Patterns of autoimmunity and subsequent chronic lymphocytic leukemia in Nordic countries

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A population-based case-control study was conducted to evaluate risk of developing chronic lymphocytic leukemia (CLL) associated with personal and/or family history of autoimmune and related diseases. Data were obtained for all (n = 7764) patients diagnosed with CLL in Sweden and Denmark over a 40-year period and with linkable relatives, 16 658 matched control subjects, and first-degree relatives of patients (n = 17 991) and control subjects (n = 39 388). Odds ratios (ORs) were calculated to quantify risk of CLL in relation to personal/family history of 32 autoimmune and related disorders. The risk of CLL was significantly increased among subjects with a personal history of pernicious anemia (OR = 1.94; 1.18-3.18), mainly in the 0- to 1-year latency period. A significantly decreased risk of CLL was found among individuals with a personal history of chronic rheumatic heart disease (OR = 0.55; 0.33-0.93), particularly persons with a long latency (10+ years) between the 2 conditions. We found no association between personal or familial occurrence of other autoimmune or related disorders and CLL. If our results are confirmed, mechanistic studies examining how pernicious anemia might promote increased occurrence of CLL and how chronic rheumatic heart disease protects against CLL, perhaps related to long-term antibiotics use, may provide insights to the as-yet-unknown etiology of CLL. (Blood. 2006;108:292-296)

Introduction

B-cell chronic lymphocytic leukemia (B-CLL) is a neoplastic disease characterized by the accumulation of small, mature-appearing lymphocytes in the blood, bone marrow, and lymphoid tissues. CLL accounts for 30% of all leukemia and is the most common form of leukemia among older adults in Western countries. Data from the United States Surveillance, Epidemiology, and End Results (SEER) Registry estimate the United States incidence in the period from 1996 to 2000 to be 3.7 per 100 000, with a median age at diagnosis of 72 years.[1] Incidence rates in men are nearly twice as high as in women. Although advanced age, Caucasian race, and family history of certain hematologic malignancies are recognized risk factors, the etiology of CLL is mostly unknown. Case-control studies have evaluated diverse environmental and occupational exposures such as pesticides, viruses, ionizing radiation, and nonionizing power-frequency magnetic fields, but have not found consistent associations.[2] Family history of CLL or other hematolymphoproliferative cancers, on the other hand, have consistently been identified as a risk factor for CLL.[3-9]

Autoimmune phenomena are a well-known complication of CLL,[10-13] almost as a counterpoint to the frequent and profound hypogamma-globulinemia that accompanies the disease.[14] The possible relationship of autoimmune disorders as risk factors for CLL has been evaluated based on the nature and functioning of lymphocytes, results of experimental studies, clinical reports, and limited data from epidemiologic studies. However, there are inconsistencies in the limited literature on this topic, and it remains yet unclear whether or not autoimmune or related disorders predispose toward increased risk of CLL.[15-18] Interestingly, there also are reports of familial aggregation of malignant lymphomas together with autoimmune diseases, but to our knowledge there is very limited information on familial occurrence of CLL and autoimmune disorders.[19-23]

In the first investigation to evaluate both personal and familial occurrence of autoimmune and related disorders, we conducted a population-based comprehensive assessment of hospital discharge records for 32 autoimmune and related conditions among all (n = 7764) CLL patients, more than 16 000 frequency-matched control subjects and more than 56 000 of their first-degree relatives in Sweden and Denmark over a 40-year-period.

