Segregation of Malignant Hematological Disease in Families with Malignant Lymphoma

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Abstract

Familial malignant lymphoma, viz. more than two cases of malignant hematological disease in a family of which one diagnosis is malignant lymphoma, was seen in 43 (37 per cent) of the families in our database of familial malignant hematological disease. Genealogical examination of the 43 pedigrees after multiple ascertainment showed an equal amount of vertical transmissions (affected parent-offspring and grandparent-parent-offspring combinations) and non-vertical transmissions (affected uncle, aunt-nephew, niece, cousin combinations) without evident Mendelian pattern and no significant difference between observed and expected patrilineal and matrilineal lines in spite of a marked predominance of males. A marked pleiotropic diversity of involved diagnoses comprised 57 (93 per cent) lymphoproliferative- and 4 (7%) myeloproliferative diseases. Both Hodgkin’s lymphoma, non-Hodgkin’s lymphoma apart from the diffuse large B-cell lymphoma and chronic lymphocytic leukemia had a strong mutual association, and a weaker yet significant association to multiple myeloma and to diffuse large B-cell lymphoma. Compared with the number of patients in the population extracted from the crude age-adjusted incidences, the observed number of patients in familial disease was significantly higher interpreted as a stronger expression of congenic susceptibility among family members with reservations related to different environmental factors. Signs of anticipation in all combinations but no birth order effect were observed. It is discussed that an epigenetic parental genomic imprinting as a modifier for the segregation of linked susceptibility loci theoretically would bring about a similar pattern with male predominance and pleiotropic diversity of diagnoses away from any Mendelian expectation.

Keywords: Malignant Lymphoma; Leukemia; Genetics; Epidemiology

Introduction

Malignant Lymphomas (ML) comprising Hodgkin’s Lymphoma (HL) and Non-Hodgkin’s Lymphoma (NHL) are characterized by malignant transformation of lymphoid cells where a monoclonal expansion of the tumor cell emerge from a mutation in a lymphoid progenitor cell at the lymphoid differential pathway [1,2]. About 40 different ML diagnoses are defined, each with specific histological, immunophenotypic and clinical features [3]. In principle, the etiology of ML consists of both a genetic inborn susceptibility and a possible environmental influence, e.g. from antigenic drive of the tumor growth from lymphotropic microorganisms, and from a possible mutagenic effect of pesticides, solvents and dyes [4-6].

The genetic etiology is supposed to be related to congenic risk alleles [7,8], so far mainly investigated in chronic lymphocytic leukemia (CLL) [9-16]. Presumably, each diagnosis within the entity malignant lymphoproliferative disorders (LPD) has its own risk alleles linked to each other, which eventually explains the observed association between LPD diagnoses with familial, pleiotropic clustering [12,13]. Such congenic risk alleles, also denoted susceptibility loci, or genetic inborn susceptibility for the specific mutation which causes the monoclon of the diagnosis, have been demonstrated by means of genome-wide association studies. In CLL, for example, up to ten or perhaps a few more susceptibility loci have been demonstrated during the last years at many different positions in the genome, and with a range of putative associations to CLL [15,16]. The same pattern is seen in HL where four or perhaps five susceptibility loci known so far are scattered throughout the genome with a range of putative associations [17,18].

The familial clustering of ML and other types of LPD has been proved in recent computerized estimations of large-scaled data from cancer registries while only few genealogical investigations based on the study of pedigrees from affected families have been published [19-21]. The computerized estimations of data from cancer registries show remarkable inconstancy in frequencies and incidences of clustered LPD diagnoses versus solitary disease, and marked differences in demographic data of the patients [22-25]. Genetic anticipation, which is increased severity in the form of lower age at onset of disease and more and more high-malignant cases down through the generations, and birth order effect with rank order by age of the affected sib in the sib ship, are also reported with marked differences [26-29]. The mode of segregation is so far largely unknown.

The purpose of the present paper is to compare these findings from mainly large-scaled computerized data with data from genealogical assessments of pedigrees from familial ML.

