Familial occurrence of chronic lymphocytic leukaemia in Norway

Summary

Background. The only known risk factor for chronic lymphocytic leukaemia (CLL) is occurrence of the disease in close relatives. The aim of this study was to determine the frequency of familial chronic lymphocytic leukaemia.

Material and method. All patients with chronic lymphocytic leukaemia notified to the Cancer Registry in the period 1.10.2007–31.12.2009 were asked to report occurrences of malignant disease in siblings, parents, grandparents and children. The information about malignant haematological disease was verified with the Cancer Registry.

Results. We found malignant haematological disease in close relatives of 42 of the 236 included patients (18 %). CLL and lymphoma were the most common diagnoses. On average, 16 family members were identified in each family. The relative risk of developing CLL was six times higher in those who had close relatives with the disease (16 of a total of 3 776 family members) than among those who did not have close relatives who were affected (76 cases among 107 223 family members of 38 159 control subjects). The increased risk of disease was also associated with other lymphoproliferative diseases. With patrilinear, but not matrilinear inheritance, we found a birth order effect, with affection of younger men in a group of siblings, while the eldest escaped.

Interpretation. Malignant haematological disease is common in the family members of patients with CLL. CLL is the most common disease, but there is extensive pleiotropy.

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The highest incidence of CLL is found in Europe and in population groups of European extraction elsewhere in the world (1). A low incidence is seen in South and East Asia, particularly among the Japanese. Migration surveys show that the incidence remains low among Asians, even those born in the Western world and in later generations (2). Familial occurrence of CLL is further evidence of a genetic predisposition.

Familial occurrence of CLL was first described by Videbæk in 1947 (3). His observations have subsequently been confirmed in more than 100 families (4). A major study based on the Swedish Leukaemia Registry found that for persons with a first-degree relative with CLL, the relative risk of developing CLL was 8.5 times as high and the risk of other lymphoproliferative diseases 2.6 times as high as for persons in the control group (2, 5, 6). We have previously shown that there is extensive pleiotropy in disease affecting close relatives of patients with CLL (6). A British cross-sectional study showed that monoclonal B-lymphocytosis could be identified in 13.5 % of 59 healthy, first-degree relatives of 21 patients with CLL (7). There were no previous studies investigating how large a proportion of patients had close family members with verified lymphoproliferative or myeloproliferative disease.

The aim of the present study was to determine the prevalence of malignant haematological disease in close relatives of patients with CLL.

Material and method

Patient population

All patients with CLL in the period 1 October 2007–31 December 2009 who were notified to the Cancer Registry were eligible for inclusion in the study. Patients were included after signing informed consent forms. The requested family data were sent together with an ordinary cancer notification to the Cancer Registry of Norway, which functioned as secretariat for the study. In those cases where the Registry received notification of a new case of CLL where the patient was not included in the study, the doctor who had sent the notification was contacted and requested to invite the patient to consent to inclusion. The study was a cooperative project between the Norwegian Society of Haematology and the Cancer Registry, and the authors of the article were the project group for the study. Norwegian haematologists were informed of the study through the Norwegian Society of Haematology, and detailed information about the study was available on the Society's and on the Cancer Registry's websites.

The study was approved by the Regional Committee for Medical Research Ethics (REK S-06353b) and the Norwegian Data Protection Authority (07/00254–2).

Genealogical mapping

Patients completed a questionnaire where they were asked to supply the name and personal identification number of siblings, parents, grandparents and children and specify occurrences of malignant disease among these relatives. Some also provided information about grandchildren, nephews, nieces, uncles and aunts. The data on malignant diseases were verified against the Cancer Registry's database or by checking the patient records of those who had died before personal identification numbers were introduced in Norway. In the case of relatives where the proband was unable to provide information about malignant disease, the occurrence of the disease was investigated with the Cancer Registry's database.

Only families whose members' malignant haematological disease was verified in the Cancer Registry were accepted as having a

Main points

- Malignant haematological disease occurs frequently in close relatives of patients with chronic lymphocytic leukaemia
- The risk of disease is not limited to chronic lymphocytic leukaemia, but also applies to other malignant haematological diseases

relative with the disease. Family trees were drawn on the basis of this information.

Diagnostic criteria

In order to make a diagnosis of CLL it was necessary to document persistent clonal B-lymphocytosis ($\geq 5 \cdot 10^9$/l) with a characteristic immune phenotype in accordance with the revised international guidelines from the International Workshop on Chronic Lymphocytic Leukemia (8). Small-cell lymphocytic lymphoma (SLL) is only distinguished from CLL by the absence of lymphocytosis. Patients with clonal B-lymphocytosis, but $< 5 \cdot 10^9$/l, lymph node tumour and/or splenomegaly and histological confirmation of lymph node and/or bone marrow affection, were included under the diagnosis small-cell lymphocytic lymphoma.

Statistical methods

Descriptive statistics were used with a specification of median, average, spread and ratio. Familial aggregation was investigated by calculating the relative risk of developing a disease through being a relative of a proband as compared to being a relative of a control subject. We did not identify our own control group; we made the control group (76 cases among 107 223 family members of 38 159 control subjects) of Goldin et al. the basis for our calculations (5).