Patients, materials, and methods

Patients, control subjects, and first-degree relatives

The Swedish Cancer Register has been in operation since 1958 with near-complete coverage.[24,25] The Swedish Multi-Generation Register[26]

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O.L., E.A.E., M.S.L., and L.R.G. designed the study; M.S.L., G.G., L.R.G., L.M., and K.H. obtained data; O.L. and E.A.E. analyzed data; O.L., E.A.E., N.E.C., G.G., L.M., K.H., M.S.L., and L.R.G. were involved in the interpretation of the results; O.L. initiated this work and wrote the report. All authors read, gave comments, and approved the final version of the manuscript. O.L., E.A.E., and L.R.G. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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includes information on parent-offspring relations for all Swedish citizens born in 1932 or later. Through iterated linkage using this register, parents, siblings, and offspring of individuals born in the year 1932 or later can be identified. The Swedish Multi-Generation Register has been merged with the Swedish Cancer Registry (all cancers diagnosed between 1958 and 1998) to create the Family-Cancer Database, which has been described in detail elsewhere.[3,27,28] In the Family-Cancer Database, all individuals registered with a first primary diagnosis of CLL (International Classification of Diseases [ICD] 7th Revision code 204.1) between 1958 and 1998 were identified as patients. For each patient, information on date of birth, date of diagnosis of CLL, and sex was collected. In addition, for each case, 2 malignancy-free control subjects who matched the case in terms of sex, year of birth, and county of residence in the year of the index patient's CLL diagnosis were chosen from the database. Matching by county of residence controlled for regional variability over time in cancer reporting. Case patients and control subjects with no relatives identified from the linkage were removed from the dataset, and duplicate control subjects also were removed. Thus, using the Family-Cancer Database, we identified all reported Swedish CLL patients, matched control subjects, and their first-degree relatives.

A similar database of case patients with CLL (ICD 7th Revision code 204.0), control subjects, and relatives was created using the Danish Cancer Registry and the Danish Central Population Registry (CPR).[3,29] The Danish Cancer Registry became a nationwide registry in 1943, but we limited the selection of CLL patients to those diagnosed after April 1, 1968, because patients with malignant disease who died before that date could not be linked to the CPR. The CPR contains links of offspring to parents (and vice versa) starting with all children born in 1968 as well as linkages (also starting in 1968) among family members living at the same address. Thus, all individuals with a first primary CLL diagnosed between 1968 and 1997 were selected from the Danish Cancer Registry. Four malignancy-free control subjects per case were chosen from the CPR. All first-degree relatives were identified by linking to the CPR. Case patients and control subjects with no relatives identified from the linkage were removed from the study, and duplicate control subjects also were removed. This resulted in fewer than 4 control subjects per case patient in the final sample. All cancer diagnoses were ascertained for relatives by linking them to the cancer registry.

Approval was obtained from the National Institutes of Health Institutional Review Board for these studies. Informed consent was waived because we had no contact with study subjects.

Autoimmune conditions

All Swedish individuals were linked with the Swedish Inpatient Register 1964-2000, which contains information on discharges from inpatient care (coded according to ICD 7th to 10th Revisions) with a population-based coverage that, county by county, encompassed 50% of Sweden in the mid-1970s and 100% since 1987. All Danish individuals were linked with the Danish Inpatient (1977-1997) and Outpatient (1994-1997) Register in a similar way. Through this linkage, we collected information on discharges listing any of the following coded autoimmune and related conditions[30]: polymyositis/dermatomyositis, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, systemic sclerosis, Addison disease, amyotrophic lateral sclerosis, autoimmune hemolytic anemia, chronic rheumatic heart diseases, discoid lupus erythematosus, Grave disease, Hashimoto thyroiditis, immune thrombocytopenic purpura, insulin-dependent diabetes (see definition later in this paragraph), localized scleroderma, lupoid hepatitis, multiple sclerosis, myasthenia gravis, pernicious anemia, polyarteritis nodosa, primary biliary cirrhosis, Wegener granulomatosis, ankylosing spondylitis, Behcet disease, chorea minor, Crohn disease, polymyalgia rheumatica, psoriasis, Reiter disease, rheumatic fever, sarcoidosis, and ulcerative colitis. There is no code that unambiguously delineates diabetes mellitus type 1 from type 2 in the hospital discharge listing for either Sweden or Denmark. Subjects with diabetes mellitus diagnosed before 30 years of age were designated as diabetes mellitus type 1 in accord with a previous study.[30]