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Material and Methods

Families

Our database on familial malignant hematological disease, viz. families with at least two affected family members (116 families), has 43 families in which ML is one of the diagnoses. The database has been collected systematically over the past decade in our clinical work with all types of hematological malignancies in Oslo and Copenhagen. Parts of this material has previously been published [20,21], but never as a comprehensive description of familial ML and never in the form like that presented here.

Inclusion

Each patient underwent a face-to-face interview about other family members with malignant blood disease and the pedigree was drawn up. To ensure maximal ascertainment, the interview was individually adjusted and modulated to include also old terminology if necessary. HL for example was earlier lympho granulomatosis, and CLL was sometimes "old man’s disease". Each patient was also asked about the number and position of healthy family members in the family tree, stillborn and extramarital persons. The patients were allowed time for discussion at home and with relatives. All information was crosschecked with the Cancer Registry in Norway and Denmark. Old hospital records with histopathological and laboratory reports were included in the crosscheck if necessary. Each family was included with signed consent of the proband and after information about the purpose of the study, that data are confidential and unrecognizable outside the study and that the study was approved by the Scientific-Ethical Committees and the Data Protection Agency in Norway and Denmark.

The affiliation of each ML proband in all 43 pedigrees was grouped into the following categories: (A) parent-offspring pairs and (B) grandparent-parent-offspring combinations (A and B represent vertical inheritance), (C) uncle, aunt-nephew, niece cousin combination and (D) sib concordance which denote two or more affected siblings without affected relatives in other generations (C and D represent non-vertical inheritance). The number of patrilineal and matrilineal transmissions was recorded in (A) and (B), in (C) it is mixed and in (D) unknown.

The mean number of healthy family members crosschecked per family was about 50 persons. The Civil Person Registry was used for crosscheck in some few cases with uncertainty about the number or position of healthy relatives in the family tree. About 30 % of the healthy family members were still alive at the end of study. About 150 generations were evaluated and crosschecked, 86 generations (Table 1) with one or more cases of malignant hematological disease.

Diagnoses

All diagnoses were based on standard criteria according to WHO classification and ICD-10 nomenclature [3]. In case the crosscheck of older family members came up with diagnoses according to former classification systems, mainly Lukes & Collins, Kiel, and Working

![Table 1](image)

**Table 1**: Malignant hematological disorders in 43 families with malignant lymphoma.

**Abbreviations**: HL Hodgkin’s lymphoma; FL follicular lymphoma grade I-III; DLBCL diffuse large B-cell lymphoma; LPL lymphoplasmocytic lymphoma; BL Burkitt’s lymphoma; T Precursor T-lymphoblastic lymphoma; MCL mantle cell lymphoma; MZL marginal zone B-cell lymphoma; NHL non-Hodgkin’s lymphoma, CLL chronic lymphocytic leukemia; LGTCL large granular T-cell leukemia; PLL T-cell prolymphocytic leukemia; MM multiple myeloma; AML acute myeloblastic leukemia; CML chronic myeloid leukemia, MF myelofibrosis; ET essential thrombocytopenia
formulation, the diagnosis was converted to the WHO system and ICD-10 nomenclature to make the material homogenous and feasible for comparison (Table 1). This conversion was generally easy with some few exceptions denoted NOS (not otherwise specified) in the tables.

Statistics

The diagnoses in familial ML were compared with the occurrence in the population by means of simple regression of the scores observed (Tables 1-3) and crude age-adjusted incidences, viz. number of patients per 100,000 persons in the population with the age of the diagnosis in question. The incidences used are an estimated mean for Norway and Denmark from the observation period 1950-2010, based on official Cancer Registry reports [30-32]. An estimated mean has been used to adjust for an increasing incidence of ML in general and a specific rise in DLBCL during the past decades [30-32]. Age at onset of disease in parent-offspring pairs, and male-female ratios were estimated by means of Wilcoxon test, pair difference. Two-sided P-value < 0.05 was considered significant. Haldane Smith test was used for estimation of birth order effect [33]. In this test the sum (6A) of the birth orders, viz. the rank in the sibship by age of affected sibs, is compared with the theoretical value, expressed as the 95 % confidence interval (CI 95%) [33].