We drew detailed family trees for each of the 42 probands in order to determine the place of the affected and healthy family members in the sibling group in the mother's and father's families. Haldane-Smith's test of the significance of birth order was used, and the average ranking in the sibling group according to age was calculated for each individual proband (9).

Results

Patients

During the study period, 388 new cases of CLL were reported to the Cancer Registry. 236 of these patients (61 %) consented to participate in the study and completed the questionnaire with information about their family. We do not know how many were invited to take part, but refused.

Familial occurrence of malignant haematological disease

Familial occurrence of malignant haematological disease was confirmed for 42 probands (18 %). A further five provided information about malignant haematological disease in close family members, but we failed to verify the information with the aid of either the Cancer Registry's database or medical records. These five were therefore not included as families with malignant haematological disease.

We verified malignant blood disease for a total of 60 family members of 42 families (Table 1). There was one other affected member in the families of 28 of the probands (67 %) and in 14 families (33 %) there was more than one. In 31 of the families (74 %) we found only lymphoproliferative disease, while in 11 families (26 %) we found a combination of lymphoproliferative and myeloproliferative disease (includes unspecified leukaemia).

The two families with the largest number of affected family members were found to have a total of ten persons, including the probands, with malignant haematological disease, and in one family there were affected members on both the mother's and father's side. Probands with more than one affected family member had more than one disease combination (Table 2). The affected family members had several different haematological malignancies, but CLL was by far the most frequent individual disease (27 %). Non-Hodgkin's lymphoma occurs just as frequently (28 %), but the collective term «non-Hodgkin's lymphoma» covers several individual diagnoses. CLL/CLL proband parent pairs make up only 35 % of the 17 proband parent pairs (Table 2).

There is an even distribution of maternal and paternal inheritance (29 descendants on the mother's side and 23 on the father's side), and a preponderance of affected men compared with women, both among the probands (26 men and 16 women, ratio 1.63) and among affected relatives (41 men and 19 women, ratio 2.16). In the first generation of descendants, there are exclusively female affected relatives in the matriline and exclusively male affected relatives in the patriline (Table 2).

Age, V_H gene usage, birth order and risk of disease

The median age of the 42 probands was 62 (average 61.9, spread 40–86).

Molecular genetic analysis to determine which gene coded for the variable part of the immunoglobulin's heavy chain in the CLL cells (preferred V_H gene) and whether the V_H gene had undergone somatic hypermutation or not (mutation status) was successful for 39 probands. The most preferred V_H genes among these patients were the same ones found most frequently in the other included patients – V_H1–69 in four patients, V_H3–7 in four, V_H3–23 in three, V_H3–30 in five and V_H4–34 in four. In 23 probands (59 %) the preferred V_H gene was mutated, in 16 probands (41 %) the preferred V_H gene was unmutated. Five probands (13 %) had biallelic CLL, i.e. the CLL cells used two V_H genes.

In 36 probands (19 with patrilineal and 17 with matrilineal inheritance) there was affection on one side of the family, while for six probands there was malignant haematological disease on both sides. The sibling birth order of the affected person differed, depending on whether the disease was in mother's or father's family (Table 3). When predisposition for CLL was inherited from father's side (patrilineal inheritance), the sick person was never the oldest of the siblings, whereas the sibling birth order of the sick person was completely random if the predisposition for CLL came from mother's side (matrilineal inheritance). There was no difference in gender distribution in the sibling groups between matrilineal and patrilineal inheritance.

Table 1 Malignant haematological disease distributed by diagnosis among 60 family members of 42 probands with chronic lymphatic leukaemia

Diagnosis	Number of persons
Lymphoproliferative diseases	**46**
Chronic lymphocytic leukaemia	16
Non-Hodgkin's lymphoma	17
Hodgkin's lymphoma	4
Acute lymphoblastic leukaemia	2
Hairy cell leukaemia	1
Myelomatosis	6
Myeloproliferative diseases	**11**
Acute myelogenous leukaemia	7
Chronic myelogenous leukaemia	3
Myeloid leukaemia, unspecified	1
Unspecified leukaemia	**3**

Table 2 Malignant haematological disease in 60 family members of 42 probands with chronic lymphocytic leukaemia and family members' relationship with probands

Relationship with proband	Gender distribution	Mother/ matrilineal Number	Father/ patrilineal Number	Siblings Number
Parents	M/F = 11/6	9	8	
Children	M/F = 0/1	1		
Grandparents	M/F = 7/1	5	3	
Grandchildren	M/F = 1/0	1		
Other second- and third-degree relatives	M/F = 17/8	13	12	
Siblings	M/F = 5/3			8
	Total M/F = 41/19	M/F = 10/19	M/F = 19/4	M/F = 3/5

Table 3 Age-based ranking of siblings with malignant haematological cancer of 36 probands with chronic lymphocytic leukaemia. The method is described in more detail by Emery (9)

Inheritance	Number of probands	Score for age-based ranking of siblings with malignant haematological disease (average)	95 % CI if there is no age-based ranking of siblings with malignant haematological disease	Size of sibling group (average)	P- value
Patrilineal	19	288	192–282	2.9	0.02
Matrilineal	17	216	186–278	2.9	0.7

We identified an average of 16 relatives (spread 6–33) in each family. We then calculated the relative risk of CLL in close relatives of patients with the disease (16 cases among 3 776 family members) compared with the control group. The risk of CLL for family members of persons with the disease was found to be six times higher than the risk of those who did not have the disease in the family.

