

The Epidemiology of Primary Biliary Cirrhosis in Southern Israel

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Key words: primary biliary cirrhosis, epidemiology, Israel, liver, immigration

Abstract

Background: The epidemiology of primary biliary cirrhosis has changed significantly over the last decade, with a trend towards increasing prevalence in many places around the world.

Objectives: To determine the overall prevalence of PBC in southern Israel and the specific rates for different immigrant groups between January 1993 and October 2004.

Methods: Multiple case-finding methods were used to identify all cases of PBC in the study region. Age-adjusted prevalence rates were compared among the different immigrant groups.

Results: A total of 47 cases of PBC were identified with an overall prevalence of 55 cases per million. All patients were women, and all except for a Bedouin Arab were Jewish. Foreign-born patients comprised 70% of our PBC cohort even though they represent only 45.4% of the regional population. This predominance of immigrants did not change when the rates were adjusted for age ($P < 0.001$). The prevalence rates were 40, 177, and 58 cases per million for those born in Israel, North Africa or Asia, and Eastern Europe, respectively. The age-specific prevalence rate for women older than 40 years varied from 135 cases per million among those born in Israel to 450 among immigrants from Eastern Europe and the former USSR to 700 cases per million among immigrants from North Africa and Asia.

Conclusions: The prevalence of PBC in southern Israel is similar to that reported from some European countries. The rate is much higher among Jews than Arabs and among immigrants to Israel compared to native Israelis.

IMAJ 2005;7:717-721

Primary biliary cirrhosis is a chronic, slowly progressive cholestatic liver disease, probably of autoimmune origin, characterized by non-suppurative inflammation and destruction of small intra-hepatic bile ducts leading eventually to advanced fibrosis, cirrhosis and liver failure [1]. In all, 95% of patients with PBC are females, mostly middle-aged women [1,2]. The diagnosis of PBC is based on well-established criteria, which include a striking cholestatic pattern on liver function tests, a positive antimitochondrial antibody test, and compatible histologic findings on liver biopsy [1,3]. Recently, the importance of a diagnostic liver biopsy has been questioned in patients

with a positive AMA and a classic cholestatic biochemical profile, in the absence of significantly elevated aminotransferases [4].

The annual incidence and prevalence of PBC ranges from 2 to 24 cases per million and 19 to 402 cases per million, respectively [2,5]. PBC affects all races, but there is a substantial variation in its worldwide prevalence. It is more common in northern Europe, especially in the United Kingdom [6] (incidence 3.1 per 100,000 population per year; prevalence 25.1/100,000 population) and the United States [7] (incidence 2.7/100,000 population per year; prevalence 40.2/100,000 population) compared to Asia [8] and Africa [9,10]. This disparity in global prevalence and incidence may reflect a combination of environmental and genetic factors in the etiology of PBC.

The epidemiology of PBC has changed significantly over the last decade, with a trend towards increasing prevalence in the UK [6,11,12] and more recently in Australia [13] where repeated studies have been done using rigorous case-finding methods. The statistical increase in the reported prevalence and incidence could reflect a steadily expanding population at risk and increased exposure to environmental etiologic agents. However, it could also be the result of growing clinical awareness of PBC, better accessibility to diagnostic autoantibody serologic tests, and more precise and well-defined case-finding methods [6,11,13].

No prospective epidemiologic survey has been conducted to date in Israel on the incidence and prevalence of PBC. Ilan and Shouval [14] presented a retrospective review of epidemiologic and clinical data in a group of Jewish patients with PBC referred to a liver transplantation center at the Hadassah Medical Hospital. The aim of the present study was to assess the prevalence of PBC in southern Israel from January 1993 to October 2004 using multiple case-finding methods.

Subjects and Methods

Setting and study population

This population-based prevalence study was designed for assessment of PBC time-point prevalence in December 2004. The geographic area of the study population was determined in accordance with health authority definitions and included

PBC = primary biliary cirrhosis
 AMA = antimitochondrial antibody

the Southern Regional Health Authority with a population of 826,000 people encompassing all urban and rural residents of southern Israel. Subjects' addresses were collected to verify residence within southern Israel.

Population statistics were obtained from the Israel Central Bureau of Statistics and data regarding specific immigrant populations were obtained from the Bureau's 2003 national census [15]. This population was used for age standardization. According to this census 451,000 of the residents in southern Israel were Israeli-born (54.6%) while 375,000 were immigrants [15]. The immigrant population was subdivided as follows: 280,000 (74.6%) came from the republics of the former Soviet Union or Eastern Europe; 90,000 (24.0%) from North Africa or Asia, and 5,000 (1.4%) from Western Europe, or North or South America [15].

