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Consanguinity and childhood acute lymphoblastic leukaemia: a case-control study

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Abstract

Background: Consanguineous marriage is widely practised across the world. Its effect on acute lymphoblastic leukaemia (ALL) is controversial as both parents share some of the genes which might increase the incidence of sharing recessive genes. However, other theories suggest that consanguinity might have a protective factor as it does for other types of cancers. This study aims to study childhood ALL and consanguinity.

Methods: This is a case-control study, conducted in the major paediatric hospital in Damascus, Syria, using medical records. Case group included children with ALL, while control group included other patients and were matched by gender and age.

Results: This study comprised 386 patients, 193 of which were cases. Overall, 136 were of consanguineous marriages (36.8%), and there was no difference in consanguinity overall between cases and controls. However, when only comparing non-consanguineous parents and fourth-degree consanguinity, fourth degree was significantly higher among case group, suggesting a negative correlation $OR = 0.387$ (0.187–0.801) in contrast to third-degree consanguinity which was no significantly different when comparing the two groups ($p > 0.05$). We found no significant association between ALL and having a family history of cancer ($p > 0.05$) or between parents' educational level and case-control groups ($p > 0.05$).

Conclusion: Our research suggests a negative association between fourth-degree consanguinity and childhood leukaemia. This was not observed with a third-degree consanguinity. Previous studies had contradicting data on consanguinity and ALL which demonstrates the need for further research.

Keywords: Acute lymphoblastic leukaemia, Consanguinity, Familial, Genetics, Levant

Background

Consanguineous marriages vary in prevalence across the world, and it is practiced for many consecutive generations in some regions [1]. While they are relatively rare in Europe and North America (approximately 1%), the rate of occurrence ranges widely in the Arab world between 20 and 50% [1]. Consanguineous marriages are more common in rural areas, in women with low education and lower socio-economic status [2, 3]. Furthermore, the children of these families are more likely to also enter into consanguineous marriages [2]. This creates generations of mating between the same kinship which stresses the importance of studying its health impact on society affecting millions of people.

Children cancer survivors' data suggests that 29% of them were at risk for hereditary cancer. This demonstrates the importance of inferring criteria to detect such hereditary syndromes and acquiring a thorough family history to reduce cancer morbidity and maximizing treatment outcomes [4]. Clustering of multiple cases of leukaemia in one family is rare and accounts for 0.23 to 0.98% in all leukaemia cases [5]. A younger age of onset

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is also noted in families with multiple cases. The risk of the disease recurrence in patients' families increases, and therefore, having a relative with leukaemia increases the risk two- to fourfold [6, 7]. Possible leukaemogens that are shared by patients' families have been sought but rarely found [8].

Consanguineous marriage is illegal and discouraged in most parts of the world between first- and second-degree relatives, whereas marriages of third-degree relatives or more are not generally as discouraged. Consanguineous marriages include first-cousin marriages which are generally most preferred [2], and they share around one-eighth of their genetic makeup. Double-first cousins, which are less common, share one-quarter of genes. First cousins once removed share one-sixteenth of genes. There are also other marriages between distant cousins [9]. However, a study showed that despite the high rates of consanguinity among Arabs, it might not have an effect on its incidence overall, as it found that some cancers such as skin and thyroid cancers decreased, while others such as lymphoma and leukaemia might increase [10]. Consanguinity was indirectly associated with childhood cancers in finding that autosomal recessive diseases are associated with childhood tumours [11]. Another study found that multifactorial inheritance is suspected for many complex disorders such as hypertension, diabetes and cancer [9]. In contrast, other hypotheses suggest an elimination or decrease in frequency of cancerous genes in populations which practice consanguinity in the long term [12].

Acute lymphoblastic leukaemia (ALL) is prevalent in children and adults and is the most common cancer in children, constituting about 75% of all paediatric acute leukaemias. The peak onset of ALL is between the ages of 3 and 4 years [13]. Investigating the relationship between consanguinity and childhood ALL would contribute to better understanding of the risk involving consanguineous marriages which continues to be widely practiced in widely accepting consanguineous societies.

