Lichen planus and liver diseases: a multicentre case-control study

Gruppo Italiano Studi Epidemiologici in Dermatologia (GISED)

Abstract

***Objective*—To assess the association of lichen planus with liver complaints and with known aetiological factors of liver diseases.**

***Design*—Multicentre case-control study. Interviews were conducted by trained medical investigators on the basis of a structured questionnaire. At the interview patients and controls were asked for consent to blood samples being taken to determine transaminase activities and the presence of hepatitis B virus surface antigen.**

***Setting*—Outpatient departments of 27 Italian general and teaching hospitals that were collaborating in the Gruppo Italiano Studi Epidemiologici in Dermatologia (GISED).**

***Subjects*—Incident cases and controls were eligible. A total of 577 patients with lichen planus and 1031 controls with dermatological diseases other than lichen planus were interviewed. Less than 1% of the people contacted refused to participate. Patients and controls were matched for sex and age in five year intervals.**

***Results*—The risk of lichen planus was higher in patients with a history of liver diseases requiring hospital admission or specialist consultation (relative risk=1·6; 95% confidence interval=1·2 to 2·2), those who had had liver biopsy (5·5; 1·9 to 15·6), and those with a history of viral hepatitis (1·9; 1·1 to 3·1). High activities of liver enzymes and positive results of tests for hepatitis B virus surface antigen were also associated with lichen planus. The association with alcohol consumption was not clearly confirmed by a dose-risk relation.**

***Conclusion*—This study adds quantitative epidemiological evidence to the clinical observation that liver disease is a risk factor for lichen planus although not a specific marker of it.**

Introduction

Lichen planus is a relatively common benign disease. Its clinical features are characteristic and affect both skin and mucous membranes. Skin lesions vary according to their location, being flat papules on the flexor surface of the wrist, verrucous lesions on the shin, and alopecic patches that leave scars on the hairy regions. Mucosal lesions are more uniform and usually present as whitish striae and, occasionally, as erosions. Results of histopathology are distinctive, with a band like lymphocytic infiltrate in the upper dermis that attacks the basal cell layer, destroying the normal architecture of the epidermis.[1] Thickening of the malpighian bodies, especially in the granular layer, is an additional feature. The aetiology of lichen planus is largely unknown. Its association with HLA -BW16, B8, and DR1 suggests the possibility of genetic predisposition.[2] HLA-DR1 is concerned in regulation of the immune response, and lichen planus has been found to be clinically associated with some immune related diseases, such as myasthenia gravis, ulcerative colitis, hypogammaglobulinaemia, thymoma, and alopecia areata.[3-7] To our knowledge there are, however, no clear epidemiological data on this issue.[8]

In recent years attention has been drawn to the possible association of lichen planus with chronic liver diseases—namely, primary biliary cirrhosis and chronic active hepatitis.[9-15] Initially considered as an adverse reaction to penicillamine used to treat primary biliary cirrhosis, lichen planus was later reported to be associated with primary biliary cirrhosis independently of the drug. Evidence for an association with chronic active hepatitis is as controversial now as it was after the first short series of patients with lichen erosivus and liver cirrhosis was described. The overall prevalence of chronic active hepatitis in patients with lichen planus varies in different studies from 11·3%[11] to 0·1%.[14]

In view of these uncertainties we did an epidemiological study of lichen planus. The aim of the study, in which 27 dermatological centres in Italy that were collaborating in the Gruppo Italiano Studi Epidemiologici in Dermatologia participated, was to assess the association of lichen planus with liver complaints and with known aetiological factors of liver diseases.

Subjects and methods

This multicentre case-control study was carried out in the outpatient departments of 27 Italian general and teaching hospitals: 17 were located in northern Italy (75·4% of the patients and 76·7% of the controls) and 10 in central and southern Italy (24·6% of the patients and 23·3% of the controls).

Between September 1986 and December 1987 trained medical interviewers identified and questioned patients with lichen planus and controls by using a structured questionnaire. The interviewers had had biomedical training and had experience in medical interviewing; the study coordinators reviewed each interviewer's report to evaluate the completeness and internal consistency of the data collected.

Information was obtained on sociodemographic factors and personal characteristics and habits (including smoking habits and alcohol consumption) and medical history of liver disorders, including data on any specialist consultations or hospital stays for liver complaints, a blood transfusion, or acute viral hepatitis.

We computed the average consumption of alcohol each day for patients and controls assuming a comparable pure alcohol content in each type of drink (that is, 150 ml of wine=330 ml of beer=30 ml of spirits= 10-12 g of pure alcohol). Wine accounted for more than 90% of all of the alcohol consumed in this population.

