 (16)	B^+	24.83 (37)	Middle	8.73 (13)
46 – 60	30.87 (46)	B^-	2.01 (3)	Matric	20.14 (30)
61 80	22.82 (34)	O^+	29.53 (44)	Intermediate	6.71 (10)
80^+	6.71 (10)	O^-	0.67 (1)	Graduate	3.36 (5)
		AB^+	17.45 (26)	Unknown	7.38 (11)
		AB^-	0 (0)		

Values presented are the percentages and numbers are in parenthesis

Table III.- Percentage distribution of Leukemia patients in different birth orders.

Birth order	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
Percent	11.41	5.37	15.44	16.78	12.75	10.06	6.04	6.04	5.37	6.04	3.36	1.34
Number	17	8	23	25	19	15	9	9	8	9	5	2

Table IV.- Distribution of Patients in relation to parental relationships, F-values and surnames.

Surname	Genetic relationships						Total	F-value
	1C	1 ½ C	2C	DR	B	U		
Arian	61.37 (27)	2.27 (1)	11.36 (5)	6.82 (3)	11.36 (5)	6.82 (3)	44	0.0402
Rajput	45.46 (5)	9.09 (1)	-	27.27 (3)	-	18.18 (2)	11	0.0312
Sheikh	33.33 (1)	-	-	-	66.67 (2)	-	3	0.2083
Jatt	29.41 (5)	5.88 (1)	23.53 (4)	-	41.18 (7)	-	17	0.0225
Mughal	-	-	-	-	-	100 (2)	2	0
Malik	50 (2)	-	-	-	50 (2)	-	4	0.0312
Awan	16.67 (1)	-	33.33 (2)	-	-	50 (3)	6	0.0106
Rehmani	75 (6)	-	25 (2)	-	-	-	8	0.0494
Gujar	22.22 (6)	-	25.93 (7)	11.11 (3)	37.04 (10)	3.70 (1)	27	0.0140
Bhatti	10 (1)	-	60 (6)	30 (3)	-	-	10	0.0122
Pathan	37.5 (3)	-	12.5 (1)	12.5 (1)	12.5 (1)	25 (2)	8	0.0247
Others	-	-	55.56 (5)	33.33 (3)	11.11 (1)	-	9	0.0056
Total	38.26 (57)	2.01 (3)	21.48 (32)	10.74 (16)	18.79 (28)	8.72 (13)	149	0.0267

Values presented are the percentages and numbers are in parenthesis

study, consanguinity was seen in 47% cases. These findings are also in line with those of Qurat-ul-Ain *et al*. (2011) who reported that incidence of ß-thalassemia was higher in outcomes of first cousin marriages as compared to unrelated couples. The inbreeding coefficient (F-value) calculated in this study was 0.0267 (Table IV) which is in good agreement with the findings of Shami *et al*. (1990), they reported that the extent of consanguinity to which an offspring is inbred is assessed by the coefficient of inbreeding (F – value). They revealed that in Pakistan 1st cousin marriages are more general than unrelated relations and the rate of inbreeding ranges from 0.0236 to 0.0286. Consanguineous marriages are favoured primarily for the economic and safety reasons regardless of other factors. This practice is believed to strengthen family ties and maintain the family structure and

property. A lack of awareness about risks of disease is basically associated with parental consanguinity.

Figure 1 shows the distribution of patients among different surnames scored in data and all other surnames which had representation of less than 2 patients were grouped as others. The highest percentage was seen in Arian and the lowest in the Mughal surname. The impact of first cousin marriages was observed through the calculation of F- values in different surnames in relation to parental consanguinity, which shows that inbreeding has a positive impact on the development of blood cancer. The highest percentage of patients was associated to first cousin relations compared to unrelated ones. The highest F-value was observed in Arian (0.0402) surname (Table IV). No supporting and opposing reference for finding out the occurrence of blood cancer on the basis of surnames were available. These findings will add new aspect to existing literature.

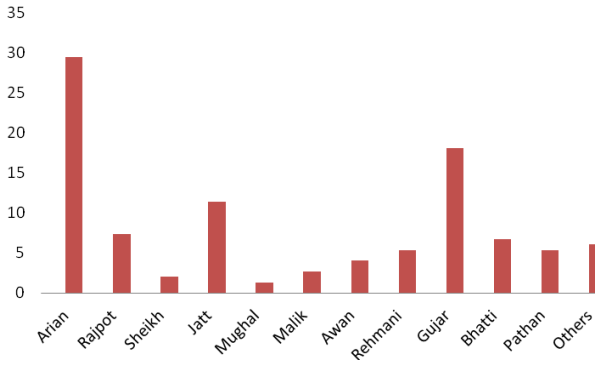

Fig. 1. Percentage distribution of patients in different surnames.

Smoking appeared to be an important risk factor for occurrence of blood cancer. Out of 149 patients 50% were smoker followed by non-smoker 43% and ex-smoker 7%. In this study (60%) patients belonged to the lower class followed by middle class (35%) and (5%) upper class. In this study socio economic status showed significant ($p<0.01$) influence on occurrence of leukemia among different marriage relationships. The first cousin marriage showed high representation of disease in lower socio economic class compared to other professions. These findings are in accordance with Clarke *et al.* (2011) who examined the incidence patterns of lymphoid malignancies among populations characterized by ethnicity, birthplace, and residential neighbourhood socioeconomic status (SES) and ethnic enclave status. Kong *et al*. (2010) reviewed that in South Korea, there had been variation in early age cancer death by socioeconomic status.