Syria has its own distinguished features as it suffered from years of war and has a unique environment and practices which might expose people to harmful substances such as shisha smoke and mate which might increase the risk of ALL [14]. We aim with this paper to study childhood ALL and leukaemia in the Syrian community that has high rates of consanguineous marriage.

Methods

Setting

Our case-control study was conducted in the Children's University Hospital of Damascus University between twenty-first August 2017 and twenty-first August 2018. This hospital is one of two major paediatric cancer centres in Syria and is the major centre across the country which provides free healthcare to patients, either referred or presented in the hospital's outpatient clinics, and it is the main centre for haematological disorders in Syria [15]. Information of case and control groups was obtained from the hospital's records. These records where from information provided by the child's caregiver when being examined by the doctors in the clinics/wards.

The patients' caregivers were asked by the supervising hospital physicians about the biological relationship between both the father and the mother and past history of cancer and leukaemia in the family. ALL was diagnosed by bone marrow aspiration and immune phenotyping. Demographic data were obtained from the records including date of birth, gender and province of origin.

Sampling

The patient group was comprised of children with ALL who were 14 years or younger. Control group was patients of the general clinic of Children's University Hospital, regardless of what they are suffering unless they were known to have certain medical conditions. Cases and controls were matched by gender and belonged to the same age groups as no significant differences between the two groups were observed with these two variables ($p > 0.05$). We did not calculate sample size due to the limited resources and unable to return to older records. Damascus University ethic committee agreed to include all the patients with ALL twenty-first August 2017 and twenty-first August 2018 that were in this hospital without going further in records. It was also deemed for the same reasons to include only one control for each case in this study.

Including and exclusion criteria

Including criteria for both groups were being 14 years old and younger. Case group had ALL diagnosed before being included. Exclusion criteria for case and control groups included patients with hereditary haematological or metabolic disorders, constitutional hereditary or aneuploidy syndromes as in Down's syndrome, Turner's syndrome, Li-Fraumeni syndrome, Klinefelter's syndrome and familial microcephaly as well as single-gene traits such as Bloom's syndrome, Von Recklinghausen neurofibromatosis, ataxia-telangiectasia, Wiskott-Aldrich syndrome, cystic fibrosis, thalassemia, sickle cell anaemia, Fanconi's anaemia, favism and haemophilia.

Ethical approval

The study was approved by the ethics committee of Damascus University. Informed consent was taken from the legal guardian after the examination and diagnosis

for both groups to be included in this research and to use and share their data for research purposes.

Definitions

Consanguinity was defined as first-degree relatives (father, mother and sibling), second-degree relatives (grandparent, uncle, aunt, nephew and niece), third-degree relatives (first cousins and double-first cousins) and fourth-degree relatives (second cousins, second cousins once removed). Family history was obtained based on the family of the subjects having malignancies in their families regardless of type of cancer or age of presentation. Family history was taken in the out-patient clinics by direct interview as self-reported family history has been found to be a reliable means to determine the individuals at risk of being predisposed to cancer [16]. All information obtained was recorded during time of diagnosis of the child.

Demographic data was split into Al-Jazira region which includes Deir ez-Zur, Ar Raqqah and Al Hasakah, and the rest of the country's regions was considered as a single region. Although Al-Jazira region has been significantly urbanized, it remains the region with highest rates of consanguineous marriage in Syria as it is strongly reinforced by social and kinship bonds. Another reason for the high consanguinity in Al-Jazira region is that the person selected for marriage is better acquainted with the family which makes him more desirable given that most of these marriages are arranged marriages and families prefer their assets to remain in the family.

Data analysis

Data were processed using IBM SPSS software version 25 for Windows (SPSS Inc., IL, USA). Chi-square test was performed to determine statistical significance between the groups of cases and controls. We calculated odds ratios (ORs) and the 95% confidence intervals for the groups using Mantel–Haenszel test by using the same software. Values of less than 0.05 for the two-tailed *p*-values were considered statistically significant.

Results

Our sample consisted of 386 patients, including 193 cases and 193 controls. We did not recruit more controls as the effect size was great. Patient's characteristics are demonstrated in Table 1. When comparing cases and controls with gender, father's and mother's educational level, having family history of cancer and living in Al-Jazeera region or not, we did not find a statistically significant association ($p < 0.05$).

