Risk of hematological malignancies in the families of patients treated for nodular lymphocyte-predominant Hodgkin lymphoma

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Abstract

Background: Familial clustering of lymphoid and/or hematological malignancies (FHM) provides an opportunity to study the responsible genes. The data is limited in patients with lymphoid and hematological malignancies.

Methods: The lymphoma database was used to identify patients seen in our institution from 1998 to 2019 with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). We studied FHM by collecting detailed history of any malignancy in the family (FM).

Results: Two hundred NLPHL patients were identified. Contacting was not possible in 30 patients due to no response to the phone calls (22) and death [1]. 170/200 patients were interviewed; represented 167 families (3 patients with a family member with NLPHL). These 170 patients provided information about 8225 family members. These 167 families had a total of 329 family members with 334 malignancies (including 167 NLPHL patients and 5 members with 2 malignancies each). Of these 167 patients, 77 (46.1%) had no FM while 90 (53.9%) patients had a positive FM; 162 family members with 167 malignancies. Among these 167 families, 31 families (18.6%) had members with FHM +/− solid cancers. These 31 families had 35 family members (25 males:10 females) with 16 lymphomas: diffuse large B cell lymphoma [2], follicular center cell lymphoma [3], chronic lymphocytic leukemia/small lymphocytic lymphoma [3], non-Hodgkin lymphoma [2], classical HL [2], and NLPHL [4]. Total of 8 leukemia: acute lymphoblastic leukemia [4], acute myeloid leukemia [3], and leukemia - no subtyping [5]. These 35 FHM members are 1st [6], 2nd (16), and 3rd [7] degree relatives of 31 NLPHL patients. There are 4 families with NLPHL in family members; all these 8 NLPHL patients are male and are alive. The median total number of 1st + 2nd +3rd degree members are 81. The decrease in the age of diagnosis from 1st generation to the 2nd generation (anticipation) was noted in 13/17 patients; 2nd generation median age at diagnosis was 29.7 years vs 1st generation age 53 years (developed malignancy 23.3 years earlier).

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Introduction

There is emerging data indicating the role of inheritance in the development of various malignancies. Familial clustering of lymphoid and/or hematological malignancies (FHM) like non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), multiple myeloma (MM), various leukemia and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) have been reported [1–9]. There is limited literature on FHM in patients with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) [10–14]. FHM provides an opportunity to study genetic and environmental factors as a causative agent for these conditions and may help in identifying the responsible genes. Almost all the data on FHM are coming from North American and European countries with smaller family sizes. Middle Eastern social setup and population is significantly different from American and European setup. Impact on FHM of large family size, tribal lifestyle, social, cultural environmental factors, consanguinity marriages, and marriages within the tribe are largely unknown and may have contributing effects. This study is to identify FHM in patients with NLPHL seen in our Medical Oncology Lymphoma clinics and to establish a FHM database in the Oncology Research Unit. We intend to use this data for future planning of comprehensive data collection, genetic counseling, genetic studies, and tissue banking.

Results

From 1998 to July 2019, 2 hundred NLPHL patients were identified. The results and the selection process are shown in Table 1 and Fig. 1. Contacting was not possible in 30 patients due to the upgrading of the national telephone system (22) and death (8). FM-CRF was available for 170/200 patients, representing 167 families (3 patients have other family members with NLPHL in the data).

Overall results of the entire cohort:

In the entire cohort of 167 patients, 77 patients (46.1%) had no FM while 90 patients (53.9%) had a positive FM; 162 family members with 167 malignancies. Among these 167 families, 31 families (18.6%) had members with FHM +/- solid cancers and, 59 families had members with solid malignancies. These 167 families, in total, had 329 family members with 334 malignancies (including 167 NLPHL patients and 5 members with 2 malignancies each). The current detailed analysis was limited to FHM.

Conclusion

FHM is frequent in NLPHL. This study provided us many important insights for planning future studies in terms of interviewing technique, time, and resource allocation and genetic testing.

Keywords: Hodgkin lymphoma, Nodular lymphocyte-predominant Hodgkin lymphoma, Familial hematological malignancy, Hereditary malignancy, Familial lymphoma, Familial malignancy
Hematological malignancies

In these 31 families with FHM, there were 35 family members (25 males:10 females) with various lymphomas and hematological malignancies. Among the 16 lymphomas, there was diffuse large B cell lymphoma (DLBCL) (7), follicular center cell lymphoma (1), CLL/SLL (1), NHL-no further pathological information (7), cHL (7), and NLPHL (4). Also, we identified a total of 8 leukemia in this group. These leukemia’s were ALL (4), AML (1), and leukemia – no further pathological information (3).

