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Prevalence of hereditary cancer susceptibility syndromes in children with cancer in a highly consanguineous population

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ABSTRACT

Background & aim: Hereditary cancer susceptibility syndromes (HCSS) are reported in up to one-third of children with cancer. Diagnosis of HCSS is crucial for implementation of surveillance protocols. We identified children who fulfilled criteria for HCSS in Saudi Arabia using the American College of Medical Genetics and Genomics (ACMG) guidelines, addressing the utility of these guidelines in a highly consanguineous population.
Methods: This multi-center cross-sectional study recruited 1858 children with cancer between January 2011 and December 2014. HCSS criteria were based on the ACMG guidelines.
Results: Seven hundred and four (40.4%) out of 1742 eligible patients fulfilled criteria for HCSS. Consanguinity was reported in 629 (38%) patients, with 50 (2.9%) first-degree, 535 (30.7%) second-degree, and 272 (15.6%) third-degree relatives affected with cancer. Two hundred and eighty eight (17.4%) leukemia and 87 (5.3%) brain tumour patients fulfilled HCSS criteria, with parental consanguinity being the most frequent criterion in both (leukemia 85.4%, brain tumors 83.9%). However, leukemia was less frequent in patients of consanguineous parents ($p = 0.023$).
Conclusion: Four out of 10 children with cancer fulfilled criteria for HCSS, most often due to consanguinity. This higher than expected prevalence suggests the need to validate consanguinity as a criterion for HCSS in highly consanguineous populations.

1. Introduction

Remarkable progress has been made in the treatment of childhood cancer and survival rates have improved as a result of multimodal and risk adapted treatment strategies [1,2]. The etiology of childhood cancer remains largely unknown. However, it is estimated that approximately 5–10% of all cases can be attributed to genetic susceptibility [3–7]. Importantly, the genetic contribution to childhood cancer may have been underestimated due to lack of recognition of many hereditary cancer susceptibility syndromes (HCSS) or the under-reporting of family history [8,9]. Study of survivors of childhood cancer suggests that 29% of children were at risk for hereditary cancer based

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on patient's cancer history, family history or presence of unique physical findings [9]. Thus, identifying patients with HCSS is crucial to ensure early diagnosis, identify need for genetic counselling, initiate cancer surveillance, reduce cancer morbidity and optimise treatment outcomes and cure [10,11].

Early age at onset of cancer, cancer/tumor type, cancer laterality, multiple primary tumors, coexistence of an associated inherited disorder, family history, cancer history of affected family members, degree of relatedness to the patient, and consanguinity have all been reported as eligibility criteria for HCSS testing and referral [12–15]. The American College of Medical Genetics and Genomics (ACMG) and the National Society of Genetic Counsellors (NSGC) recently developed practice guidelines and "a single set of comprehensive personal and family history criteria" to assist health-care practitioners identify individuals who may benefit from genetic counselling and testing services [15]. Among others, history of parental consanguinity is one of the referral criteria for genetic counselling and testing in these guidelines [12–15]. This criterion is included also in recently proposed recommendations by the German Society for Pediatric Oncology and Hematology (GPOH) and in a recently published systematic review suggesting an easy-to-use selection tool in pediatric cancer patients [13,14]. The utility of consanguinity in highly consanguineous populations has not been addressed.

Consanguineous marriages have been practiced for generations in many parts of the world. The rate of consanguinity varies greatly across continents, regions and countries [16–18]. In Europe and North America, the rate is estimated to be less than 1%, while in Arab countries the rate ranges between 20% and 50% [16]; in Saudi Arabia, the rate is between 29.7% and 56% [16,17].

Constitutional mismatch repair deficiency (CMMRD) is a recessive disorder that predisposes to cancer and could potentially be more frequent in highly consanguineous populations [19]. However, the prevalence of CMMRD among children with cancer has not been well studied in our population. The role of consanguinity as a risk for HCSS associated with CMMRD and in disorders other than CMMRD remains largely unknown.

The aim of the present study was first, to estimate the prevalence of HCSS among children with cancer and identify those eligible for genetic counselling based on the ACMG and NSGC practice guidelines in Saudi Arabia, a country with high consanguinity rate, and second, to evaluate the influence of consanguinity on the pattern of cancer among patients and their families.