Segregation analysis

X²-test statistics with one degree of freedom was used to test for difference between observed and expected number of patr- and matrilineal transmissions in vertical inheritance (category A and B). The expected numbers were calculated on the assumption that the material is random distributed with frequencies for patrilineal (father-son: np²; father-daughter: npq) and matrilineal transmission (mother-son: nq²; mother daughter: npq) where p and q denote the proportions of males and females, respectively, and n the total number of families included [34].

Pattern recognition

Trends towards a likely Mendelian pattern in the distribution of affected family members in the families was done from a visual inspection of each pedigree compared with the standard pattern in autosomal dominant-, autosomal recessive- and X- and Y-linked hybridization [35].

Results

Diagnoses

ML was found in 43 (37 per cent) of 116 families with two or more

<table>
<thead>
<tr>
<th>Family number</th>
<th>Father</th>
<th>Son</th>
<th>Daughter</th>
<th>Rank of affected sib/ total number of sibs</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>HL 63</td>
<td>CLL 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>86</td>
<td>HL 49</td>
<td>CLL 58</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>FL 55</td>
<td>CLL 43</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>DLBCL 67</td>
<td>HL 36</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>DLBCL 74</td>
<td>CLL 46</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>DLBCL 54</td>
<td>CLL 43</td>
<td>3/3</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>LPL 65</td>
<td>MM 42</td>
<td>2/4</td>
<td></td>
</tr>
<tr>
<td>5-29</td>
<td>MZL 66</td>
<td>CLL 42</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CLL 66</td>
<td>DLBCL 64</td>
<td>3/3</td>
<td></td>
</tr>
</tbody>
</table>

Age at onset, father-offspring: P= 0.02 (Wilcoxon test, pair difference, two-sided) Birth order effect 6A (95%CI): 114 (74-130) P > 0.05 (Haldane Smith test)

<table>
<thead>
<tr>
<th>Mother</th>
<th>Son</th>
<th>Daughter</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>DLBCL 70</td>
<td>DLBCL 49</td>
</tr>
<tr>
<td>27</td>
<td>BL 68</td>
<td>CLL 47</td>
</tr>
<tr>
<td>67</td>
<td>LPL 75</td>
<td>HL 26</td>
</tr>
<tr>
<td>75</td>
<td>NOS 70</td>
<td>CLL 61</td>
</tr>
<tr>
<td>107</td>
<td>CLL 82</td>
<td>FL 46</td>
</tr>
<tr>
<td>16</td>
<td>CLL 78</td>
<td>LPL 76</td>
</tr>
</tbody>
</table>

Age at onset, mother-offspring P = 0.032 54 (40-74) P>0.05 (Haldane Smith test)

Table 2: Familial malignant lymphoma. Parent-offspring combinations.
cases of malignant hematological disease. The diversity of malignant hematological disorder associated with familial ML includes 17 different diagnoses, 13 Lympho proliferative Disorders (LPD), and 4 Myelo proliferative Disorders (MPD) in 101 patients, 97 (96 per cent) with LPD and 4 (4 per cent) with MPD. Per family, we found 2.3 cases (mean) of LPD, 0.1 cases (mean) of MPD and 1.2 cases (mean) of ML (Table 1).

The number of affected family members was significantly higher than expected (P < 0.001) estimated from the crude, age-adjusted Scandinavian incidences, viz. the number of patients per 100,000 persons in the population. About 2,000 persons were screened within the 43 families, 50 persons as a mean per family, giving: HL incidence 2.5/100,000, expected per 2,000 persons 0.05, observed 11; NHL incidence 8.0/100,000, expected 0.16, observed 41; CLL incidence 5.5/100,000, expected 0.1, observed 37; multiple myeloma (MM) incidence 5.0/100,100, expected 0.1, observed 5 (Table 1). Based on these figures, the 43 ML probands are associated especially with CLL (37 patients), and ML (52-43 = 9 patients). In spite of nearly the same incidences of CLL and MM in the Scandinavian population (5.5 versus 5.0/100,000), only 5 cases of MM were seen in the families compared with 37 CLL patients (Table 1). No cases of ALL were noted (Table 1).