Diagnostic criteria for PBC

The diagnosis of PBC was based on published diagnostic criteria [7,11]. Definite PBC was defined by the presence of all of the following: a) clinical features consistent with a chronic cholestatic disorder of more than 6 months duration, with a greater than 1.5-fold increase in alkaline phosphatase and an aspartate aminotransferase level less than 5 times the upper limit of normal; b) a positive AMA test with a titer of 1:40 or greater; and c) compatible histologic findings on liver biopsy results according to the Ludwig histopathologic classification [16]. Probable PBC was defined as the presence of any two of the above criteria.

The study population included all definite and probable cases of PBC [Table 1]. Subjects who did not fulfill the criteria for either definite or probable PBC were excluded from data analyses [7,11,17]. The date of diagnosis was defined as the first time that two of the diagnostic criteria were observed.

Data collection

Several case-finding methods were used in this study. First, a formal request was sent to all gastroenterologists in the study region to report known cases of PBC. The Soroka Medical Center is the main provider of health services and the referral center for patients from the city of Beer Sheva and the rest of southern Israel. Its gastroenterologists work in clinics in the periphery as well as in the medical center. An identical official request to identify all known cases of PBC was also addressed to gastroenterologists affiliated with the Barzilai Medical Center, the second largest hospital in the Negev, which provides service to the city of Ashkelon and its surrounding area. In addition, we turned to the gastroenterology and hepatology services of the three hospitals in Israel with liver transplantation units to identify patients from our area with PBC who underwent liver transplantation during the study period 1993 to 2004. Second, a retrospective search was also done of medical admissions data for ICD-9 codes with the word "biliary cirrhosis" at the Soroka University Hospital from 1993 to 2004. Third, data from the hospital immunology laboratory were reviewed to identify all positive AMA tests during this period and these were matched with documented PBC patients being followed in our clinic. Fourth, all liver biopsy results with the final diagnosis of PBC at our

Table 1. Diagnostic criteria for PBC

PBC diagnosis	N	Abnormal AP and GGT		
		AMA	Compatible liver histology	
Definitive	30	+	Positive	Compatible
Probable	16	+	Positive	Not done
	1	+	Negative	Compatible

AP = alkaline phosphatase, GGT = gamma-glutamyl transpeptidase

hospital during the study period were identified and reviewed by one of the investigators (D.B.) for further corroboration of the histologic diagnosis reported in the patient's record. Fifth, all hospital autopsy certificates from 1993 to 2004 were reviewed for possible undocumented cases of PBC.

The data collected from the medical records included date of birth, gender, ethnic origin, date of diagnosis, clinical variables at diagnosis including presenting symptoms (e.g., persistent fatigue, pruritus), portal hypertension complications and associated diseases, Child-Pugh classification, main therapy, and outcome (e.g., liver transplantation or PBC-related death). The laboratory variables at diagnosis included AMA titer, serum levels of alkaline phosphatase (IU/L), gamma-glutamyl transferase (IU/L), total bilirubin (mg/dl), alanine and aspartate aminotransferases (IU/L), albumin (g/dl), prothrombin ratio (international normalized ratio), and total cholesterol (mg/dl).

Histologic findings were classified according to the Ludwig classification [16]. Extrahepatic biliary obstruction was excluded by abdominal computed tomography or abdominal ultrasound in all patients identified with PBC.

Statistical analysis

Prevalence rates are presented as cases per million and compared among different patient groups by the chi-square test. The indirect standardization method was used to avoid the potential confounding influence of age. Comparison of prevalence rates were performed using the actual population, rather than calculated projected rates. We used *t*-tests and ANOVA to compare continuous variables, and Pearson's chi-square test for categorical variables. The Bonferroni test was used for post-hoc analyses. All reported *P* values are two-sided and the level of *P* < 0.05 was considered statistically significant.

Results

Global and specific prevalence

We identified 47 cases of PBC. Of these, 30 patients (64%) had definite PBC and 17 (36%) had probable PBC. The overall prevalence rate was 55 cases per million. All patients were Jewish women, except for one woman of Arab origin. The mean age was 59 ± 12 years (interquartile range 50–69). The study population comprised 22 patients who immigrated to Israel from Eastern Europe or the former USSR (47%), 14 Israeli-born patients (30%), and 11 patients who immigrated to Israel from North Africa or Asia (23%). Israeli-born patients were significantly younger (50.9 ± 11 years) than North African-born immigrants (60.1 ± 9.1 years) or Eastern European, mainly USSR-born immigrants

(63.9 ± 11.6 years) ($P = 0.005$). The post-hoc analysis shows that the significance is due to the difference between those born in Israel and Eastern Europe or the former USSR ($P = 0.004$). The mean age of Israeli-born patients at the time of diagnosis was 47.1 ± 12.5 years, North African or Asian-born immigrants 56.6 ± 11.9 years, and Eastern European or former USSR-born immigrants 59.3 ± 13.6 years ($P = 0.027$). Although immigrants to Israel comprise 45.4% of the southern Israeli population, they constituted 70% of our PBC cohort; this difference remained when the prevalence was adjusted for age ($P < 0.001$).