Table 1: Patient’s characteristics and outcome

| Variable | Total numbers | Percentage |
|----------|---------------|------------|
| Patients with NLPHL | 200 | 100 |
| No data available | 30 | 15 |
| Malignancy related data available | 170 | 65 |
| Total families* of 170 patients | 167 | – |
| Male | 130 | 76.5 |
| Female | 40 | 23.5 |
| Median age | 20.9 years | Range (5–64) |
| Age < 21 | 86 | 50.6 |

Type and frequency of familial malignancies

| Family with no malignancy | 77 | 46.1 |
| Families with malignancy | 90 | 53.9 |
| Families with hematological only* | 14 | 8.4 |
| Families with hematological + solid | 17 | 10.2 |
| Families with solid cancers only | 59 | 35.3 |
| Total malignancies in family members | 167 | – |
| Total members with malignancy | 162 | – |
| Malignancy confirmed | 73 | 43.7 |
| Confirmed among 35 hematological** | 28 | 80 |
| Confirmed among 135 solid** | 45 | 33.3 |
| Malignancy unconfirmed | 94 | 56.3 |
| Unconfirmed among 35 hematological** | 7 | 20 |
| Unconfirmed among 135 solid** | 90 | 66.6 |
| First degree members | 51 | 31.5 |
| Second degree members | 85 | 52.5 |
| Third degree members | 26 | 16 |

Common familial malignancy by groups*

| Hematological malignancies | | |
| Non-Hodgkin lymphoma | 16 | 9.6 |
| Hodgkin lymphoma | 11 | 6.6 |
| Leukemia | 8 | 4.8 |

| Solid malignancies | | |
| Gastrointestinal | 36 | 21.6 |
| Female genital | 13 | 7.8 |
| Breast | 18 | 10.7 |
| Cancer not otherwise specified | 19 | 11.4 |
| Lung / Head and Neck | 17 | 10.2 |
| Others | 27 | 16.17 |

Percentages are counted for 170 available patients
*6 patients from 3 families with NHLPH as the only malignancy are counted as 3 families
**Percentages among the hematological and solid malignancies
5 Patient with 2 malignancies each are also adjusted accordingly
Among these, 28/35 (80%) of FHM were “confirmed”. These 35 FHM members are 1st (14), 2nd (16), and 3rd (5) degree relatives of 31 NLPHL patients. In these 31 families, another 30 members had 32 different solid cancers.

**Families with NLPHL**

There are 4 families with NLPHL in family members; all these 8 NLPHL patients are male and are alive. Family-001, age at the time of diagnosis of 2 brothers was 38, and 40 years, their sister with follicular center cell lymphoma was 36 years at diagnosis. Family-002, two brothers, 12 and 20 years at diagnosis. Family-003, 47 years and his nephew was 33 years, and Family-004, 14 years, and his 3rd degree male cousin 25 years at diagnosis.

We also checked the age at diagnosis in the same generation (25 patients) with FHM (siblings (1st degree) and cousins (3rd degree)). Age of our NLPHL patient: age of the family member with - diagnosis is shown in this format: 21:24-DLBCL, 32:28-DLBCL, 8:21-DLBCL, 21:25-cHL, 13:19-cHL, 12:20-NLPHL, 38:40-NLPHL+sister age 36-follicular center cell, 25:30-cHL, 12:10-ALL, 21:4-ALL, 18:7-ALL, and 56:80-lymphoma-no further details.

**Family information and degree of relation**

Information regarding consanguinity marriages was available in 96 patients; 32/96 patients (33%) reported consanguine marriages of their parents. The median number of 1st, 2nd and 3rd degree relatives was 10 (range 3–26, 104 patients answered), 21 (range 4–54, 104 patients answered), and 50 (range 10–187, 82 patients answered; with 30 of them simply marked/said “more than a specific number”, i.e. 50+,90+, ...) respectively. Median collective 1st + 2nd + 3rd degree members are 81. These 170 patients provided information about 8225 family members. Based on the median numbers of the relatives, approximately 13,700–14,000 total family
member’s information is needed to be captured if all these patients can provide a detailed answer.

Anticipation
Decrease in the age of diagnosis from 1st generation to the 2nd generation (anticipation) was studied in 17 applicable FHM patients; 13/17 showed this anticipation phenomenon. The median age of our patients (2nd generation) with NLPHL was 29.7 years vs 53 years in the parents or a 2nd degree relative (1st generation). The cancer was seen at a median of 23.3 years earlier.

Solid cancers
Due to the reasons already explained, no “extra” and meticulous efforts were carried out confirm the reported cases. We identified 135 sold cancers in these patients and were able to confirm 33.3% cases. Detailed results are shown in Table 1 and Fig. 1.

Discussion
We are reporting the first initiative towards a comprehensive data collection of FM and FHM from the Middle East. The data collection is ongoing and approximately (1000/2000 cases completed). The current analysis is limited to NLPHL due to resources. This data not only showed that the FHM exists here, but the magnitude is also large and warrants a properly planned coordinated approach.