The rate of lymphoma subtypes in the population compared with that of the 43 families shows predominance of HL in familial ML (expected 10%, observed 21%, P< 0.05) , and a significant reduction of DLBCL in familial ML (expected 30-35%, observed 23 %, P<0.01) (Table 1).

A total of four cases of MPD in 43 families with about 2,000 persons...
screened is significantly more than expected (P<0.01) and indicate an association between LPD and MPD.

The male/female ratio was generally higher in familial ML (expected 1.3, observed 1.7, P < 0.005) and highest in HL (expected 1.5, observed 2.7), sample size 8 males and 3 females (Table 1), counts too small for convincing statistical description.

Segregation

Vertical transmission was seen in 22 families (Tables 1 and 2), non-vertical transmission in 21 families (Tables 1, 3). Ten LPD diagnoses were seen in the vertical transmission while 13 LPD diagnoses were seen in non-vertical transmissions (Tables 1-3). All 4 cases of malignant myeloproliferative disorders were found in non-vertical transmissions (Tables 1 and 3). Taken together, the distribution of affected family members in all 43 pedigrees do not fit into one, common Mendelian modality of segregation. Neither was such pattern recognition successful with the diagnoses ML, NHL, HL and CLL separately.

A birth order effect was not observed in familial ML (Tables 1-3). Neither did we see a birth order effect from an estimation of patrilineal (6A 282, 95% CI: 211 – 299, n = 16, P>0.05) vs. matrilineal (6A 162, 95% CI: 158 – 238, n =16, P>0.05) transmissions.

The age at onset of disease was significantly higher (P<0.01) in parents than in offspring apart from two families with parental HL (nos. 86 and 114, Table 2).

The number of patrilineal and matrilineal transmissions was the same when all types of transmissions were evaluated (Table 1).

Patrilineal transmission was predominant in the direct vertical transmissions, 13 transmissions from father’s side and 7 from mother’s side (Table 1) due to surplus of affected males in this material. The observed vs. expected numbers of patrilineal and matrilineal transmissions were not different (X²-test with one degree of freedom), and no mode of transmission such as father-son (F-S), father-daughter (F-D), mother-son (M-S) or mother-daughter (M-D) was superior after correlation for the gender of the included patients in the asserted vertical transmission (Tables 1 and 2):

ML correlated. n 22, p 0.65, q 0.35, F-S expected npq² = 9, observed 10. F-D expected npq = 5, observed 5. M-S expected npq = 5, observed 2. M-D expected npq² = 3, observed 1 (P ranging between 0.5 and 0.25).

LPD correlated. n 22, p 0.67, q 0.33. F-S expected 10, observed 10, F-D expected 5, observed 5, M-S expected 5, observed 6, M-D expected 2, observed 1 (P ranging between 0.5 and 0.25).

CLL correlated. n 18, p 0.64, q 0.36. F-S expected 7, observed 9. F-D expected 4, observed 4, M-S expected 4, observed 5, M-D expected 2, observed 0 (P ranging between 0.25 and 0.1).

 Combined patrilineal- and matrilineal transmission, viz. affected family members in both father’s and mother’s line, was seen in only 2 families, both with affected parent-offspring (Tables 1 and 2).

Sex concordance in sibling pairs (male-male np), (female-female np) compared with sex discordance (male-female and female-male npq) showed no significant findings: Male-male plus female-female expected 9, observed 13. Male-female, female-male expected 8, observed 5 when n 18, p 0.64, q 0.36 (P ranging between 0.25 and 0.1).