We determined the prevalence of PBC for each of the three subgroups with the most patients [Table 2]. The prevalence was 40 cases per million for Israeli-born patients, 58 for immigrants from Eastern European or the former USSR, and 177 cases per million for immigrants from North Africa or Asia. The prevalence of PBC for immigrants from North Africa or Asia was significantly higher than the others after correcting for age ($P = 0.019$) and was significantly lower among patients born in Israel ($P = 0.043$).

We performed a separate analysis for women over the age of 40 (the group at greatest risk for PBC) [Figure 1]. The prevalence rates ranged from 135 per million among Israeli-born women to 450 among immigrants from Eastern Europe and the former USSR to 700 per million among immigrants from North Africa or Asia. Corresponding age-specific prevalence rates are not readily available for Eastern Europe or the former USSR. In Britain the age-specific rate for this group is 939.8 cases per million [6]. A study from Australia reported 344.2 cases per million among patients born in the UK who immigrated to Australia compared with 160.3 cases per million for Australian-born women older than 40 years living in Victoria, Australia [13].

Clinical and laboratory features

Table 3 summarizes some of the main features of our patients at the census date. The most common symptoms were fatigue (70%) and pruritus (36%). Fourteen patients (30%) were asymptomatic. Of the 49 patients 39 (83%) were classified as Child-Pugh A, 2 (4%) as Child-Pugh B and 6 (13%) as Child-Pugh class C. All six patients with Child-Pugh C were immigrants: four from Eastern Europe or the former USSR and two from North Africa or Asia. A liver biopsy was performed in 30 (64%) of the patients, of whom 2 (7%) were classified as Ludwig's stage I, 7 (23%) stage II, 9 (30%) stage III and 12 (40%) stage IV. Women from Eastern Europe or the former USSR had a higher rate of stage IV (well-established cirrhosis) compared to the other two groups ($P = 0.015$). The most common co-morbid condition in the 47 cases was osteoporosis in 31 (66%) and hypothyroidism in 22 (47%) of the reported cases.

Patients from Eastern Europe or the former USSR had higher levels of gamma-glutamyl transpeptidase activity than women born in Israel or from North Africa or Asia, although the dif-

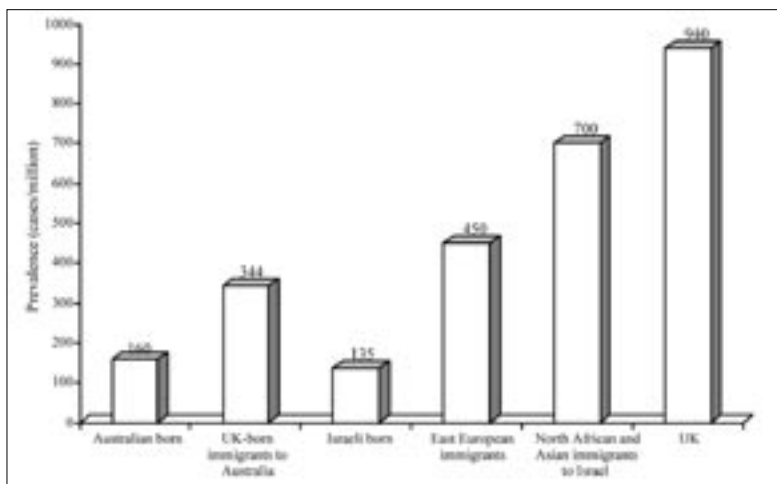


Figure 1. Prevalence (cases per million) of PBC in women older than 40 years. Data for Australia is from Sood et al. [13], and data from the UK from James et al. [6]

ference did not reach statistical significance (400 ± 235, 320 ± 170, and 245 ± 155 IU/L respectively, $P = 0.09$). The level of total bilirubin was significantly higher in patients from Eastern Europe or the former USSR than in the other women (1 ± 0.6 and 0.6 ± 0.2 mg/dl respectively, $P = 0.01$), but their alkaline phosphatase level was not significantly higher than in other groups (432 ± 223 and 384 ± 202 IU/L respectively, $P = 0.3$). There were no significant differences between three groups of patients in terms of transaminase levels. The albumin level was

