Prevalence of Hereditary Cancer Susceptibility Syndromes (HCSS) in Acute Lymphoblastic Leukemia (ALL): A Cross-Sectional Study in a Highly Consanguineous Population.

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Abstract

Background: Hereditary cancer susceptibility syndrome (HCSS) has been reported to impact cancer predisposition at an early age, therefore, identification of HCSS has found to be crucial for surveillance, managing therapeutic interventions and referring the patients and their families for genetic counselling. The aims of this study are to assess the prevalence of HCSS as hereditary leukemia and hematologic malignancy syndrome by using ACMG guidelines and to assess parental consanguinity as the criterion for referring patients for the genetic counselling.

Methods: A total of 300 acute lymphoblastic leukemia subjects were recruited from the Children's Hospital, Lahore, Pakistan during the period of December 2018 to September 2019. Structured self-reporting questionnaire based on family and medical history of the disease was utilized for the data collection.

Results: In our cohort, 60.40% of ALL patients were identified to have HCSS and among them 40.65% patients solely fulfil the criteria due to the presence of parental consanguinity. Parental consanguinity was shown to have protective impact on the onset at early age of disease [OD=0.44 (0.25-0.77), p-value= 0.00] while family history of cancer increase the risk of cardiotoxicity [OD= 2.46 (1.15-5.24), p-value=0.02]. Parental consanguinity in the population shows no significant impact on the family history of cancer and the number of relatives with cancer.

Conclusions: The higher prevalence of HCSS in Pakistani population is attributed to the presence of parental consanguinity in more than 50% of the patients when assessed through ACMG guidelines. Our study suggests revisiting ACMG guidelines for the criterion of parental consanguinity in the highly consanguineous population and formulating the score based criteria for the identification of inherited ALL for genetic counselling.

1. Background

According to the global cancer observatory 2018, Asia is the most leukemia burdened region in the world with an incidence rate of 48.7% and a mortality rate of 53.7% (1). In Pakistan, Acute Lymphoblastic Leukeima (ALL) is a predominant childhood cancer with an incidence rate of 20.8% as reported by the Punjab cancer registry 2017 (2). Remarkable progress has been observed in improving the survival rate of the acute lymphoblastic leukemia due to implementation of the risk-adapted therapy and with greater understanding of biological heterogeneity of the disease (3). However, the etiology of leukemia is still unknown, and the major cause reported for this cancer is the same as other cancers involving the interaction of environmental factors and genetic susceptibility (4–7). Hereditary cancer susceptibility syndromes include the predisposition to leukemia, often at an early age, caused by inherited mutations or polymorphisms. The identification of the HCSS aids in the cancer surveillance and screening, optimizing of the therapeutic response and advising the patient for genetic counselling to reduce the risk of cancer. The outcome of these practices helps to decline the incidence and morbidity rate of inherited leukemia

among children (8, 9). It is estimated that 5–10% of the leukemia cases are attributed to the genetic susceptibility (10). However, Knapke et al., reported 29% of the survivors of childhood cancer to have HCSS and due to the presence of the familial history of cancer (11). The assessment of hereditary cancer susceptibility syndromes (HCSS) as hereditary leukemia and hematologic malignancy syndromes was found crucial for patients with familial history of cancer in first and second degree relatives (12).

Based on the evidence, early onset of cancer (13, 14), family history of cancer especially in a first and second degree of relatives (15), racial or ethnic differences (16) and consanguinity (17) are considered to be the major risk factors of hereditary cancer and are included in the various criteria established for the identification of HCSS, formulated by different consensus groups to identify the patients and families at risk of developing cancer and refer them for genetic counselling (18). The guidelines provided by the American College of Medical Genetics (ACMG) utilize consanguinity along with the familial history of cancer (19). Apart from one study conducted in the highly consanguineous population of Saudi Arabia, data on the contribution of consanguinity to hereditary leukemia and hematologic malignancies syndromes is are lacking. Consanguineous marriages are practiced around the world and reported to have severe implications if practiced in consecutive generations (20). In Europe and America, the rate of consanguinity is reported to be less than 1%, and in Arab countries the rate is 20–50% (21), whereas in Pakistan, it is reported to be 60% (22). Among them, the most predominant degree of relatedness is the first cousins (20). In adults, constitutional MMR deficiency (CMMRD) syndrome has also been identified in the highly consanguinity population and is characterised by haematological malignancies and brain tumour however its prevalence in paediatric patients is underreported (23, 24).