At the interview patients and controls were asked for consent to blood samples being taken to determine alanine aminotransferase and aspartate aminotransferase activities and the presence of hepatitis B virus surface antigen. Oral informed consent was obtained from each subject before data or samples were collected.

The patients had been diagnosed consecutively in the participating centres as having lichen planus (incident cases). Histopathological sections stained with haematoxylin-eosin were required in patients with lesions confined to the mucosae, lichen planus verrucosus, and lichen planopilaris and were reviewed by a dermatopathologist (GZ). A total of 577 patients aged 15-85 (median 50) years were interviewed; 528

A full list of participating centres and investigators is given at the end of this paper.

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(91·5%) had lichen planus of the skin or the mucous membranes, 18 (3·1%) erosive lichen planus of mucous membranes, 15 (2·6%) hypertrophic lichen planus, and 16 (2·8%) other varieties of lichen planus. Only four of the patients initially ontacted refused the interview. The controls were the first two patients of the same sex and in the same five year age category seen for a dermatological complaint (that they had not had diagnosed previously) in the same centre after a patient with lichen planus. In six centres, however, only one control was selected for each of 123 patients. If a control refused the interview the next eligible subject was selected. Only nine controls refused to participate. Subjects were not included if they were attending for autoimmune disorders or for other diseases associated with liver dysfunction (for example, lupus erythematosus, porphyria cutanea tarda). In all, 1031 controls, aged 16-88 (median 47) years, were included in the analysis; 233 had been examined for eczema, 124 for pityriasis rosea, 106 for urticaria, 88 for psoriasis, 78 for neoplastic diseases, 65 for exanthema, 51 for skin infections, 24 for burns, and 262 for other skin diseases. Table I gives the distribution of patients and controls according to age and sex.

TABLE I—*Number (percentage) of patients with lichen planus (n=577) and controls (n=1031) according to age and sex*

	Patients	Controls
Men	296 (51·3)	529 (51·3)
Women	281 (48·7)	502 (48·7)
Age (years):		
<20	29 (5·0)	90 (8·7)
20-49	286 (49·6)	497 (48·2)
≥50	262 (45·4)	444 (43·1)

We derived the relative risks of lichen planus, together with their 95% confidence intervals,[16] from data stratified for age and sex by the Mantel-Haenszel procedure.[17] Furthermore, to allow simultaneously for the effects of differences among the centres and several potential confounding factors we used unconditional multiple logistic regression, fitted by the method of maximum likelihood.[18] Estimates derived from unconditional regression are probably conservative compared with those obtained using the matched approach. The differences, however, are generally negligible, and the analysis included several variables that were not considered in the matched design. Therefore we chose to use analyses that disregarded matching for age and sex. Included in the regression equations were terms for age, sex, centre, education, alcohol consumption, smoking habits, blood alanine aminotransferase and aspartate aminotransferase activities, presence of hepatitis B virus surface antigen, history of liver diseases, results of liver biopsy, and presence of acute viral hepatitis.

Results

Table II shows the distribution of patients and controls according to history of liver complaints requiring a specialist consultation or hospital stay or liver biopsy; the corresponding relative risks were 1·6 (95% confidence interval 1·2 to 2·2) and 5·5 (1·9 to 15·6). The risk of lichen planus was also increased in patients with a history of acute viral hepatitis (relative risk 1·9; 1·1 to 3·1). In the patients, chronic active hepatitis was diagnosed (and confirmed by the results of histology) in three patients and primary biliary cirrhosis was diagnosed in only one; in the controls one diagnosis of chronic active hepatitis and one of primary biliary cirrhosis were reported. These differences were not significant. The results of liver biopsy also gave the following diagnoses: fatty liver infiltration (four patients and one control), cirrhosis (five patients and two controls), acute hepatitis (two patients), and hepatic carcinoma (one patient).

TABLE II—*Relative risks of lichen planus according to liver diseases and having had liver biopsy**

	Patients	Controls	Relative risk† (95% confidence interval)
Liver disease	124/577	138/1022	1·6 (1·2 to 2·2)
Liver biopsy	16/571	5/1000	5·5 (1·9 to 15·6)
Acute viral hepatitis	35/574	36/1029	1·9 (1·1 to 3·1)

* Data were missing for some patients and controls.
† Estimates from multiple logistic regression equation, including terms for age, sex, centre, education, alcohol consumption, and smoking habits.

Results of assays of alanine aminotransferase and aspartate aminotransferase activities and of tests for hepatitis B surface antigen (table III) were consistent with the above findings. In subjects with raised alanine aminotransferase and aspartate aminotransferase activities (≥50 U/l) the relative risk of lichen planus was about twice that in subjects with normal activities (<50 U/l), the values being 1·9 (95% confidence interval 1·3 to 2·7) and 2·1 (1·3 to 3·6) for the two enzymes respectively. In subjects positive for hepatitis B virus surface antigen the estimated relative risk, compared with those with a negative test result, was 1·8 (1·0 to 3·2).

