Risk of lymphoma in patients with dermatitis herpetiformis

Bárdur Sigurgeirsson, Bjarni A Agnarsson, Bernt Lindelöf

Abstract

***Objective*—To provide accurate estimates of the risk of lymphoma in patients with dermatitis herpetiformis.**

***Design*—Comparison of observed and expected incidence of cancer in patients with dermatitis herpetiformis.**

***Subjects*—976 patients aged 4 to 97 years with no clinical signs of coeliac disease who were admitted to hospital between 1963 and 1983.**

***Setting*—Data from Swedish Cancer Registry.**

***Main outcome measures*—Incidence and type of cancer.**

***Results*—106 cancers were diagnosed in 94 patients. The relative risk was 1·4 (95% confidence interval 1·1 to 1·7) in male patients and 1·2 (0·8 to 1·7) in female patients. When the individual cancer sites were analysed a significant risk was found only for malignant, non-Hodgkin's lymphoma in male patients, with a relative risk of 5·4 (2·2 to 11·1).**

***Conclusions*—The risk of lymphoma is greater in male patients with dermatitis herpetiformis, and this calls for increased surveillance in these patients.**

TABLE I—*Age distribution at time of first admission to hospital in 976 patients with dermatitis herpetiformis*

Age (years)	No of female patients	No of male patients	Total
0-4	1	0	1
5-9	1	2	3
10-14	2	0	2
15-19	5	9	14
20-24	17	14	31
25-29	20	19	39
30-34	20	21	41
35-39	31	22	53
40-44	27	20	47
45-49	23	41	64
50-54	34	45	79
55-59	32	67	99
60-64	38	69	107
65-69	43	54	97
70-74	43	66	109
75-79	31	55	86
80-84	21	42	63
≥85	20	21	41
Total	409	567	976

Department of Dermatology, Karolinska Hospital, Stockholm, Sweden
Bárdur Sigurgeirsson, *dermatologist*
Bernt Lindelöf, *dermatologist*

Department of Pathology, University Hospital of Iceland, Reykjavik, Iceland
Bjarni A Agnarsson, *pathologist*

Correspondence to:
Dr B Sigurgeirsson,
Háaberg 39,
220 Hafnarfjördur, Iceland.

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Introduction

An increased incidence of gastrointestinal lymphoma has been documented in several studies of coeliac disease. Patients with dermatitis herpetiformis have long been thought to have an increased risk of developing cancer, and there are numerous case reports of patients with dermatitis herpetiformis and lymphoma. To our knowledge, however, no large study has been done to confirm this relation and estimate the risks of lymphoma. In a retrospective study of 109 patients with dermatitis herpetiformis malignant tumours were found in seven, giving a relative risk of 2·4.[1] In Sweden another retrospective study of 96 patients, however, failed to show any relation with malignancy.[2]

It is therefore of interest to determine whether patients with dermatitis herpetiformis without clinical signs of coeliac disease are at risk of developing lymphomas. To provide more accurate estimates of the risk we studied a population based patient cohort of patients with dermatitis herpetiformis who were admitted to hospital in Sweden between 1963 and 1983. Follow up was complete up to 1987 and therefore ranged from five to 25 years after the first evaluation in hospital for dermatitis herpetiformis.

Patients and methods

PATIENTS

From 1964 to 1983 the Swedish National Board of Health and Welfare collected nationwide information about people who were admitted to hospital in the country. In 1964, when this registry started, it covered only 20% of the population (8·3 million), but its coverage increased over the following years so that by 1969, 60% of the population was covered. Since 1970 this registry has been virtually nationwide. The information includes a unique individual identification number used in all population statistics in Sweden, the dates of admission and discharge, diagnosis, and nature and dates of operations.

From this registry we selected the diagnosis of dermatitis herpetiformis by using code 704 00 from the Swedish adaptation of the *International Classification of Diseases*, seventh revision (ICD-7), for 1964-8 and code 693 99 from ICD-8 for 1969-83.