Table V.- Percentage distribution of patients exposed to different risk factors

Risk factors	%
Smoking	23.18
Petro chemicals	10.78
Hair dyes	4.04
Paint or dyes	2.16
Ascites	6.74
T.B.	1.35
Jaundice	9.43
Inguinal hernia	5.39
Repeated therapies	8.09
Pesticide exposures	14.56
Chemical exposures	8.63
Ionizing radiation	4.04
Genetics Bcr-abl translocation	1.35
Congenital syndrome	0.27

Table IV represents the percentage distribution of patients exposed to different risk factors (*e.g.*, environmental, genetic or infectious). Parental or self-smoking was the dominant risk factor observed in (23.18%) patients followed by pesticide exposure (14.56%) exposure to petrochemicals (10.78%). Most of the blood cancer patients had the previous history of TB, inguinal hernia, family history of jaundice and sugar other than same and other types of cancer in family. Wrong diagnosis and use of wrong medicine was another important participating aspect in the occurrence of blood cancer. Farmers, drivers and workers were most generally affected with blood cancer that may be due to pesticide exposures and vehicular and other exhaust fumes and smoke and exposure to paint and dyes. ALL exposure was greatly related with after birth paint exposure and a tremendous liability was seen when paint was used by a person instead of mother. In comparison, a meaningful greater exposure for AML was

associated with solvent but not with paint exposure (Scelo *et al.*, 2009). These findings are similar to Amigou *et al*. (2011) who evaluated the impacts of exposure to vehicles pollution on the liability of early age leukemia. There had been significant relationship between acute leukemia and a high mass of abundant traffic roads. Ghosh *et al*. (2011) determined that high prevalence of leukemia might be linked with exposure to coal dust, long term professions such as a carpenter or machinist and an affirmative family background of cancer.

Table VI.- Clinical findings of leukemia patient.

Clinical features	Frequency (%)
ALL (n=39)	
Weakness, weight loss	64% (n=25)
Spleenomegaly	7% (n=3)
Anemia,	100% (n=39)
Fatigue, Fever	5% (n=20)
Bone and joint pain	46% (n=18)
Testicluar Involvement	5% (n=2)
Hepatospleenomegaly,	64% (n=25)
Lymphoadenopathy	13% (n=5)
Hepatomegaly	10% (n=4)
Body aches	13% (n=5)
Bruising	23% (n=9)
AML n=24	
Weakness, pallor, fatigue	83% (n=20)
Bone and joint pain	42% (n=10)
Fever, weight loss	42% (n=10)
Bleeding	21% (n=5)
Hepatomegaly	29% (n=7)
Gingival hypertrophy,	25% (n=6)
Splenomegaly	13% (n=3)
Lymphadenopathy	38% (n=9)
CML (n=63)	
Fatigue, splenomegaly	25% (n=16)
Hepatomegaly	16% (n=10)
Weight loss, pallor	14% (n=9)
Fever, night sweat	10% (n=6)
Anemia, Dyspnea. Bruises	32% (n=20)
Bleeding, Shortness of breathe	19% (n=12)
Ascites	8% (n=5)
Cholethiasis	5% (n=3)
Hepatospleenomegaly	59% (n=37)
CLL = 23	
Weakness, fatigue,	39% (n=9)
Weight loos, pallor	52 (n=12)
Lymphadenopathy,	30% (n=7)
Hepatomegaly, splenomegaly	26% (n=6)

Table VI shows the clinical findings of leukemia patients scored in this study. In this study CML was most commonly occurring followed by ALL. One patient was a diagnosed case of Down's syndrome. Patients were afflicted with bone pains involving lower sternum and joints. All were anaemic and lymphadenopathic with variable degree of involvement of cervical, axillary and inguinal lymph nodes. Mild to temperate hepatomegaly was a general observation. Splenomegaly was moderate; bleeding and bruising were observed either alone or in combination. Two patients showed signs of raised intracranial pressure or testicular involvement. All patients complained weakness, fever, fatigue, a variable degree of weight loss and mucosal bleeding. All were anaemic, 6% had gingival hypertrophy. In chronic myeloid leukemia five patients have the Philadelphia positive bcr-abl translocation (Table VI). Above clinical findings are in accordance with Aziz and Qureshi (2008) who determined the most common demonstrating features in every type of leukemia including anaemia, fever, fatigue, bone pains, pallor, bleeding, adenopathies, weight loss, spleenomegaly and hepatomegaly.

CONCLUSIONS

In this epidemiological study there was a significant ($P< 0.05$) gender related variation in the prevalence of leukemia. Parental or self-smoking was the dominant risk factor observed in patients followed by pesticide exposure and exposure to petrochemicals. Birth order, blood group, family history, consanguinity, socio-economic status, education, surnames and locality appeared as important risk factors in the occurrence of Leukemia. Research of the risk factors leading to leukemia is pertinent to identify strategies to develop protective policies and interventions.

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