TABLE III—*Relative risks of lichen planus according to alanine aminotransferase and aspartate aminotransferase activities and result of test for hepatitis B surface antigen**

	Patients	Controls	Relative risk† (95% confidence interval)
Alanine aminotransferase ≥50 U/l	70/577	69/1030	1·9 (1·3 to 2·7)
Aspartate aminotransferase ≥50 U/l	36/577	26/1030	2·1 (1·3 to 3·6)
Positive for hepatitis B surface antigen	26/561	27/1008	1·8 (1·0 to 3·2)

* Data were missing for some patients and controls.
† Estimates from multiple logistic regression equation, including terms for age, sex, centre, education, alcohol consumption, and smoking habits.

Table IV presents the relation between alcohol consumption and lichen planus. The proportion of those who ever drank alcohol was slightly higher in patients (73·8% of patients *v* 68·6% of controls), but there was no evidence of a dose related risk. The estimated relative risk of lichen planus was 1·4 for subjects who reported drinking one or two alcoholic drinks each day and 1·4 for those who drank three or more; the trend in risk was not significant.

TABLE IV—*Relative risks of lichen planus according to alcohol consumption**

Average consumption of alcohol (drinks per day)†	Patients	Controls	Relative risk‡ (95% confidence interval)
Never or occasional	147	316	
1-2	264	434	1·4 (1·1 to 1·7)
≥3	150	258	1·4 (1·0 to 1·9)

χ^2=3·2; p=0·07.
* Data were missing for 16 patients and 23 controls.
† 1 drink=150 ml of wine=330 ml of beer=30 ml of spirits=10-12 g of alcohol.
‡ Estimates from multiple logistic regression equation, including terms for age, sex, centre, education, smoking habits, and history of liver diseases.

Discussion

Our results provide quantitative epidemiological backing for the suggested clinical relation between liver diseases and lichen planus.[11 19-28] A self reported history of a liver complaint (that is, acute viral hepatitis or a hospital stay or specialist referral for liver disorders), raised alanine aminotransferase and aspartate

aminotransferase activities, and a positive result for hepatitis B virus surface antigen about doubled the risk of lichen planus. A history of having had liver biopsy gave an estimated risk of lichen planus of about five.

Potential sources of bias should be considered in interpreting these findings. Data were collected in 27 different centres and patients and controls were drawn from hospitals and institutions covering comparable catchment areas, the rate of participation was almost complete, and a detailed inspection of the data showed that the association was consistent in various centres and geographical areas. It is unlikely that the cutaneous disease of the patients and controls influenced the reporting of liver disease; recall bias can hardly affect such variables as whether the patient had had a hospital stay, liver biopsy, or history of viral hepatitis, and the possible relation between lichen planus and liver diseases was probably not known to the subjects interviewed. The association was confirmed by the results for alanine aminotransferase and aspartate aminotransferase activities and positive results for hepatitis B virus surface antigen at the time of the interview. These findings could also hardly be explained by confounding, as allowance for major potential distorting factors (including socioeconomic state and alcohol consumption) did not appreciably change the estimated relative risks. As our controls had dermatological conditions they were comparable with the patients in relation to major determinants for seeking medical advice. Studies have suggested that psoriasis might be associated with alcohol consumption and liver diseases[29 30]; the inclusion of controls with psoriasis in our study may, therefore, have tended to cause any association with these variables to be underestimated. Analysis of our data excluding these controls did not, however, change the estimated relative risks. Finally, it is reassuring that the association was stronger for the strongest clinical variable (history of liver biopsy), although the number of subjects was small.

The association of lichen planus with liver diseases has already been suggested chiefly on the basis of anecdotal reports or clinical series. Rebora and Rongioletti, in a retrospective study, contacted 44 patients who had been managed over 26 years in their dermatological unit. In all, 11·3% of their patients with lichen planus had had chronic active hepatitis, exceeding the expected prevalence of chronic liver disorders in their geographical area.[11] In a study from the Mayo Clinic 24 patients with primary biliary cirrhosis and lichen planus were identified, seven of whom had not been treated with penicillamine.[28] The same research group was not able to confirm the association of lichen planus with chronic active hepatitis observed by Rebora and Rongioletti. Based on a computerised review of cases of lichen planus seen over 31 years, they found that only four patients (0·1% of the total number seen) had had chronic active hepatitis diagnosed at any time during that period.[14] Korkij *et al*, in a case-control study of 136 patients with lichen planus and 272 controls, observed an excess of liver abnormalities in the patients, three of whom had chronic active hepatitis.[22]

Our study was focused on a broad spectrum of liver abnormalities in patients with lichen planus. We confirmed the association of lichen planus with liver diseases. Clinically, however, liver disease in such patients is difficult to define, escapes specific diagnosis, and extends over a long period, explaining the excess number having had liver biopsy.