Discussion

In this study we identified up to five generations of family members of 236 patients with CLL, and we found that 42 probands (18 %) had close relatives with malignant haematological disease. As far as we know, this is the first time familial occurrence of malignant haematological disease has been mapped by means of genealogical methodology among patients with CLL recruited in a population-based study. This method has enabled us to identify far more close relatives than would have been the case with register-based studies (5, 10–15).

In the biggest register study, which covered 9 717 Swedish patients with CLL, only 29 947 first-degree relatives were identified, i.e. three for each patient (5). We identified five times as many relatives per proband. This may be part of the explanation for why we found malignant haematological disease in almost twice as many close relatives of the patients as have been found in earlier studies (18 % versus 10 %) (4). We excluded families when we were unable to verify information about disease among relatives in the Cancer Registry, even if it was highly probable that the information was correct. There may be a selection bias in our material, since only 61 % of those diagnosed as having CLL during the study period were included in the study.

Goldin et al. found, like us, that the increased risk of first-degree relatives of patients with CLL developing a malignant disease was not limited to this disease, but also extended to other lymphoproliferative diseases of the B-cell type (5). They found that the relative risk of developing CLL was 8.5 times higher than in the control population; we found it to be six times higher.

The fact that we find a somewhat lower relative risk of CLL is probably attributable to the fact that we were able to identify far more close relatives (16 relatives/family) than was possible in the register-based studies (three relatives/family) (5). Moreover, our estimate is a minimum figure because several of the family members were naturally not followed long enough to exclude the possibility that they may develop CLL in the course of their lives. There was a relatively long observation window in the Swedish material which allowed for the development of disease in relatives (CLL diagnosed in the period 1958–2004).

Our data indicate that the probability of finding first-degree relatives of patients with CLL who have another lymphoproliferative disease is greater than the probability of finding relatives with CLL. This is entirely consistent with the data of Goldin et al., but because other lymphoproliferative disease occurs considerably more frequently than CLL, the relative risk is lower (RR 2.6) (5). A weakness of our study is that we did not have a Norwegian control material, but we have shown that the incidence of CLL in Norway is the same as in the rest of Scandinavia and the Western world (16).

Clinical phenotypes of familial and sporadic CLL have been compared in two earlier studies (17, 18). The stage at the time of diagnosis, treatment needs and survival were comparable, but the male predominance appeared to be absent in familial CLL. The explanation given was that women have a stronger genetic predisposition for CLL than men (19). We also see signs of this in our study. In the proband-parent combination there are as many affected male as female relatives, but there is a pronounced association between women and matrilineal inheritance and men and patrilineal inheritance (Table 2).

Earlier studies have suggested that familial CLL is diagosed at a lower age than sporadic disease (20). In line with this, we found a somewhat lower average age at the time of diagnosis for familial disease (61.9) than in the whole material (65.9) (16), but others have shown convincingly that this is a bias due primarily to the fact that the next generation has a shorter follow-up period than the parent generation (5). Quite another matter is that in parent-child pairs with CLL, age at the time of diagnosis is higher in the parents than in the children. This has been taken as support for the anticipation hypothesis (earlier onset of disease and more serious manifestation in subsequent generations) but in our earlier studies we have not found statistical backing for the hypothesis (21).

Our earlier observations indicate that familial predisposition for CLL results in pronounced pleiotropy with respect to disease manifestations in family members (6). This is in line with the studies of Goldin et al. (5, 12), and is confirmed by the study in question. Our observations with respect to age, V_H gene usage and gender distribution are arguments for familial CLL not being distinct from sporadic CLL (16). This view is supported by other studies (17, 18).

The molecular basis for susceptibility to CLL has not been fully mapped, but 7–8 gene loci have been found to be associated with extra susceptibility to the disease and its pleiotypes. The loci that predispose for the disease that have been mapped so far are associated with genes that code for immune regulatory proteins (22). Inheritance has not been firmly established, but there appears to be complex inheritance that does not follow traditional patterns. We show in this study that in patrilinear inheritance at least, susceptibility to CLL and other lymphoproliferative diseases appears to be transferred to the younger men in the sibling group. This confirms our earlier findings in another cohort (21).

CLL can be regarded as a genetic disease with familial and ethnic aggregation and with variable and gender-dependent penetrance. Our current understanding is that variants of susceptibility loci that predispose subjects to disease contribute individually to a moderate extent (odds ratio < 1.5), but they occur frequently, at any rate in the Caucasian population, and each patient has several variants that predispose him or her to the disease (19, 23–25).

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