Discussion

Bias in our material is related to the low-grade disorders which sometimes are overlooked due to no or only minor symptoms. Typical examples are MGUS (Monoclonal Gammopathy of Uncertain Significance), stage A CLL and polycythemia vera. The impact of this systematic bias is presumably equal in the multiple familial cases, in solitary disease, and in the incidences used for a comparison between occurrence of disease in families and in the population. One main problem with the underestimated low-grade cases is their absence in the family trees when to estimate the number and position of healthy persons vs. patients. We do not have a systematic screening of all family members in affected families for a precise estimation of this bias. Such a screening will imply the recruitment of healthy, uninformed people without formal social contact with the proband, e.g. family members at a distance from the proband in the pedigree and therefore, it will not be approved by our national ethical committees. Furthermore, the unknown number of early abortions, experienced as a late, strong menstruation, which should rightly be included in the family size when to estimate parity, invalidate our data while legal- and late abortions and still born persons are already included. About 30 per cent of the healthy family members are alive at the time of investigation and still at risk for later malignant hematological disease which could change the findings. We saw a significant higher age at onset of disease in parents than in offspring (Tables 1-3), interpreted as a sign of anticipation with the reservation that the age of the mother at the time of delivery has a trend towards a higher age during the course of the observation period, and that age at onset as a parameter in anticipation theoretically should be related to the mean age of onset of the disease in question. In CLL for example, we found the highest age at onset in the parents [20] with some few exceptions related to e.g. parental HL with a generally lower age at onset than in CLL (cf. family nos. 86 and 114 Table 2). Finally, environmental factor such as infections with antigenic drive and toxic reagents with mutagenic effect, which evidently can affect the expression of ML [6] may have changed in the observation period.

With these reservations, 13 LPD diagnoses and four MPD diagnoses were found within the pleiotropic diversity to familial ML (Tables 1-3). A strong linking between NHL and HL and between ML and CLL was seen in contrast to a weaker association between ML and MM. The higher rate of affected males in familial than in solitary cases (Tables 1-3) may well be explained by a stronger expression of genetic LPD-susceptibility and hence a higher rate of affected males in families with multiple cases than in families with solitary cases. These genealogical data convey a description of the so-called first generation familial disorders known from large-scale estimations of malignant hematological disease [22-25] and prove that no simple Mendelian segregation is on question.

The predominance of HL and the reduction in DLBCL in familial ML (Tables 1-3) can be interpreted as an unequal affinity in the pleiotropic clustering (“HL goes together with HL, but DLBCL has its own ways”). Such positive and negative linking between LPD-diagnoses would be the expected outcome of segregation of mosaics of susceptibility alleles with unequal putative associations. In some segregation, one would predict an additive enhancement of the susceptibility alleles in the mosaic; in other segregations no such synergism would be expected. Finally, an antagonistic, suppressive effect between the susceptibility alleles in the mosaic is a theoretical outcome which could explain the occurrence of single cases (without signs of familial aggregation) of disease in the population.

In such a genetic system with linked susceptibility, male predominance, and segregation away from any Mendelian expectation, the presence of a modifier of segregation should be considered [36]. In principle, such a modifier causing transgenerational segregation
distortions is a genetic mechanism which violate Mendel's first law about equal representation of the two alleles at a heterozygous locus in the functional products of meiosis (egg or sperm) [36]. Models with modifiers linked and unlinked to the primary heterozygote locus have been described for instance in parental genomic imprinting [37-43], all with different segregation in males and females explained by a an unequal effect of the modifier in spermogenesis and oogenesis [36,44].

It is intriguing that the malignant hematological disorders fulfill a number of criteria for the presence of a modifier, among other things the lack of a clear Mendelian pattern in the segregation down through the generations of affected families in combination with male predominance, seen in large subsets of disease, for example in ML and CLL. Genomic imprinting with maternal down regulation, viz. "imprinting of paternal susceptibility" has previously been attributed to CLL-susceptibility as a possible mechanism in the transmission of CLL via feto-maternal microchimerism [20], but very few genealogical publications on the segregation of malignant hematological disease exists for CLL. Genomic imprinting with maternal down regulation, viz. 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30. Report from the Norwegian Cancer Registry

31. Danish Cancer Registry

32. LYFO, Danish Lymphoma Group


