

Liver and biliary

Primary biliary cirrhosis in men

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SUMMARY To determine whether primary biliary cirrhosis differed in men and women we reviewed the presenting features and clinical course of 39 men and 191 women with primary biliary cirrhosis followed at this unit between 1970 and 1984. Age and severity of disease at time of diagnosis were similar in both groups. Pruritus was significantly less common in men than in women both at diagnosis and throughout the period of follow up ($p < 0.01$). The difference in incidence of pruritus at diagnosis was most evident when the male group were compared with a group of premenopausal women, an observation which is consistent with involvement of sex steroid metabolism in the origin of pruritus. Skin pigmentation was also less marked in men at diagnosis ($p < 0.05$). Autoimmune associated conditions, especially sicca syndrome, were more common in women. Survival was similar among men and women although hepatoma developed significantly more frequently in male patients ($p < 0.01$).

One of the most remarkable features of primary biliary cirrhosis is its rarity in men who in most series comprise less than 15% of cases.¹⁻³ The question as to whether men with primary biliary cirrhosis have the same pattern of disease as women has been the subject of one previous investigation only.⁴ Rubel and coworkers in a retrospective study in which the clinical and histological features of 30 men with primary biliary cirrhosis were compared with 30 women matched for age, found little difference between the two groups. With the use of such a small group of female patients, when the clinical spectrum of the disease is so wide, there may have errors consequent upon selection bias and furthermore the lack of follow up data prevented comparison of the course of the disease in affected men and women. In the present study we have compared the presentation and course of primary biliary cirrhosis in all men and women followed prospectively in this Unit over the past 15 years.

Methods

PATIENTS

Of the 230 patients with primary biliary cirrhosis, 39 (16%) were men. Criteria for diagnosis comprised a clinical presentation and histological picture

diagnostic of, or compatible with, primary biliary cirrhosis and a serum alkaline phosphatase greater than twice the upper limit of normal. Although not required for diagnosis, serum antimitochondrial antibodies were present (at a titre > 1 in 40) in 97% of men and 74% of women and serum IgM was raised in 75% of men and 80% of women. Two hundred and ten patients took part in prospective clinical trials.⁵⁻⁷ Of the men, seven received azathioprine, four received d-penicillamine, six received cyclosporin and 17 received a placebo, while among the women 41 received azathioprine, 40 received d-penicillamine, 27 received cyclosporin and 93 received a placebo. Twenty five patients were in two trials.

Symptoms and signs for the male and female groups were compared at the time when the diagnosis was first established. In order to investigate the possible influence of circulating sex hormones, the presenting symptoms of male patients were also compared separately with two subgroups of female patients: a premenopausal group of 18 women at or below the age of 40 years and 42 postmenopausal women with an age greater than or equal to 60 years at time of diagnosis.

STATISTICAL METHODS

The frequency of discrete and continuous variables was compared using the χ^2 test, and Student's *t* test respectively. Survival was estimated by life table analysis both from date on which the diagnosis was

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established and from the onset of symptoms (or in asymptomatic patients from first detected liver abnormality) and compared in the male and female patients using the log rank test.⁸

Results

The mean age at diagnosis was similar in men and women, 55 and 54 years respectively, with a similar wide range in each group. The distribution of early and advanced disease as shown by histological staging and by serum bilirubin was also similar (Table 1).

Comparison of symptoms and signs up to the time of diagnosis showed that pruritus had been present in significantly fewer men than women (45% vs 68%, $p < 0.01$) (Table 2). Although the frequency of pruritus increased progressively through the course of follow up, the difference between maximum percentage affected – 64% of men and 86% of women – remained statistically significant ($p < 0.01$). Pigmentation was also recorded at diagnosis less frequently in men than women (35% vs 55%, $p < 0.05$). There were no significant differences in the frequency, at diagnosis or subsequently, of jaundice, xanthomata, gastrointestinal haemorrhage, hepatomegaly, splenomegaly, or ascites. The median duration of symptoms before diagnosis was