With these methods we identified 1040 patients in whom dermatitis herpetiformis was listed in the registry for the first time from 1964 to 1983. Patients with concomitant coeliac disease were excluded, leaving 976. There were 567 males and 409 females with a mean (range) age of 57·8 (4 to 97) years. There were seven (0·7%) children (0 to 15 years of age) (table I). The average follow up was 8·9 years for cancer (to 1987) after correction for deaths during the study period. The number of person years of observation was 8662 after correction for deaths.

SWEDISH CANCER REGISTRY

Information from the Swedish Cancer Registry, Stockholm (1958-87) and the 976 patients' records was correlated to identify people with cancer. Nationwide information on incidence of cancer in Sweden has been available since 1958, when compulsory registration began.[3] The cancers are classified according to ICD-7 as recommended by the World Health Organisation. The cancer registry collects information on diagnosed cancers from clinicians and pathologists. If a person has more than one cancer, each is registered separately. Basal cell carcinomas are not registered. The completeness of registration is close to 100% for all cancers.[4]

ORIGINAL MEDICAL RECORDS

As the number of patients was so large, and some patients had had numerous stays in different hospitals in Sweden since 1964, we judged it impossible to review all the hospital records, though we did review a sample of 63 records. A dermatologist (BL) reviewed the records and classified them. Six records were not available at the local hospital, 51 (98%) patients were classified as definitely having dermatitis herpetiformis, and one (2%) patient was classified as not having this diagnosis. Dermatitis herpetiformis was diagnosed on clinical and histopathological grounds and was not always confirmed by immunohistochemistry.

STATISTICS

We estimated the expected number of cancers by using incidence data from the cancer registry and a specially developed computer program, CANEST (CANCER ESTimates).[5] The programme calculated the risk of cancer for each patient individually. The calculation was based on incidence data for the years between the first diagnosis of dermatitis herpetiformis and 1987 or

death if the patient died before 1987. Information about deaths in the cohort was obtained from the Swedish Cause of Death Registry. Total risk was calculated from the sum of the individual risks. The relative risk of cancer, which is the ratio between observed and expected numbers of malignancies, was used to assess the risk of cancer. The observed numbers of cancers in the cohort were obtained from the cancer registry. We assumed that the distribution was normal and calculated 95% confidence intervals accordingly.[6] This method has been described elsewhere in detail.[5] A result was considered significant when the lower limit of the 95% confidence interval exceeded 1·0.

All statistics that were not carried out with the CANEST program and tabulations were processed with the SPSS statistical package.

Results

Among the 976 patients with dermatitis herpetiformis, 106 cancers were diagnosed in 94 patients at the same time or after dermatitis herpetiformis was first diagnosed. The relative risk was 1·4 (95% confidence interval 1·1 to 1·7) in male patients and 1·2 (0·8 to 1·7) in female patients. This increase in risk was not significant when we excluded lymphomas. When we analysed individual cancer sites we found a significant increase only for malignant, non-Hodgkin's lymphoma in males (relative risk 6·4; 2·7 to 12·5). Table II summarises these results. The total number of lymphomas diagnosed in this group of patients (before and after diagnosis of dermatitis herpetiformis) was 14. Original paraffin blocks (in one case cytological material) of 12 of the 14 tumours diagnosed as lymphoma were made available to us. We reviewed this material and carried out immunoperoxidase studies with antibodies of leucocyte common antigen (LCA), B cell antigen CD20 (L26, Dako), and T cell antigen CD45RO (UCHL1, Dako). One of the 14 cases was on review found to be a carcinoma, leaving 13 cases of lymphoma. The mean time lag between the first admission to hospital and the diagnosis of lymphoma was 4·6 years, and the mean age at diagnosis of lymphoma was 79·6 years. Table III summarises the characteristics of these 13 cases.