Our data are difficult to interpret biologically as the association between lichen planus and liver disorders apparently is not restricted to a single specific aetiological factor, and liver disorders in our study were a poorly defined entity. Moreover, the association with liver disease is relatively limited in terms of relative risks (between 1·5 and 2 for various indicators), and hence, in terms of attributable risk, it could explain only a small fraction of the cases of lichen planus (about 10%). Thus other factors probably play a part in the pathogenesis of the disease. Even though hepatitis B virus surface antigen was associated with lichen planus, it is difficult to accept that lichen planus is one of the clinical expressions of hepatitis B virus infection. In fact, the increased risk of lichen planus in patients with liver disorders (high transaminase activities) was still significant after adjustment for a positive result for hepatitis B virus surface antigen and a history of viral hepatitis (data not presented). We suggest that there may be an indirect relation, for instance, between lichen planus and other hepatotropic viruses that are possibly transmitted in a way similar to hepatitis B virus such as non-A non-B hepatitis, cytomegalovirus, and Epstein-Barr virus. Lichen planus could be a stereotypic cell mediated reaction to either a specific virus or several viruses, some of them hepatotropic.

Alcohol consumption seems to be associated to some extent with lichen planus. The risk did not, however, increase with increasing exposure. Alcohol may be a cofactor in inducing hepatic damage, but our finding may have been due to a poorly controlled confounding effect.

A reaction very similar to lichen planus is observed in chronic graft versus host disease,[31] biopsy specimens of the liver showing various changes. Initially, mixed inflammatory cells, consisting predominantly of lymphocytes, infiltrate the portal zones; later, portal fibrosis develops, leading to bile duct atresia. Chronic graft versus host disease that occurs after a period of engraftment seems to be produced by cells that differentiate within the host and to be a syndrome of disordered immune regulation with features of immunodeficiency and autoimmunity.[32 33]

Although these biological interpretations seem at present too vague or speculative to provide plausible explanations for our epidemiological observations, their uncertainties do not eclipse the findings of this study—that is, the association between various indicators of liver disease and the risk of lichen planus.

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Analysis of serial measurements in medical research

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Abstract

In medical research data are often collected serially on subjects. The statistical analysis of such data is often inadequate in two ways: it may fail to settle clinically relevant questions and it may be statistically invalid. A commonly used method which compares groups at a series of time points, possibly with *t* tests, is flawed on both counts. There may, however, be a remedy, which takes the form of a two stage method that uses summary measures. In the first stage a suitable summary of the response in an individual, such as a rate of change or an area under a curve, is identified and calculated for each subject. In the second stage these summary measures are analysed by simple statistical techniques as though they were raw data. The method is statistically valid and likely to be more relevant to the study questions. If this method is borne in mind when the experiment is being planned it should promote studies with enough subjects and sufficient observations at critical times to enable useful conclusions to be drawn.

Use of summary measures to analyse serial measurements, though not new, is potentially a useful and simple tool in medical research.

Introduction

A common study design in medical research is to give patients some intervention and then observe what happens to them over time. For example, blood glucose concentrations may be measured several times after a glucose drink. In many cases there may be more than one group of patients, possibly randomised to different treatments. Despite its apparent simplicity the analysis of this form of study presents statistical problems which, judged from published work, are not widely appreciated. The purpose of this paper is to propose a general simple method for a clinically useful and statistically valid analysis. We consider only studies in which each patient receives a single treatment or intervention, so excluding escalating dose studies or crossover trials which require more complicated analysis. Though we also restrict attention to outcome variables that are quantitative because these occur most commonly, the methods can also be applied to ordered data such as pain scores.

Types of time dependency

It is helpful to distinguish two main ways in which the outcome variable may change with time.

Peaked—In many studies the outcome variable starts from a baseline (sometimes zero), rises to a peak, and then returns to baseline. This is displayed as a peaked curve (fig 1). For example, in a study of post prandial energy expenditure during pregnancy the metabolic rate was measured in women after a 12 hour fast and then at 30 minute intervals for two hours in response to a test meal.[1] This was done during pregnancy and again once lactation had stopped. The metabolic rate rose to a peak after about 60 minutes and then fell steadily. Women were found to have a reduced energy expenditure during pregnancy. In that study the interest lay in both the total response and the time to reach the maximum value.

Growth—Sometimes the outcome variable steadily increases or decreases with time and does not start to return to its initial value over the period of study. This is displayed as a growth curve (fig 1). A recent study investigated the role of peripheral vascular tone in