Statistical analysis

We calculated odds ratios (ORs) as measures of relative risks using unconditional logistic regression. We assessed the association between personal history of defined autoimmune conditions and CLL among patients and control subjects. ORs were adjusted for age, sex, calendar period, and region using logistic regression. When the number of subjects with the autoimmune condition in CLL patients or control subjects was 0, we instead present unadjusted P values derived using Fisher exact test. Using logistic regression, we examined the relationship between CLL risk and latency, that is, time from first inpatient discharge listing a defined autoimmune condition (0-1, 2-4, 5-9, 10 or more years). Since risk of autoimmune and related conditions may differ depending on the age of diagnosis at CLL, we separately analyzed the relationship between autoimmune and related conditions and early diagnosis (< 50 years), midlife diagnosis (50-70 years), and late diagnosis (> 70 years) CLL, respectively. We also stratified our analyses by gender. Similarly, to measure associations between CLL and a hospital discharge diagnosis of autoimmune or related conditions in one or more family members (denoted: family history of autoimmune or related conditions), we used logistic regression, adjusting for age, gender, calendar period, and region as well as for personal history of that condition.

To test the robustness of these models in relation to potential variation in diagnostic procedures over time, subanalyses stratified by calendar period (< 1980 versus ≥ 1980) were conducted.

Results

A total of 5927 CLL patients, 11 796 matched control subjects, and corresponding relatives of patients (n = 14 371) and control subjects (n = 28 943) were included in the Swedish dataset. In the Danish dataset, we included 1837 CLL patients, 4862 matched control subjects, and corresponding relatives of patients (n = 3620) and control subjects (n = 10 445). As expected, due to the relatively high median age at CLL diagnosis and given inherent database truncations, the largest proportion of identified first-degree relatives were offspring (Table 1). The total number of patients versus control subjects with a personal history of autoimmune and related conditions was 280 versus 472, respectively. Among affected patients, the distribution of autoimmune and related conditions per individual was: 1 condition (94%), 2 conditions (5%), and 3 conditions (1%); and for control subjects the corresponding numbers were 92%, 7%, and 1%, respectively.

We first examined risk of CLL in relation to personal history of autoimmune and related conditions (Table 2). Substantially increased risk for CLL was found among subjects with a history of autoimmune hemolytic anemia (OR = 108.40, 95% CI 14.99-784), and an association with pernicious anemia also was significant (OR = 1.94, 95% CI 1.18-3.18). The association with Sjögren syndrome almost reached statistical significance (OR = 3.96, 95% CI 0.99-15.85). Conversely, we found a significantly decreased risk for CLL among subjects with a personal history of rheumatic heart disease (OR = 0.55, 95% CI 0.33-0.93). CLL was not related to personal history of other autoimmune or related disorders.

When analyses were stratified by time between first hospitalization for autoimmune and related conditions and subsequent CLL diagnosis, we found that 48 of the 54 patients with autoimmune hemolytic anemia had hospital discharge diagnoses of this disorder a few weeks to months before the diagnosis of CLL. Similarly, a significant excess of CLL was observed within 1 year of hospital discharge for patients with pernicious anemia (OR = 8.37, 95% CI 3.14-22.35), based on 20 patients versus 5 control subjects, and Sjögren syndrome ($P = .032$), based on 3 patients versus 0 control subjects. For chronic rheumatic heart disease, risk of CLL did not

Table 1. Characteristics of CLL patients and control subjects

Variable	Sweden		Denmark	
	Patients	Control subjects	Patients	Control subjects
Total number	5927	11 796	1837	4862
Age in y at CLL diagnosis, median (interquartile range)	69 (61-76)	NA	62 (54-69)	NA
Age group at CLL diagnosis, n (%)				
Young-adult onset CLL, 50 years or younger	380 (6)	761 (7)	301 (16)	1016 (21)
Midlife onset CLL, 51-70 years	2904 (49)	5786 (49)	1180 (64)	3208 (66)
Late onset CLL, older than 70 years	2643 (45)	5249 (44)	356 (20)	638 (13)
Sex, n (%)				
Male	3854 (65)	7660 (65)	1287 (70)	3403 (70)
Female	2073 (35)	4136 (35)	550 (30)	1459 (30)
Year of CLL diagnosis, median (interquartile range)	1985 (1977-1993)	NA	1990 (1984-1994)	NA
First-degree relatives, n (mean no. per proband)				
Parents	1101 (0.2)	2200 (0.2)	121 (0.1)	414 (0.1)
Siblings	930 (0.2)	1870 (0.2)	80 (0.1)	218 (0.1)
Offspring	12 340 (2.1)	24 873 (2.1)	3419 (1.9)	9813 (2.1)