TABLE II—*Observed and expected numbers of malignancies in 976 patients with dermatitis herpetiformis*

	Male patients		Female patients	
Site of malignancy	Observed/ expected	Relative risk (95% confidence interval)	Observed/ expected	Relative risk (95% confidence interval)
All sites	71/52	1·4 (1·1 to 1·7)	35/29	1·2 (0·8 to 1·7)
Non-Hodgkin's lymphoma	7/1·3	5·4 (2·2 to 11·1)	3/0·7	4·5 (0·9 to 13·2)

Discussion

The association between dermatitis herpetiformis and lymphoma was first proposed in 1970, when Gjone and Nordöy described a patient with dermatitis herpetiformis and lymphoma.[7] Since then several cases of dermatitis herpetiformis and malignancy, particularly lymphomas, have been reported.[8-10] At least six series have reported on the incidence of lymphomas among patients with dermatitis herpetiformis. Although not confirmed in all studies, there seems to be an increased incidence of lymphomas in patients with dermatitis herpetiformis (table IV). In the only study in which relative risks have been calculated a risk of 100 for developing lymphoma was found and a risk for cancer on the whole was 2·4.[1]

TABLE IV—*Incidence of lymphoma in series of patients with dermatitis herpetiformis*

Study	Years in which data were collected	No of patients	No (%) of lymphomas observed
Davis *et al*[13]	?	42	1 (2·4)
Leonard *et al*[1]	1969-81	109	3 (2·8)
Buckley *et al*[14]	1954-80	119	1 (0·8)
Gawkrodger *et al*[15]	1971-81	76	2 (2·6)
Christiansen *et al*[2]	1979-83	96	0
Reunala *et al*[9]	1969-84	499	5 (1·0)
Present study	1964-83	976	14 (1·3)

Our study confirms the increased risk of lymphoma, although the relative risk seems much lower (6 *v* 100) than in the study of Leonard *et al.*[1] Interestingly, the ratio of patients with lymphoma is not so different (1·3% *v* 2·8%). They estimated the incidence of lymphoma by using figures from the 1976 cancer registry for the whole study period, but we calculated the incidence individually for each patient by using data on incidence specific for age and date for the corresponding years. Obviously the quality of the incidence data used to calculate the expected number of malignancies is as important as the observed number of cancers. In our study the estimated number of cancers is reliable as since 1958 the cancer registry has provided yearly incidence figures which allow for accurate estimations of cancers.

The increased risk of lymphoma in the gastrointestinal tract of patients with dermatitis herpetiformis is probably the result of a polyclonal stimulation of lymphocytes by gluten that causes transformation into a malignant clone. If this is true patients on a gluten free diet probably have a lower risk of developing a lymphoma. Interestingly, however, in our study most lymphomas were found outside the gastrointestinal tract and most were of B cell phenotype. Only one case could thus be classified as T cell lymphoma associated with enteropathy as defined by O'Farrelly *et al.*[11] This must be clarified in future studies. We found an

TABLE III—*Characteristics of 13 patients with dermatitis herpetiformis and lymphoma*

Case No	Age (years) at first admission for dermatitis herpetiformis	Sex	Time lag between first admission and diagnosis of lymphoma (years)	Survival (years) after diagnosis of lymphoma	Classification of lymphoma	Phenotype	Site
1	78	M	5	0	Immunoblastic	B	Widespread extranodal, including small intestine
2	68	M	<1	1	NA	NA	NA
3	62	M	4	1	Immunoblastic	T	Nodal
4	54	M	3	Alive	Large cell	B	Appendix
5	63	M	8	0	Small lymphocytic (histology NA*)	NA	Nodal
6	65	F	4	1	Immunoblastic	T	Small intestine
7	65	F	3	1	NA	NA	NA
8	62	F	<7	10	Large cell	Null	Colon
9	63	M	13	Alive	Large cell	B	Skin
10	73	F	0	12	Unclassified (cytology)	NA	Nodal
11	62	M	1	0	Large cell	B	Skin
12	66	M	8	0	Small lymphocytic	B	Nodal
13	63	M	<6	11	Small lymphocytic	Null	Nodal

NA=not available. Null=Non-B, non-T.