Given the high incidence of consanguinity in the population under study, we hypothesized that the prevalence of HCSS is high.

2. Patients and methods

2.1. Study participants

This is a multicenter cross-sectional study conducted in ten institutions that manage most of the childhood cancer cases across Saudi Arabia. After obtaining informed consent, patients aged 14 years or younger diagnosed with cancer between January 2011 and December 2014 were enrolled in the study. Pediatric oncologists in Saudi Arabia treat children under the age of 14 years based on national policy. The present study was organized by the Saudi Arabian Pediatric Hematology Oncology Society (SAPHOS), funded by Sanad children's cancer support association, and approved by the ethics committee review boards of all participating institutions.

2.2. Data collection

A trained team of health care professionals interviewed parents of the index child. The team was trained prior to the start of the study on how to conduct face-to-face interviews following a structured questionnaire to collect personal and/or family history of cancer. Standardized face-to-face interviews were conducted with parents in the Arabic language at each of the participating institutions. The interview questions include the presence and degree of consanguinity in parents and grandparents, and the degree of relationships among family members affected by cancer. For relatives with a positive history of cancer, further information was collected including: age at diagnosis of the first occurrence of cancer, cancer type, cancer site, and histology if known. Structured site-by-site closed ended interviews were conducted to capture cancer site of family members with a history of cancer. For quality assurance, interviews were audited by random call back of interviewed parents or play back of recordings by the primary investigator in each institution. Patient charts were also reviewed to obtain the following data: date of birth, gender, nationality, vital status, date of cancer diagnosis, number of primary cancer diagnoses, cancer histology/site/laterality according to the International Classification of Cancer, third Edition (ICD-O-3) coding [20]. The presence of any associated disorder or syndrome was also recorded. Data collected from participating institutions were entered remotely using REDCap (Research Electronic Data Capture) electronic data capture tools hosted and stored centrally in a secure Microsoft SQL database at SAPHOS central office [21].

2.3. HCSS criteria

In the present study, the prevalence of HCSS was assessed following the practical guidelines for cancer predisposition assessment developed by the ACMG and NSGC [15]. These guidelines were used also to define types of cancer associated with Lynch syndrome and Li–Fraumeni syndrome (LFS).

2.4. Statistical analysis

Data are presented as frequencies, percentages and ratios. Categorical and continuous variables were compared using Chi-square and *t*-test, respectively. A positive family history of cancer was defined as a first-degree relative (father, mother, and/or sibling), second-degree relative (grandfather, grandmother, uncle, aunt, half-sibling, niece, and/or nephew) and/or a third-degree relative (cousin and/or great grandparent) affected with cancer. Further sub grouping of family history of cancer by age and type was also considered. Chi-square or Fisher's exact tests were used to compare patients with and without family history of cancer as well as patients of consanguineous and non-consanguineous parents, as appropriate. The association between consanguinity and family history of cancer in first, second and/or third degree relatives of patients, number of relatives affected with cancer, age of onset of cancer and maternal versus paternal family association were assessed using logistic regression models and expressed as odds ratios (ORs) with 95% confidence intervals (CI). All statistical models were adjusted for child's gender and age at diagnosis. Patients with no family history of cancer and those without a history of parental consanguinity were used as a reference group in the analysis, as appropriate. A level of significance of 5% (p-value < 0.05) was considered statistically significant. Statistical analyses were performed using SPSS statistical software, version 24.0 for Windows (SPSS Inc, IL, USA).

3. Results

3.1. Patient characteristics

One thousand eight hundred and fifty eight children with cancer were enrolled. A total of 116 patients were excluded due to parental refusal to consent or missing data. Thus, 1742 patients were included in our analysis (see consort diagram for details Fig. 1). Only 85 (4.9%) patients had underlying syndromes/inherited disorders (Table 1). Of those, 38 (2.2%) had Down syndrome, 14 (0.8%) neurofibromatosis type-I, and 33 (1.9%) other disorders (Table 1). A total of 1657 (95.1%)