Table 1 *Defining characteristics of male and female group at diagnosis*

	Men	Women
Patient (n)	39	191
Mean age in years at diagnosis and (range)	55 (32–70)	54 (30–77)
AMA	97%	74%
Serum IgM > 2 g/l	75%	80%
Serum bilirubin $\mu\text{mol/l}$		
Median and (range)	44 (3–192)	33 (4–390)
normal range < 15 $\mu\text{mol/l}$		
Serum bilirubin > 20 $\mu\text{mol/l}$	76%	70%
Serum alk phos IU/l		
Median and (range)	645 (102–1900)	640 (51–2100)
(normal range < 85 IU/l)		
Serum alk phos > 160 IU/l	92%	95%
Histological stage:		
I & II	41%	42%
III & IV	59%	58%
Median follow up	37 months	42 months
Mortality	22 (56%)	94 (49%)

Table 2 *Comparison of symptoms and physical findings at diagnosis, and associated conditions*

	Men	Women
<i>Symptoms</i>		
Pruritus (%)	45	68*
Jaundice	44	53
GI haemorrhage (%)	23	15
Asymptomatic (%)	23	12
<i>Signs</i>		
Pigmentation (%)	35	55†
Hepatomegaly (%)	89	95
Splenomegaly (%)	51	56
Ascites (%)	14	10
Xanthoma (%)	8	18
<i>Associated features</i>		
Sicca (%)	15	33†
Scleroderma (%)	8	13
Raynaud's phenomenon (%)	3	13
Fibrosing alveolitis (%)	3	2
Hyper/hypothyroidism (%)	5	8
Rheumatoid arthritis (%)	0	3

* $p < 0.01$

† $p < 0.05$.

12 months in men and 13 months in women with a wide range within both groups. Nine (23%) men and 22 (12%) women were without hepatic symptoms at the time of diagnosis ('asymptomatic primary biliary cirrhosis').

When the female patients were stratified into pre- and postmenopausal groups as defined and symptoms at diagnosis compared with those in male patients, there was a lower frequency of pruritus in men (45%) than in either female group (premenopausal 65%, postmenopausal 57%), although only with the premenopausal group did this difference achieve statistical significance ($p < 0.05$). Serum bilirubin concentrations were similar in premenopausal women (median 40 $\mu\text{mol/l}$, range 12–198) and men.

Associated autoimmune conditions occurred significantly less often in men than women (Table 2), whereas non-insulin dependent diabetes mellitus was found in significantly more men than women (13% and 3% respectively, $p < 0.01$).

SURVIVAL

Twenty two (56%) male and 94 (49%) female patients died and the survival curves of men did not differ significantly from that of women whether from date of diagnosis or recorded time of onset of symptoms (Figs 1 and 2). The 50% survival periods were similar for male and female patients being about eight years from onset of symptoms and just

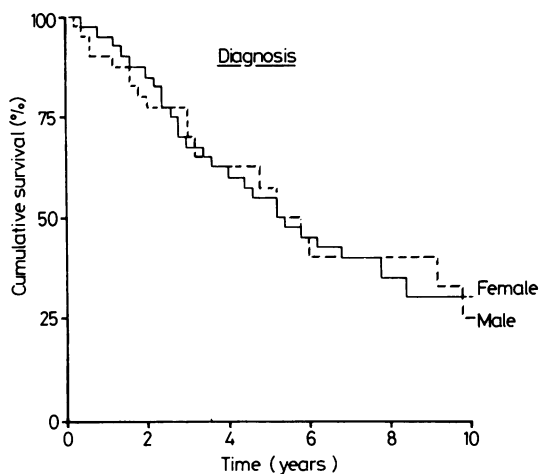


Fig. 1 Cumulative survival for male and female patients estimated from date of diagnosis.

