

Low prevalence of primary biliary cirrhosis in Victoria, Australia

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Abstract

A prevalence study of primary biliary cirrhosis was carried out in the state of Victoria, Australia, by means of a mail survey of specialist physicians and a review of hospital records. Eighty four cases were identified, giving a prevalence of 19.1 per million population (95% confidence limits (CI) 15.3, 23.7), which is among the lowest in published reports. The prevalence in the Australian born, at risk population (women over the age of 24) was 51 per million (95% CI 37.5, 67.9). Both these figures are considerably lower than those in populations of similar age distribution in the UK and northern Europe. Since most Victorians are descended from British or European settlers, the low prevalence of primary biliary cirrhosis in this study supports the hypothesis that local environmental factors may be important in the pathogenesis of this disease.

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Primary biliary cirrhosis (PBC), although an uncommon disorder, has been described in most ethnic groups and nationalities. Studies of prevalence in different countries and regions have generated widely varying results,¹⁻⁷ ranging from <10 to 154 per million of the population (Table). This has led to the suggestion that an environmental agent may be an aetiological factor in PBC, and that this may be more important than genetic predisposition.^{1 8-10}

This study, conducted in the state of Victoria, is the first to examine PBC prevalence in Australia. Victoria is the second most populous Australian state (4.39 million people). From the first white settlement until

the second world war most immigrants came from Great Britain and Ireland. Since the 1950s there has been a high rate of immigration from many regions, including the United Kingdom, southern Europe, and more recently South East Asian countries and the Indian subcontinent. Thus, there are substantial populations from different ethnic groups.

Besides providing an overall figure for the prevalence of PBC in Victoria, this study gave us the opportunity to compare prevalence in different ethnic groups in this environment, and to compare our data with those published from overseas. In this way we were able to gain further insight into the relative importance of genetic and environmental influences in the aetiology of PBC.

Methods

The study was approved by the ethics committees of each of the hospitals that allowed access to patient records, and conformed to the National Health and Medical Research Council's Guidelines on Privacy of Information. Population statistics were obtained from the Australian Bureau of Statistics, Collins Street, Melbourne, Victoria 3000 and the Australian Bureau of Immigration Research, Carlton, Victoria, 3053.

In the first phase of the study we wrote to all consultant physicians in Victoria who were thought likely to be caring for, or to have been consulted on, patients with PBC. These comprised all hospital specialist physicians with an interest in hepatology, gastroenterology, or rheumatology, and all general physicians. A total of 216 consultants were contacted. A further survey of Victorian dermatologists at their regular regional meeting identified only three cases, all of whom had already been identified in the first phase of the study.

In the initial mail survey doctors were asked if they had had any PBC patients under their care in the period 1.11.90 to 31.01.91, and, if so, how many. Non-respondents were contacted by telephone. In the second phase of the survey those doctors who had indicated that they were caring for PBC patients were sent a questionnaire about each of their patients. The information requested included the patient's initials, sex, date of birth, country of birth, age when they came to Australia, date of presentation, domicile at the time of presentation, symptoms at presentation, most recent liver function tests (LFTs), anti-mitochondrial antibody result, liver biopsy result if performed, clinical course (well/worsening/ill), and any further comments. Non-respondents were

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Prevalence of primary biliary cirrhosis and methods of case ascertainment in previous epidemiological studies, compared with the present study

Study	Year	Cases (no)	Prevalence per million	Methods
Sheffield	(1) 1980	34	54	PS*, AMA†
Malmö, Sweden	(2) 1984	33	92	HR‡
EASL	(3) 1984	569	5-75	PS
Orebro, Sweden	(4) 1985	36	128	AMA
Newcastle, England	(5) 1989	347	154	PS, AMA, HR
Ontario, Canada	(6) 1990	206	22	PS
Umeå, Sweden	(7) 1990	86	151	PS, AMA, HR
Victoria, Australia	1993	84	19	PS, AMA, HR

*PS=post-al survey of physicians, †AMA=follow up of positive anti-mitochondrial antibody tests, ‡HR=review of hospital records.

contacted by telephone and encouraged to return their questionnaires.

Patients were regarded as definitely having PBC if their anti-mitochondrial antibody result was positive, liver function tests were cholestatic, and liver biopsy was consistent with the diagnosis. They were classified as probable PBC if no biopsy was available but the anti-mitochondrial antibody test was positive and liver function tests were cholestatic. Patients who had undergone liver transplantation for PBC ($n=2$) were excluded.