In these 170 NLPHL, we have observed 54% FM, almost 18% FHM, and even confirmed 80% of FHM and 33.3% of sold cancers too. We identified 31 families; 35 members of FHM. An interesting observation is relatively similar ages of diagnosis in many paired family members despite different hematological malignancies. Given the small sample size and early ages of diagnosis for most NLPHL, HL, and ALL, it is difficult to draw any conclusion.

We encountered many unexpected hurdles and learning experiences. Due to the large family size and time limitations of “regular clinic visit” in our current practice setup, only 50–60% of the patients filled the complete numbers of their relatives in the FM-CRF, especially cousins. Also, many patients were not fully aware of FM. Contacting patients/their parents with the cell phone or after 5 pm from the hospital number was not very encouraging either as this was not answered much time due to an “unknown” phone number. Searching a patient’s relative treated at our institution was not easy either due to English spelling; National Identity Documents are in Arabic and English spelling was entered by hospital staff as they “decided”. It was not uncommon to have 4–8 various spelling combinations of first + last name for the computer search. Confirmation of reported diagnosis was also difficult as reported by Chang et al. [15]. Many relatives were not eager to provide any information with limited confirmation through the Saudi Cancer Registry. Not only this, in the Middle East, multiple marriages, tribal social lifestyles, consanguinity marriages in the same tribe, and issue of half-uncle and aunties and half-cousins is making it very clear that a very meticulous time-consuming customized data collection in a proper pedigree software is needed for future analysis. Also, coronavirus disease – 19 pandemic in February 2020 in the Kingdom of Saudi Arabia, like the whole world, resulted in significant limitations in the staffing, verification process, and expansion of study setup that is likely to last for many more months.

There is limited literature on the familial aspect of NLPHL and other FHM [1–9]. CLL appears more common in families [4, 7]. Australian Familial Haematological Cancer Study (AFHCS) identified 24 families with apparent predisposition to hematological malignancy and suggested that at least 200 such families may exist within Australia. This was published by Carmichael C and Scott H in their society journal (not indexed) “Cancer Forum” 2007:31;160–164, “Familial aspects of haematological malignancy” (https://www.cancer.org.au). InterLymph Consortium Study, one of the largest, reviewed pooled case-control division (10,211 cases and 11,905 controls) also confirmed an increased familial risk of lymphomas.

Only a few reports are showing FM in NLPHL patients [10–14]. The largest data is from the Finnish Registry data on NLPHL and the standardized incidence ratio was 19% in the 1st degree relatives 18. They evaluated 692 patients and 4280 1st degree relatives [13]. We are likely to have almost 40% more 1st degree relatives. Giles et al. identified 13 potential families with NHL and found that the overall risk for 1st degree relatives of an affected individual was 3.15–3.61 [3].

This study provided us many important insights, both in terms of FM and FHM findings and the unique insights for planning these studies in the Middle Eastern countries in terms of interviewing technique, time and resource allocation, methods for confirming malignancies, and utilization and limitation of established national cancer registries. Once our targeted larger data is available, we will be in a better position to execute the main project of genetic counseling and genetic analysis using the latest techniques. This will be a project by itself to explain and educate accessible patients/family members about the importance of FM and involve them in our future genetic studies.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13053-021-00175-0.
Additional file 1: Supplementary Data 1. Family history of malignancy questionnaire in Arabic and the translation: For the patients

Abbreviations
FHM: Familial clustering of lymphoid and/or hematological malignancies; NHL: Non-Hodgkin lymphoma; HL: Hodgkin lymphoma; MM: Multiple myeloma; CLL/SLL: Chronic lymphocytic leukemia/small lymphocytic lymphoma; NLPHL: Nodular lymphocyte-predominant Hodgkin lymphoma; FM-CIF: Family history of malignancy (FM) case report form; DLBCL: Diffuse large B cell lymphoma; AFHCS: Australian Familial Haematological Cancer Study

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Consent to participate
As per the local Research Advisory Council policies

Availability of data and material
All authors had full access to all data and approved this submission. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Data sharing: Data is a "retrospective/prospective database" and is owned by the institution. This data is under the custody of the principal and co-investigators as per the Institutional Research Advisory Counsel and Research Ethics Committee guidelines. It is not available to the public for sharing. Full or part of this data can be shared after an official request/approval of the institutional Research Advisory Counsel and Research Ethics Committee.

Code availability
Not applicable.

Ethical standards
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Abstract / presentation
No

Authors’ contributions
All authors had full access to all data. All authors have read and approved the final manuscript. SA was the principal investigator, helped in data collection, analysis of the data and takes primary responsibility for the paper; the final manuscript. SA was the principal investigator, helped in data collection, analysis of the data and takes primary responsibility for the paper; AA, MAE and AM collected data and helped in the interpretation. MAE is also an assistant professor of Clinical Oncology, Faculty of Medicine, Menoufi University, Egypt.

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Consent for publication
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Competing interests
None - Authors declare no conflict of interest

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