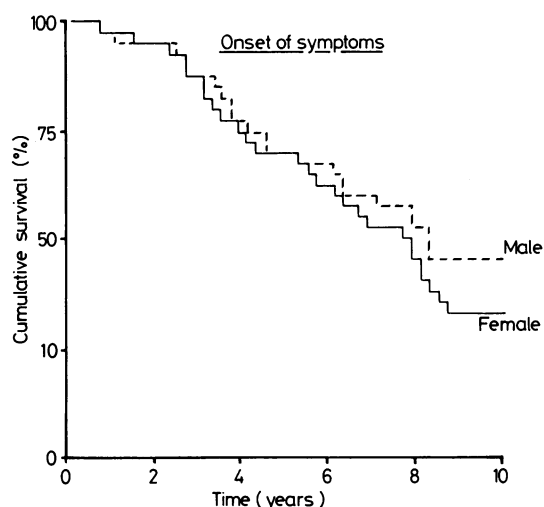


Fig. 2 Cumulative survival in male and female patients estimated from time of first symptoms recorded.

over five years from date of diagnosis in both groups. Hepatoma developed in four (10.3%) male and three (1.6%) female patients ($p < 0.01$). All those affected had stage IV liver disease at the time hepatoma first became apparent. The interval from diagnosis of primary biliary cirrhosis to diagnosis of hepatoma ranged from 18 to 120 months in the men and 0 to 66 months in the women.

Discussion

This study shows that at the time of diagnosis,

despite a similar severity of hyperbilirubinaemia and histological staging, pruritus was significantly less common in men than women with primary biliary cirrhosis, and this disparity between men and women persisted throughout the follow up period. Stratification of the female cohort according to age showed that young women in particular have pruritus at diagnosis. Other evidence that circulating sex steroids may contribute to the higher frequency of itching in women with primary biliary cirrhosis includes the clinical reports of primary biliary cirrhosis patients in whom pruritus began during pregnancy or whilst taking an oral contraceptive preparation.⁹ Some correlation of pruritus with increased serum bile acids has also been suspected¹⁰⁻¹² but whether this is a causal relationship is far from clear. The association is not an absolute one because pruritus with normal serum bile acids and raised serum bile acids without pruritus have been reported.¹⁰ It is unlikely that circulating sex steroids precipitate pruritus by increasing total serum bile acid concentrations. Indeed a reduction in total serum bile acids is reported after administration of exogenous sex steroids.¹³ Whether the occurrence of pruritus is affected by a more subtle interaction of circulating sex steroids and, for example, the unbound fraction of serum bile acids or the concentrations of individual bile acids is unknown.

In the present study pigmentation was also more frequent at diagnosis in women than in men. The pigmentation of the skin in primary biliary cirrhosis is caused by the increased deposition of melanin¹⁴ and Reynolds has suggested that this is due to scratching consequent on pruritus, and observing a pigment free area in the interscapular area which is difficult to reach.¹⁴ The increased incidence of pigmentation among the more pruritic group in the present study is consistent with this hypothesis.

The finding that autoimmune associated conditions were less common in men with primary biliary cirrhosis than women is not surprising in view of the known association of autoimmunity with female sex. The greater frequency non-insulin dependent diabetes mellitus in the male patients was an unexpected finding and has not been reported previously.

This study is the first to compare the clinical course of primary biliary cirrhosis in men and women and shows that notwithstanding the extreme female preponderance, there was no evidence that gender does affect survival. A number of the patients in the present series were on azathioprine, which has a moderate effect on survival,¹⁵ d-penicillamine and cyclosporin A, but the proportion of patients receiving these agents as opposed to a placebo agent was similar in both the male and female group. The occurrence of hepatoma in

primary biliary cirrhosis and its significantly increased frequency in men with primary biliary cirrhosis has been reported previously by us.^{16,17} There is no evidence that patients receiving either azathioprine or cyclosporin are at greater risk of developing hepatocellular carcinoma than the control patients.^{7,15} All of the patients had an established cirrhosis and it is presumably because hepatoma is a complication of end stage liver disease that overall survival in men is not affected despite its greater predilection for that gender.

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