We also surveyed the coded hospital discharge summaries of all seven of Victoria's major teaching hospitals (Alfred Hospital, Austin Hospital, Heidelberg Repatriation Hospital, Prince Henry's Hospital, Royal Melbourne Hospital, St Vincent's Hospital, and Western Hospital) for all patients with the diagnosis of biliary cirrhosis. Records were available at the hospitals for the following periods: Alfred Hospital 1983–90, Austin Hospital 1983–90, Heidelberg Repatriation Hospital 1974–90, Prince Henry's Hospital 1981–91, Royal Melbourne Hospital 1979–90, St Vincent's Hospital 1980–90, Western Hospital 1986–90. Where patients with definite or probable PBC were found, the records were examined to verify the diagnosis and to ensure that patients were alive at the time of the survey. Where patients had been discharged or lost to follow up before the survey period we obtained up to date information by contacting their local medical officer. At two hospitals (Heidelberg Repatriation and Austin Hospitals), it was possible to identify from laboratory records all patients who had tested positive for anti-mitochondrial antibodies since 1980.

Prevalence rates among the patient groups were compared by χ^2 test. To avoid the potential confounding influence of age, the method of indirect standardisation was used.¹¹ Ninety five per cent confidence intervals of prevalence rates were obtained from Poisson distribution tables.¹²

Results

CASE ASCERTAINMENT

In the postal survey, 211 doctors responded (98%), 47 of whom were currently caring for 59 PBC patients. A further 25 patients were detected by surveying hospital records, giving a total of 84. No additional cases were detected by the follow up of patients with positive anti-mitochondrial antibody results at the Heidelberg Repatriation Hospital or Austin Hospital. Seventy one patients had definite PBC and 13 probable PBC, giving a prevalence of 15.5 (definite) to 19.1 (total) per million (95% confidence intervals (CI) 15.3, 23.7). In accordance with the known predominance of PBC in women, there were 77 women and seven men with the disease. Ages ranged from 38 to 86 years. Most cases (57 of 84) had been diagnosed in Melbourne or its suburbs which reflects the urban concentration of the population in this state (Melbourne population approximately 2.9 million). There did not

seem to be any geographical clustering of cases within or outside Melbourne.

CLINICAL PRESENTATION

Clinical information at the time of diagnosis was available for 76 of the 84 patients. Twenty seven (36%) were asymptomatic at diagnosis and had been detected because of abnormal liver function tests. All except three of these patients remained well at the time of the survey, a mean of 4.5 years later (range 1–13). Forty nine patients (64%) were symptomatic at diagnosis and had presented on average 3.5 years (range 1–14) before the survey. At the time of the survey most of these patients were described as stable but six had deteriorated and five were described as ill.

PREVALENCE IN RACIAL GROUPS

Of the 84 cases, those born in Australia comprised 58% of the total ($n=49$), immigrants from the UK and Ireland 16% ($n=13$), and patients from the rest of the world 26% ($n=22$; Germany 2 patients, Greece 3, Holland 1, Hungary 1, India 1, Italy 5, 'middle' Europe 1, Philippines 1, Poland 1, Russia 2, Turkey 2, Ukraine 1, USA 1). All immigrants had been diagnosed after arrival in Australia. Prevalence figures for the different ethnic groups were 14.8 per million (95% CI 11.0, 19.6) for the Australian born population, 47.4 per million (25.3, 81.1) for immigrants from the UK and Ireland and 27.4 per million (17.1, 41.4) for immigrants from the rest of the world. The prevalence among immigrants from the UK and Ireland was significantly higher than in the Australian born population, and immigrants from the rest of the world ($p<0.0002$). There is, however, a noticeable difference in age distribution of Australian born people compared with UK and Ireland immigrants. After correction for age, the differences in prevalence between the Australian born population and UK and Ireland immigrants were no longer statistically significant ($p=0.12$).

AGE SPECIFIC PREVALENCE

The youngest patient with PBC was aged 38 years. In the Australian born population the prevalence rate in the at risk group for PBC (that is, women >24 years) was 51 per million (95% CI 37.5, 67.9). In these Australian born women the prevalences in the age groups <35 , 35–44, 45–54, 55–64, and >64 were 0, 40, 38, 81, and 122 per million respectively. We considered that numbers were too small in the immigrant groups to calculate the age specific prevalence.

Discussion

The overall prevalence of PBC in the Victorian population, 19.1 cases per million, is among the lowest recorded (Table). It is similar to the prevalence of PBC in Ontario (22.4 definite cases per million), but well below the figures

reported from northern Europe and the UK (54–154 definite cases per million) (Table).