Clinical implications

- Patients with dermatitis herpetiformis have long been thought to have an increased risk of developing cancer
- This study found that non-Hodgkin's lymphoma seemed to be the only cancer significantly more common in such patients
- Male patients were at greater risk than female patients
- Patients with dermatitis herpetiformis should be checked regularly for signs of lymphoma

average time lag of 4·5 years between the first admission to hospital and diagnosis of dermatitis herpetiformis and the subsequent diagnosis of lymphoma. If the time is calculated from the first appearance of symptoms it is probably longer, and this is supported by published case reports in which the mean time between diagnosis of dermatitis herpetiformis and lymphoma is much longer, as long as 14 years.[12] Many of the patients in our study may have had dermatitis herpetiformis for some time before the first admission for the condition. The same probably applies to the mean age of our patients, which is much higher than that previously reported (65 *v* 54). The mean age at diagnosis of lymphoma is high, and there is a high mortality after diagnosis.

Our findings show that patients with dermatitis herpetiformis have a moderately increased risk of cancer compared with the general population. If lymphomas are excluded this risk does not exist. On the other hand, patients with dermatitis herpetiformis have a definite increase in risk of lymphoma. In these patients an extensive search for lymphoma at regular intervals is therefore warranted.

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Prediction of hypoxaemia at high altitude in children with cystic fibrosis

P J Oades, R M Buchdahl, A Bush

Abstract

***Objective*—To assess the usefulness of a hypoxic challenge in a laboratory at sea level in predicting acute desaturation at altitude in children with lung disease.**

***Design*—Comparison of responses to hypoxic challenge in different settings.**

***Subjects*—22 children (12 boys) aged 11 to 16 years with cystic fibrosis in whom the mean forced expiratory volume in one second was 64% (range 24-100%).**

***Setting*—Lung function laboratory, the Alps, and aboard commercial jet aircraft.**

***Main outcome measures*—Spirometric lung function at sea level and finger probe oximetry with air and 15% oxygen. Oximetry during high altitude flight and on a mountain at altitude of 1800 m.**

***Results*—Significant desaturation (range 0 to 12%) occurred with all hypoxic challenges ($P < 0{\cdot}002$). The best predictor of hypoxic response from a single reading was the laboratory test ($r^2 = 76\%$ for flight and $r^2 = 47\%$ for mountain altitude), but the mean errors of prediction were not clinically significantly different. In six children who showed the greatest desaturation the laboratory test overestimated desaturation, but other predictors underestimated desaturation in three by up to 5%.**

***Conclusions*—The laboratory hypoxic challenge directly predicted the worst case of desaturation during flight and at equivalent high altitude. Spirometry and baseline oxygen saturations may underestimate individual hypoxic response. The test may have wider applications to other patients with stable chronic lung diseases, particularly in determining who needs supplementary oxygen during air travel and who should be advised against holidays at high altitude.**

Department of Paediatrics, Royal Brompton National Heart and Lung Hospital, Sydney Street, London SW3 6NP
P J Oades, *paediatric registrar*
R M Buchdahl, *honorary senior lecturer*
A Bush, *senior lecturer in paediatric respiratory medicine*

Correspondence to:
Dr Oades.

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Introduction

As altitude increases the partial pressures of inspired gases fall. This results in lower alveolar partial pressures of oxygen and a risk of hypoxaemia. Thus healthy children living at high altitude have lower oxygen saturations than those at sea level.[1] The hazards to patients with cystic fibrosis with hypoxic lung disease of holidaying at high altitude have been described.[2] Additionally, although cabins of commercial aircraft are pressurised during flight at high altitude, the cabin altitude is still between 1525 and 2134 m,[3] equivalent to breathing down to 15% oxygen at sea level. Passengers with obstructive lung disease may already have low alveolar partial pressures of oxygen and are therefore more prone to serious desaturation during flight.[4] We examined whether desaturation at altitude and hence a requirement for additional inspired oxygen could be predicted from spirometry, oxygen saturations, and a hypoxic challenge at sea level.