While case group had more participants with parents of no consanguineous marriage or a third-degree consanguinity, control group had more participants with fourth-degree consanguinity ($p = 0.0003$). When comparing having no consanguineous parents with having fourth-degree consanguinity, control group had more participants with fourth-degree consanguinity $p = 0.0087$, $OR = 0.387$ (0.187–0.801). However, the authors found no statistical significance when only comparing case and control groups with not having consanguineous parents and having third-degree consanguinity ($p = 0.764$). Consanguinity degrees among case and control groups are demonstrated in Table 2.

Discussion

To our knowledge, this is the first study investigating this topic to be conducted in the Levant region, a highly consanguineous region. Given the study was conducted in a countrywide centre for all of the country's paediatric oncologies in the Paediatrics Hospital, it is likely that this is a representative sample of the prevalence and distribution for paediatric oncologies. It is hard to study socioeconomic status in Syria as the standards are

Table 1 Characteristics of children in case and control groups

Characteristic	Cases ($n = 193$)	Controls ($n = 193$)	Total ($n = 386$)	*p*-value
Age (years) at diagnosis				
0–4	70 (36.3%)	81 (42%)	151 (39.1%)	
5–9	94 (48.7%)	96 (49.7%)	190 (49.2%)	0.107
10–14	29 (15%)	16 (8.3%)	45 (11.7%)	
Gender				
Male	119 (61.7%)	120 (62.2%)	239 (61.9%)	0.917
Female	74 (38.3%)	73 (37.8%)	147 (38.1%)	
Place of living[a]				
Al-Jazira	49 (26.3%)	50 (26.2%)	99 (26.3%)	0.971
Other governorate	137 (73.7%)	141 (73.8%)	278 (73.7%)	

[a] Seven patients did not have a validated place of living data

Table 2 Comparison of characteristics between case and control groups

	Cases (%)	Controls (%)	*p*-value	Odds ratio
Non-consanguineous	123 (63.7%)	107 (55.4)	0.819NS	0.951 (0.621–1.458)
Consanguineous	70 (36.3%)	86 (44.6%)		
Non-consanguineous	123 (63.7%)	107 (55.4%)	0.0003	-
3rd-degree consanguinity	58 (30.1%)	47 (24.4%)		
4th-degree consanguinity	12 (6.2%)	39 (20.2%)		
Non-consanguineous	123 (68%)	107 (69.5%)	0.764	1.073 (0.675–1.706)
3rd-degree consanguinity	58 (32%)	47 (30.5%)		
Non-consanguineous	123 (91.1%)	57 (79.9%)	0.009	0.387 (0.187–0.801)
4th-degree consanguinity	12 (8.9%)	20 (20.1%)		

NS, not significant. When comparing cases and controls with having third consanguinity and fourth consanguinity, $p = 0.0090$ and $OR = 0.360$ (0.165–0.787), which indicates that fourth-degree consanguinity was associated with a decreased risk of leukaemia compared to not having consanguinity or to having a third-degree one

much different than other countries, and it is not socially acceptable to ask about the monthly income [17].

Jaber et al. [18] demonstrated that marriages between people of the same kinship were not associated with an increased risk of cancer. However, such marriages have been associated with higher risks of congenital malformations, abortions, stillbirths, recessive gene disorders and other types of morbidity and mortality. Furthermore, Kurita et al. [19] described 20 families in which familial leukaemia occurred in several siblings, six of the aforementioned families had consanguineous marriages and parents were first cousins (30%), compared to just (4.5%) of families with non-familial leukaemia ($p < 0.01$).

A study in the UAE with 117 patients, 69 of which were ALL patients, suggested that consanguinity was a protective factor among lymphoma patients. The prevalence of consanguinity was lowered from 50.5% in the general population to 12% in non-Hodgkin lymphoma and 14% in Hodgkin lymphoma, but they also found that leukaemia incidence had increased in consanguineous patients [20]. An earlier study also conducted in the UAE suggested that in consanguinity versus non-consanguinity, the relative risk of leukaemia was 1.66, but it did not specify the type of leukaemia [21]. This was also the case in a Qatari study [22] conducted on 21 patients with leukaemia where there was a higher prevalence of consanguinity in leukaemia patients without specifying the type.