The approach to case ascertainment used in this study was similar to that used by Witt-Sullivan *et al*⁶ in Ontario, Canada, in that individual specialists likely to have cared for PBC patients were contacted by mail and, where necessary, by telephone. We also examined the records of all the major teaching hospitals over an appropriate period, and this yielded a further 25 patients. We did not have the opportunity to seek out all patients with positive anti-mitochondrial antibody tests in Victoria over this period, since, unlike the position in the UK where there are regional immunology laboratories,^{1,5} there is no reference laboratory for the state to which all such immunological tests are sent. While this might have meant that some cases of PBC were not included in our study, it was reassuring that the survey of anti-mitochondrial antibody results in two teaching hospitals over the 10 year period 1980–89 yielded no extra cases of PBC. The virtually complete (98%) response rate from physicians who were contacted provided further reassurance that we were unlikely to have missed a significant number of cases. Thirty six per cent of cases in the present study were asymptomatic at the time of diagnosis. This is very similar to the studies in the north east of England (32%),⁵ Sweden (37%),⁷ and Canada (29%).⁶ It is therefore unlikely that there was significant under-reporting of asymptomatic cases in our study.

Most of the data on the epidemiology of PBC come from studies conducted in European countries. The data in the Table show that there is a noticeable variation in the reported PBC prevalence in different countries and regions. The most striking examples of this apparent regional variation were found in the 1984 study conducted for the European Association for the Study of the Liver, in which the PBC prevalence in 32 European centres varied from as low as 5 per million in some to as high as 75 per million.³ While these findings must be interpreted with caution, since referral patterns and diagnostic facilities may have differed between centres, they support the view that either environmental or racial/genetic factors contribute to the pathogenesis of the condition.¹⁰ It has been suggested that one way of investigating this possibility further would be to compare the prevalence of PBC in European countries with those in other areas of the world with large populations of European origin, such as Australia and South Africa.¹⁰ The comparison between the Australian born population in the present study and the population in a contemporary UK study⁵ is particularly interesting, since most middle aged or elderly Victorians born in Australia are of Anglo-Irish descent.¹³ PBC prevalence in the at risk group of native born Victorians (women greater than 24 years old; 51 per million) is well below that in women aged greater than 18 years from north east England (276 per million).⁵ This lends support to the view that environmental factors may be important, since

both groups of women can reasonably be considered as deriving from the same gene pool.

One factor that must be taken into account in comparing the PBC prevalence in different geographical areas is the possibility that population age distributions differ. This is particularly important for PBC because it is predominantly a disease that affects women of middle and old age. Similarly, comparisons with historical data need to allow for ageing of the population and differences in life expectancy. Differences in the age profile cannot have accounted for the much lower PBC prevalence in the Australian born population than that reported from the United Kingdom since the age distribution of women in the two countries¹⁴ is very similar (age <35, 35–44, 45–54, 55–64, and 65–74; Victoria, 54%, 15%, 10%, 9%, 13% versus UK; 47%, 13%, 11%, 10%, and 18%). Furthermore, even in the subgroup of Victorian women with the highest prevalence of PBC (age >64, 122 per million), the prevalence is well below that in the total group of women aged more than 18 years in north-east England (276 per million). In Umea, Sweden, point prevalences for PBC of women aged 30–39, 40–49, 50–59, and 60–69 respectively were reported.⁷ These were 33, 257, 455, and 391 per million respectively. The prevalence figures for native born Victorian women from the current study were lower in all comparable age groups (0, 40, 38, 81, and 122 per million in women <35, 35–44, 45–54, 55–59, 60–64, and >64). Thus, comparisons of Australian born women within specific age groups with their contemporaries in northern Europe indicates that prevalence in Australia is diminished across all age groups.

Because there has been a large intake of migrants from the UK to Victoria in the past 50 years, this study also allowed us to examine the potential impact of a change of environment on expression of the disease. If environmental factors that favour the development of PBC are absent in Australia, immigrants might be expected to have a reduced prevalence of PBC compared to that in their native country. The current study indicates that this might be the case. The prevalence of PBC in female UK immigrants to Victoria aged greater than 24 years was 103 per million (53.4–180.7) compared to a prevalence of 276 per million in women aged greater than 18 living in England.⁵ Although the confidence limits for the prevalences in the immigrant population indicate significant differences from the UK population, the immigrant group is relatively small and this necessarily makes statistical comparisons subject to uncertainty.

It will be of interest to extend this study to the rest of Australia and to repeat the present study in the future to determine whether the differences in prevalence are maintained between Australian and European populations. There is evidence that the aetiology of PBC could be partly environmental, perhaps related to an infectious agent.¹⁰ The current study supports the environmental notion and, if confirmed by future Australian studies, may

prove to be an important pointer to a better understanding of the condition.

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