The aim of the present study was to estimate the prevalence of HCSS in the acute lymphoblastic leukemia subjects in the Pakistani population to refer the patients for genetic counselling and to assess the role of consanguinity in the identification of HCSS in the highly consanguineous population.

2. Materials And Methods

2.1. Study cohort and research ethics

The cross sectional study was conducted at the University of the Punjab and the Research Ethics and Biosafety Committee approved the study protocol related to the data collection from the human subjects. The research was conducted accordance with the Declaration of Helsinki. The study population comprised of 300 acute lymphoblastic leukemia patients (Pre B-ALL and Pre T-ALL) of age 15 years or younger, diagnosed during December 2018 to September 2019. An informed consent was obtained from the patients or their guardian and data related to the personal information of patients and medical history of the disease was obtained. The exclusion criterion included any other type of leukaemia and patients seropositive for infectious diseases. The first degree relatives refer to the parents and siblings of the subject, second degree relative refer to the half-sibling, grandparents, uncle, aunt, niece and nephew and the third degree relatives refer to other cousins and great grandparents of the affected child.

2.2. Data collection

The data was collected from the Children's Hospital, Lahore, Pakistan by using subjective self-reporting questionnaire. The standardized face to face interviews were conducted to collect the data regarding family history of disease. Patient charts were consulted to obtain data related to the age of the patient, gender, number of primary cancer and associated disorders. The complete blood cell count, echocardiogram and ultrasound reports of the patients were consulted for the WBC count, hepatospleenomegaly and cardiotoxicity. The flow cytometry reports (FCM) were assessed for the presence of Pre T-ALL and Pre B-ALL markers. The patients who had positive family history were interviewed further regarding degree of family history with cancer and number of relatives with cancer.

2.3. Assessment of HCSS and statistical analysis

The assessment of HCSS among the target population was done according to the guidelines provided by American College of Medical Genetics (ACMG) and Genomics and the National Society of Genetic Counselors (NSGC) (19). It includes comprehensive personal and family history criteria that help in identification of high-risk individuals and referral for genetic counselling. The data were presented in the form of percentages and to assess the impact of the family history and familial consanguinity, Chi-square test was employed. The logistic regression model was used to assess the association of family history and familial consanguinity with ALL. All the models for the statistical analysis were expressed in the form of odds ratios (OR) and 95% confidence interval (CI).

3. Results

3.1. Patient characteristics and identification of HCSS

In the present study, three hundred patients of acute lymphoblastic leukemia (ALL) were recruited for the study and among them 2 (1.66%) were excluded due to the presence of underlying disorders/syndromes i.e. Down syndrome (Fig. 1). The mean age at the time of diagnosis was 6.62 ± 3.5 and the male to female ratio was 2.59:1. Parental consanguinity was found in 151 (50.67%) and familial history was present in 66 (22.14%) patients. In our cohort, 257 (86.24%) patients had Pre-BALL and 41 (13.75%) patients had Pre-TALL. Only one patient had more than one primary cancers and it includes acute lymphoblastic leukemia with Ewing sarcoma. Hepatoslpeenomegaly was found in 35.90% patients while cardiotoxicity was observed in 34 (11.41%) patients (Table 1). The consort diagram (Fig. 1) displays that 180 (60.40%) patients meet the ACMG criteria and referral for genetic counselling. Among them 145 (48.65%) have solely consanguineous parents, 29 (9.73%) patients have family history of LS-associated cancer in 1st and 2nd degree relatives and 6 (2.01%) patients have sibling with a childhood cancer.

Table 1
Anthropometric characteristics and history of patients with ALL.

Characteristics	Number	Percentage (%)
Mean age at diagnosis ± SD	6.62 ± 3.5	
Gender		
Male	215	72.14%
Female	83	27.85
Parental consanguinity		
Yes	151	50.67
No	147	49.32
Family History of Cancer		
Yes	66	22.14
1st degree	6	9.09
2nd degree	47	71.21
3rd degree	20	30.30
No	232	77.85
No of primary cancer		
One	299	99.66
Two	1	0.34
Type of ALL		
Pre B-ALL	257	86.24
Pre T-ALL	41	13.75
WBC count		
< 50,000	285	95.63
≥ 50,000	13	4.36
Hepatospleenomegaly		
Yes	107	35.90
No	191	64.09
Cardiotoxicity		