CLL indicates chronic lymphocytic leukemia; NA, not applicable.

Table 2. Relative risk of CLL in relation to personal and family history of autoimmune conditions

Autoimmune condition	Personal history				Family history			
	pa	co	OR	95% CI	pa	co	OR	95% CI
Autoantibodies detectable								
Systemic involvement								
Polymyositis/dermatomyositis	17	22	1.58	0.84–2.99	15	36	0.87	0.47–1.59
Rheumatoid arthritis	68	136	1.03	0.76–1.38	49	129	0.81	0.58–1.13
Sjögren syndrome	6	3	3.96	0.99–15.85	1	3	0.71	0.07–6.81
Systemic lupus erythematosus	3	8	0.83	0.22–3.16	13	23	1.22	0.62–2.42
Systemic sclerosis	7	5	2.75	0.87–8.69	5	6	1.89	0.58–6.23
Organ involvement								
Addison disease	0	8	0	($P = .062$)	4	4	2.25	0.56–9.03
Amyotrophic lateral sclerosis	2	7	0.54	0.11–2.61	3	0	Inf*	($P = .032$)
Autoimmune hemolytic anemia	54	1	108.4*	14.9–784	1	5	0.42	0.05–3.58
Chronic rheumatic heart disease	18	67	0.55*	0.33–0.93	14	23	1.44	0.74–2.81
Discoid lupus erythematosus	0	1	0	($P = 1.00$)	0	2	0	($P = 1.00$)
Grave disease	3	13	0.50	0.14–1.77	8	19	0.90	0.39–2.06
Hashimoto thyroiditis	2	4	1.07	0.20–5.88	4	2	4.75	0.87–25.99
Immune thrombocytopenic purpura	5	5	2.16	0.62–7.51	0	8	0	($P = .062$)
Insulin-dependent diabetes	0	0	NA	NA	12	17	1.80	0.86–3.78
Localized scleroderma	0	0	NA	NA	1	0	Inf	($P = .32$)
Lupoid hepatitis	0	0	NA	NA	0	0	NA	NA
Multiple sclerosis	9	25	0.80	0.37–1.72	20	37	1.18	0.68–2.04
Myasthenia gravis	2	1	4.78	0.43–53.02	4	3	2.71	0.61–12.13
Pernicious anemia	31	32	1.94*	1.18–3.18	9	18	1.21	0.54–2.70
Polyarteritis nodosa	1	1	1.93	0.12–30.91	0	3	0	($P = .56$)
Primary biliary cirrhosis	1	5	0.42	0.05–3.62	2	3	1.38	0.23–8.31
Wegener granulomatosis	0	2	0	($P = 1.00$)	0	3	0	($P = .56$)
Autoantibodies not detectable								
Ankylosing spondylitis	6	9	1.41	0.50–3.98	11	13	1.71	0.76–3.82
Behcet disease	0	0	NA	NA	0	0	NA	NA
Chorea minor	0	0	NA	NA	0	0	NA	NA
Crohn disease	4	21	0.42	0.14–1.21	28	55	1.13	0.73–1.74
Polymyalgia rheumatica	22	42	1.06	0.63–1.79	11	24	1.08	0.53–2.21
Psoriasis	10	35	0.57	0.28–1.15	15	32	1.03	0.56–1.91
Reiter disease	0	2	0	($P = 1.00$)	8	11	1.66	0.67–4.14
Rheumatic fever	3	9	0.66	0.18–2.43	7	18	0.84	0.35–2.02
Sarcoidosis	8	19	0.90	0.39–2.07	12	31	0.82	0.42–1.61
Ulcerative colitis	9	22	0.89	0.41–1.94	39	59	1.40	0.94–2.08