In this study, the investigators found that fourth-degree consanguinity of the parents was associated with less incidence of ALL among children.

Several studies have reported consanguinity as a causative factor in leukaemia among patients with no apparent recessive gene disorder [11, 23–27]. In addition, it may be that clustering of malignancies in consanguineous families could also be explained by these families being affected by the same environmental factors through living in common residences, contributing to the development of a certain phenotype. However, we found no such an association with family history and ALL.

In addition, the results of our study are consistent with those of Jastaniah and colleagues in their study [28]. This study was conducted on 642 ALL patients, which is the largest and most recent study conducted on the subject. This study showed a lower frequency of ALL in a consanguineous union than in a non-consanguineous union. Therefore, these suggested protective factors being inherited in consanguineous unions rather than permissive factors. However, we excluded inheritable medical conditions that my dispose to having leukaemia such as Fanconi's anaemia.

Consanguinity raises the rate of homozygosity for the embryo for such oncogenes, which makes it a knockout embryo. However, at times, this renders the embryo incompatible with life which justifies the increased incidence of foetal wastage from abortions, stillbirths and neonatal deaths [2, 18]. This leads to a decreased frequency in this oncogene which could mask a higher incidence of this tumour in this population [2]. Still, despite the increased foetal mortality from repeated abortions in the offspring in consanguineous marriages, one Bahraini study [29] showed there might be no significant difference in the rates of foetal wastage than originally identified.

In our study, we showed that fourth-degree consanguinity was associated with less incidence of ALL. However, this may suggest that our sample was affected by Neyman's bias (survival bias), indicating that children with consanguineous parents died before reaching diagnosis of ALL because they suffered from more aggressive leukaemia. This might be mostly prominent for third-degree consanguinity, not the fourth degree, as closer degree might have had a greater effect that our sample was able to demonstrate this protective factor of consanguinity. Furthermore, we may also speculate that

consanguinity carries more risks of other fatal pathologies, causing a higher mortality in children before presenting with leukaemia. These factors could explain the lower incidence of leukaemia among the consanguinity population. Additionally, evolutionary mechanism could contribute to decrease the incidence of hereditary factors that lead to death before reproductive age in a homozygous state, causing these recessive factors to keep running through generations of consanguineous families.

One previous study compared the median age of diagnosis for childhood cancer between consanguineous and non-consanguineous groups and did not identify a significant statistical difference [28].

We did not find a significant difference in the incidence of ALL between Al-Jazira region and other regions ($p > 0.05$), suggesting the regional environmental factors had no significant effect on the incidence of leukaemia. This is consistent with the previous study showing no definitive link established between environmental factors and ALL [30, 31]. This is important as Syrians may be frequently predisposed to leukaemogenic substances [14] which may explain why ALL in Syria has distinguished features such as higher incidence of L2 and T-ALL [15].

Sample size, not including many centres and not including many confounding factors such as genes, is one of major limitations of this study in addition to the study design. This might affect the generalisability of results, but given that this is one of the few studies in the aspect and due to the very limited resources in Syria, we believe that these results can be used for future studies.

Conclusions

In conclusion, fourth-degree consanguinity rates were less in children with childhood ALL. This finding differs from a range of other studies conducted in the region. As such, further research is indicated to better understand and reach a more definitive conclusion on the relationship between consanguinity and childhood leukaemia particularly as consanguinity is very widely practiced in many countries across the globe.

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Authors' contributions
AK, conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, original draft and writing — review and editing. MA, data curation, formal analysis, software, original draft and writing — review and editing. AG, software, methodology, conceptualization, validation, writing editing and investigation. BK, software, methodology, conceptualization and investigation. BM, software, project administration, conceptualization, writing editing and investigation. BZ, software, project administration and investigation. OH, project administration, resources and validation. The authors read and approved the final manuscript.

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Availability of data and materials
Data is available upon request.

Declarations

Ethical approval and consent to participate
The study was approved by the ethics committee of Damascus University. Informed consent was taken after the examination and diagnosis for both groups to be included in this research and to use and share their data for research purposes.

Consent for publication
Written consent was taken.

Competing interests
The authors declare that they have no competing interests.

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