Characteristics	Number	Percentage (%)
Yes	34	11.41
No	264	88.59

3.2. Impact of parental-consanguinity and history on the characteristics of ALL

The parental consanguinity was observed in 151 indexed patients included in the study. Based on the age of patient, WBC count, hepatospleenomegaly and cardiotoxicity and sub-types of ALL the data were divided into two groups: consanguineous and non-consanguineous. The statistical analysis showed that the parental consanguinity had protective impact when compared with age of the patient. No significant association was observed with other variables. The patient with the two primary cancers has the history of parental consanguinity (Table 2). In our cohort, 66 (22.14%) patients have family history of cancer in first, second and third degree relatives. The impact of familial history of cancer was also analyzed with the age of patient, WBC count, hepatospleenomegaly and cardiotoxicity observed during the time of treatment and types of ALL the data. Except cardiotoxicity, no significant association was observed with other variables. Familial history of cancer increase 2.46 times risk of the outcome of cardiotoxicity during the course of treatment (Table 3).

Table 2
Impact of parental consanguinity on the characteristics and type of ALL patients with no associated disorder.

Characteristics	Parental consanguinity (n = 151)	No parental consanguinity (n = 147)	Odds ratio (95% CI)	P-value
Age of the patient				
< 10	105 (69.53%)	123 (83.67%)	0.44 (0.25–0.77)	0.00*
≥ 10	46 (30.46)	24 (16.32%)		
WBC count				
< 50,000	144 (95.36%)	141 (95.91%)	0.87 (0.28–2.66)	0.82
≥ 50,000	7 (4.63%)	6 (4.08%)		
Hepatospleenomegaly				
Yes	56 (37.08%)	51 (38.77%)	1.11 (0.69–1.78)	0.66
No	95 (62.91%)	96 (65.30%)		
Cardiotoxicity				
Yes	15 (9.93%)	19 (12.92%)	0.74 (0.36–1.52)	0.41
No	136 (90.06%)	128 (87.07%)		
Sub-type of ALL				
Pre-BALL	132 (87.42%)	125 (85.03%)	1.22 (0.63–1.36)	0.55
Pre-TALL	19 (12.58%)	22 (14.96%)		
BCR-ABL translocation	1 (0.66%)	0	-	-
Two primary cancers in the affected child	1 (0.66%)	0	-	-

Table 3
Impact of familial history on the characteristics and type of ALL patients with no associated disorder.

Characteristics	Familial history of disease (n = 66)	No familial history of disease (n = 232)	Odds ratio (95% CI)	P-value
Age of the patient				
< 10	49 (74.24%)	179 (77.15%)	0.85 (0.45–1.60)	0.62
≥ 10	17 (25.75%)	53 (22.84%)		
WBC count				
< 50,000	65 (98.48%)	220 (94.82)	3.54 (0.45–27.78)	-
≥ 50,000	1(1.51%)	12 (5.17)		
Hepatospleenomegaly				
Yes	21 (31.81%)	86 (37.06%)	0.79 (0.44–1.41)	0.43
No	45 (68.18%)	146 (62.93)		
Cardiotoxicity				
Yes	13 (19.69%)	21 (21.98%)	2.46 (1.15–5.24)	0.02*
No	53 (80.30%)	211 (90.94)		
Sub-type of ALL				
Pre-BALL	57 (86.36%)	200 (86.20%)	1.01 (0.45–1.24)	0.86
Pre-TALL	9 (13.63%)	32 (13.79%)		
BCR-ABL translocation	0 (0.00)	1 (0.43%)	-	-
Two primary cancers in the affected child	0 (0.00)	1 (0.43%)	-	-

3.3. Family history association with parental consanguinity

In our data, the ALL subjects with family history of cancer with parental consanguinity (24.50%) were more than non-parental consanguinity (19.73%) however, no significant impact of parental consanguinity on the family history of cancer was observed. We also assessed the impact of parental consanguinity on the degree of family history of cancer. The results of statistical analysis showed no significant impact of parental consanguinity on first, second, third and first and second degree of family history however, the odds ratio of first degree relative [4.14 (CI = 0.45–37.60)] was higher as compared to the second 1.18 [(0.62–1.20)], third [1.72 (0.60–4.90)], first and second degree relatives [1.31 (0.71–1.43)] with cancer. The association of the number of relatives of cancer with the parental consanguinity did not show any significant association as well (p-value < 0.05) (Table 4).

Table 4
Impact of parental consanguinity on family history of cancer and number of relatives with cancer.