P values (2-sided) based on the Fisher exact test are given when patients or control subjects have 0 individuals with the specified condition. ORs for personal history were adjusted for age, calendar time of CLL diagnosis, sex, and region. ORs for family history were adjusted for age, calendar time of CLL diagnosis, sex, region, and personal history of the same disorder.

pa indicates patients; co, control subjects; OR, odd ratio; CI, confidence interval; NA, not applicable; and Inf, infinity.

*P values $<.05$.

differ significantly from unity until 10 or more years after discharge diagnosis of chronic rheumatic heart disease when a significantly reduced risk of CLL was observed (OR = 0.30, 95% CI 0.10-0.84).

When analyses were stratified by age at CLL diagnosis, in total there were 11, 129, and 140 subjects with autoimmune or related conditions out of 681, 4084, and 2999 CLL patients who were younger than 50 years of age, 51 to 70 years of age, and older than 70 years of age at diagnosis. For pernicious anemia and Sjögren syndrome, this was reflected in equally elevated, although imprecise, risk estimates in the latter 2 age groups (data not shown). For autoimmune hemolytic anemia, the risk estimates and numbers in the midlife and the late-onset CLL groups were (OR = 53.31, 95% CI 7.23-393; n = 26 patients versus 1 control) and ($P < .0001$; n = 28 patients and 0 control subjects), respectively. For subjects with personal history of chronic rheumatic heart disease, decreased risk of CLL was observed only among those with CLL at age older than 70 years (OR = 0.45, 95% CI 0.22-0.93; n = 9 patients versus 39 control subjects).

When we stratified our analyses by gender, the risk estimates were very similar for males and females, respectively (data not shown). When numbers permitted, we conducted subanalyses stratified by calendar period (< 1980 versus ≥ 1980) with similar findings (data not shown).

For family history, we found a significantly increased risk of CLL among subjects with a family history of amyotrophic lateral sclerosis ($P = .032$); however, the estimate was based on very few observations (Table 2). CLL was not related to family history of other conditions under study. Subjects with single or multiple autoimmune or related conditions were not aggregated together in families, nor were they in families with more than one CLL case.

Discussion

In our systematic evaluation of autoimmune conditions and CLL, an important negative observation was that we did not observe a generally increased risk of CLL following these conditions. Specifically, for 29 of 32 conditions under study, we found no statistical association. None of the 32 autoimmune and related conditions under study showed both a positive personal and family history of the same disorder to be associated with a significantly increased risk of CLL. A very strong association was observed for personal history of autoimmune hemolytic anemia and subsequent CLL, primarily within 1 year of diagnosis of CLL. However, since autoimmune hemolytic anemia is a well-known complication of CLL,[13,31] it is most likely that this association reflects reverse causality due to undetected cases of CLL manifesting in patients who show autoimmune hemolytic anemia as their first symptom.

Likewise, we found no relationship between family history of autoimmune or related conditions in first-degree relatives and risk of subsequent CLL for 31 of 32 conditions investigated. Risk of CLL was significantly increased among subjects whose first-degree relatives had a diagnosis of amyotrophic lateral sclerosis, based on 3 patients versus 0 control subjects. However, given the lack of specific prior hypothesis as well as the number of autoimmune and related conditions under study, we consider the relationship of amyotrophic lateral sclerosis in first-degree relatives with risk of CLL to be a chance finding. Our data thus provide no support for the hypothesis that genetic factors predisposing to autoimmune disorders also influence susceptibility to CLL.