	Parental consanguinity		OR (95% CI)	P-value
	YES (N = 151)	NO (N = 147)		
Family history of cancer				
Yes	37 (24.50%)	29 (19.73%)	1.32 (0.76−1.29)	0.32
No	114 (75.49%)	118 (80.27%)		
First degree relatives	4 (10.81%)	1 (3.45%)	4.14 (0.45−37.60)	-
Second degree relatives	25 (67.57%)	22 (68.96%)	1.18 (0.62−2.20)	0.61
Third degree relatives	10 (27.03%)	6 (20.69%)	1.72 (0.60−4.90)	0.30
First and second degree relatives	29 (78.37%)	22 (75.86%)	1.31 (0.71−2.43)	0.38
Number of relatives with cancer				
1	141(93.37%)	142 (96.59%)	0.49 (0.16−1.48)	0.20
≥ 1	10 (6.62%)	5 (3.40)		

4. Discussion

This study assesses the prevalence of hereditary cancer susceptibility syndrome (HCSS) in childhood acute lymphoblastic leukemia patients and to our knowledge this is the first study conducted in the Pakistani population using the ACMG practice guidelines. We demonstrated that 60.40% of the paediatric ALL patients fulfils the criteria for the assessment of HCSS (Fig. 1). A previous study conducted in the highly consanguineous population of Saudi Arabia using the ACMG practice guideline has identified 40% cancer patients with HCSS that is lower than the Pakistani population (12). This may be due to the fact that our study population focus only the childhood ALL while the study subjects in Jastaniah and co-workers, comprise of all the cancers diagnosed in multi-institutions in Saudi Arabia. Knapke and co-workers also reported 29% childhood cancer survivors to meet the criteria for the HCSS however different criteria were established for the assessment of HCSS that comprise of medical and familial history of cancer (11).

ACMG guidelines limits the parental consanguinity for the leukemia and brain tumours as these cancers have been reported to be associated with Constitutional mismatch repair deficiency (CMMRD) syndrome (25). In our cohort, 48.65% patients with HCSS were referred to the genetic counselling solely due the presence of parental consanguinity (Fig. 1). We also assessed association between parental consanguinity and family history with anthropometric characteristics, chemotherapy related toxicity and subtype of ALL. The results showed that age at the diagnosis of disease, hepatospleenomegaly and

subtype of ALL was comparable among consanguineous and non-consanguineous patients however consanguineous showed significantly protective impact age at diagnosis of disease (Table 2). This is in concordance with the previous studies performed in highly consanguineous populations of Middle East that suggests that consanguinity confers protective effect to the development of the adult cancers at an early age (26–28). In the previous studies, different germ line genetic variations have been associated with the chemotherapy related cardiotoxicity (29, 30). We also found that cardiotoxicity to be comparable in patients having family history of cancer when compared with patients without family history of cancer and it showed that the familial history of cancer asserts increase risk of toxicity in ALL patients (Table 3). At present, the outcome of chemotherapy related toxicities has not been utilized by the ACMG guidelines as a criterion for the assessment of HCSS and our study suggests it to be factored into the assessment guidelines.

It is interesting that despite high consanguinity (50.67%) in the population only 29 patients have shown to have of family history of cancer in 1st and 2nd degree relatives moreover, 2 (0.66%) patients have shown to have associated syndrome that is Down syndrome (Table 1). In our cohort, only 1 (0.34) patient has second primary cancer. This reflects that HCSS or CMMRD is not much prevalent in our population otherwise these numbers would be higher. It may also be attributed due short the follow up duration of the patient. It can also be conclude that high frequency of consanguinity alone does not increase the risk of family history and the results were consistent when compared with the 1st, 2nd and 3rd degree of relatedness and number of relatives with cancer (Table: 4).

The results of our study are in concordance with the recommendations made by the Jastaniah et al. that suggest the score based criteria based on multifactorial genetic risks factors, the toxicology profile and physical features along with the personal and family history of cancer for the identification of HCSS especially for the high consanguineous populations (12). Genetic evaluation of large number of patients may not be feasible especially for developing country therefore in order to manage the resources "Genetic testing for all children with cancer" approach is needed to be re-evaluated. To assess the prevalence of the germ line mutations or variation related to hereditary cancer susceptibility the population based screening using high throughput techniques is needed to be performed. The possible limitations of the study include self-reporting bias related to the family history of disease and lack of availability of pathology reports of the relatives having history of cancer. The self-reporting bias was reduced by using a structured standardized self-reporting questionnaire conducted by the trained individual. Various studies have been performed to analyse the validity of self-reporting of family history of cancer and found that the sensitivity ranges from 0.78 to 0.90 (31, 32) moreover the recall bias is expected to be lowered due to the extended family support system of Pakistani culture.