An increased risk of CLL following autoimmune conditions has been suggested in some previous smaller case series[15-17] but not in a case-control study including more than 300 CLL patients.[18] Also, one small study reported more autoimmune diseases among first-degree relatives of CLL patients compared to relatives of control subjects.[19] Our results therefore add substantially to and clarify the restricted literature on the topic of autoimmune conditions prior to CLL, because we had access to a substantially larger (n = 7764) population-based investigation and information on family history of autoimmune disease among first-degree relatives of patients and control subjects retrieved through nationwide record linkage.

The observed almost 2-fold excess of CLL diagnosed within a year of hospital discharge for pernicious anemia could entirely be due to early diagnosis of asymptomatic CLL patients rather than etiologic in nature, or it could be a chance finding due to multiple comparisons. However, we recently found an excess of multiple myeloma[30] and non-Hodgkin lymphoma (NHL) (O. L., unpublished data, May 2006) diagnosed within a short period of time after hospital discharge for pernicious anemia. The possible relationship between pernicious anemia and CLL, multiple myeloma, and NHL also could reflect early diagnosis. However, since pernicious anemia has been reported as a risk factor for CLL in some case reports[32] but has not been observed to be a complication of CLL, it might as well be possible that the underlying pathogenic mechanisms of the association between pernicious anemia and hemato-lymphoproliferative cancers may include shared genetic, host and/or environmental susceptibility of the 2 conditions.

A completely unexpected finding was an almost 50% decreased risk of CLL among subjects with a history of chronic rheumatic heart disease. While this could be a chance association due to multiple comparisons, the patterns suggest that the finding should be followed up. The observed protective effect was strongest among subjects older than 70 years and among those with more than 10 years of latency following hospitalization for rheumatic heart disease. We speculate that this could reflect the usage of long-term antibiotic prophylaxis, which normally is given to patients with chronic rheumatic heart disease.[33] Since CLL may be associated with the occurrence of bacterial infections, it is possible that long-term prophylactic penicillin leads to decreased occurrence of bacterial infections, resulting in a reduced number of secondary inflammations, which lowers the risk of CLL.[34] We also have recently reported a 50% decreased risk of multiple myeloma among subjects with a previous personal history of chronic rheumatic heart disease.[30] Unfortunately, the information available in our database for both studies does not provide the detailed clinical data that would allow us to evaluate this hypothesis directly. Thus, these findings need to be tested in future epidemiologic studies that include medical record validation of detailed clinical, diagnostic, prognostic, and treatment data.

In our study, we used a register-based case-control design, which minimized recall bias, allowed us to evaluate risk according to age and gender, and provided a very large population-based sample. By including all CLL patients diagnosed in Sweden and Denmark during a 40-year period with one or more linkable relatives, we were able to conduct the largest study on autoimmunity and subsequent risk of CLL to date, with enough power to report convincingly null findings. Limitations include incomplete numbers of first-degree relatives of all patients and control subjects, lack of information on all potential confounders, lack of validation of the hospital discharge diagnoses of autoimmune and related conditions, and failure to capture those autoimmune diseases diagnosed in outpatient settings. However, because personal and family history of autoimmune and related disorders were

assessed among matched control subjects using the same hospital discharge registries, underdiagnosis of autoimmune and related disorders in subjects or their first-degree relatives should be nondifferential between patients and control subjects, and thus any bias should have been conservative, that is, toward a null association.[35,36] Another limitation is the large number of tested autoimmune and related conditions, which implies that one has to interpret detected associations with caution due to multiple comparisons.

Recent literature has described restricted V_H gene usage in CLL cells, suggesting that there might be a common antigen involved in CLL pathogenesis[37] and consistent with the established understanding that clonal V_H mutations seen in B-CLL cells are the product of a classic antigen-driven somatic hypermutation process.[38-40] Our findings fit within this framework and broadly suggest that the common antigens involved in the pathogenesis of CLL are less likely of autoantigen type and more likely represent extrinsic environment factors, speculatively of infectious origin.

In summary, personal and family history of autoimmune and related conditions generally was not associated with risk of CLL. The association patterns found with pernicious anemia and chronic rheumatic heart disease suggest avenues for future etiologic studies.

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