5. Conclusion

Results of our cross-sectional study in acute lymphoblastic leukeima have identified 60.40% patients with hereditary cancer susceptibility syndrome (HCSS) by using ACMG guidelines. Parental consanguinity was the leading criteria for the identification however the findings of our study underscore revisiting this

criterion especially in highly consanguineous populations. Population based screening of mutations and variation related to hereditary susceptibility is needed to be performed in Pakistani population that aims to contribute to the development of genetic-screening tool for the early assessment of cancer.
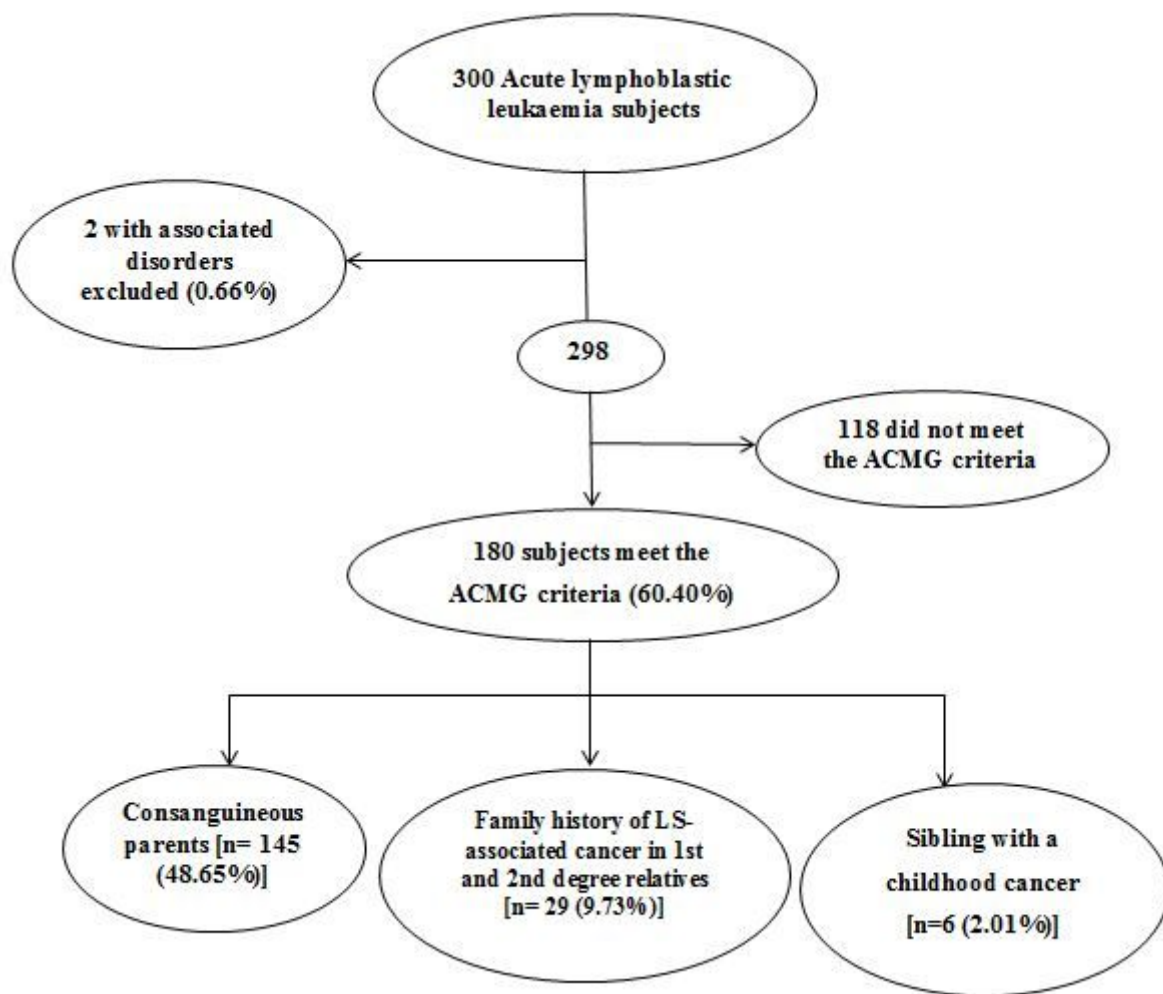
Declarations

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Figures

Figure 1

Consort diagram showing the selection of ALL patients with HCSS by using ACMG guidelines.