Table 2. Prevalence of PBC in southern Israel, by region of birth [N (%)]

Region of birth	N	Prevalence* (cases/million)	P**
Israel	14 (30)	40	0.043
North Africa or Asia	11 (23)	177	0.019
Eastern Europe or former USSR	22 (47)	58	0.23
Total	47	55	

* Standardized for overall age distribution of southern Israel

** Chi-square test for comparison with overall population

Table 3. Characteristics and co-morbid diseases of patients with PBC, by region of origin [N (%)]

	Israel (n=14)	North Africa or Asia (n=11)	East Europe or former USSR (n=22)	P
Fatigue	10 (71)	8 (73)	15 (68)	0.96
Pruritus	3 (21)	5 (46)	9 (41)	0.38
Portal hypertension	2 (14)	2 (18)	5 (23)	0.82
Biopsy: stage IV	4 (31)	1 (13)	7 (78)	0.015
Hypothyroidism	4 (31)	4 (36)	14 (64)	0.11
Sjogren syndrome	2 (14)	1 (9)	3 (14)	0.92
Diabetes mellitus type II	0 (0)	2 (18)	4 (18)	0.23
Osteoporosis	7 (50)	7 (64)	17 (73)	0.24
Obesity	1 (8)	2 (18)	4 (18)	0.67

significantly lower among patients from Eastern Europe or the former USSR than others (3.4 ± 0.6 and 3.9 ± 0.5 g/dl respectively, $P = 0.023$).

All study patients were receiving ursodeoxycholic acid and 5/47 (10%) colchicine therapy. No patient was taking methotrexate or mycophenolate mofetil. Two of the patients underwent liver transplantation.

Discussion

Knowledge relating to the epidemiology of PBC has advanced throughout the world over the past decade, with a steady increase in reported prevalence rates, probably thanks to well-designed studies with multiple case-finding methods that evaluated longitudinal data [6,11,13]. PBC is most common in Northern Europeans and relatively rare in Asian and African populations [6,11].

Our study, using several well-accepted case-finding methods, found the prevalence rate for PBC in southern Israel to be 55 cases per million. Forty-seven PBC patients were identified; 31 fulfilled the three diagnostic inclusion criteria for a definitive diagnosis of PBC and 16 patients met at least two diagnostic criteria for probable diagnosis. We did not exclude patients who met other diagnostic criteria but did not have a formal histopathologic diagnosis, because such a decision would have led to an underestimation of the true prevalence of PBC in the general population. In addition, there is increasing evidence that liver biopsies may not be necessary to establish the diagnosis of PBC; in the context of a positive AMA, a cholestatic biochemical profile with AP greater than 1.5 times the upper limits of normal and absence of a marked increase of aminotransferases [4]. Based on our data we believe that the number of PBC patients in Israel is greater than previous estimations. Furthermore, even though we utilized several data sources, we still feel that the prevalence rate that we found may underestimate the real prevalence of this disease in southern Israel, since most of the patients in our study were symptomatic (70% of the cases with fatigue) at the date of initial diagnosis. Asymptomatic patients are less likely to present for medical attention, so we may have missed asymptomatic patients (20–60% in most reported series) [18,19], who did not present to a gastroenterologist in our area during the study period. Hypothetically, there could also be elderly or frail patients with well-defined criteria for probable PBC who did not undergo liver biopsy and are being followed by their family physician only.

The only article on PBC published in Israel over the last 15 years reported a point prevalence of 6.7 cases per million for a 10 year study period [14]. However, that epidemiologic study underestimated the real frequency of PBC because it did not use multiple case-finding methods and was restricted to a select population attending a tertiary care hospital with liver transplantation capacity. Nevertheless, some of the findings in that study were similar to ours. These include the mean age at presentation, the high rate of fatigue as the most common symptom (70% in both series), and the preponderance of Jewish

patients (22 Ashkenazi Jews, 8 Sephardic Jews and no Arabs in the Jerusalem series; in the present series there were 27 Ashkenazi Jews, 19 Sephardic Jews and just 1 Bedouin Arab). Because the Arab population receives the same healthcare as Jews in all the main healthcare organizations in Israel, these data probably reflect an increased susceptibility for PBC among Jews compared to Arabs, possibly due to a genetic component of the disease rather than environmental or social factors. However, this aspect was not addressed in our study.

The present data show that the prevalence of PBC in the Israeli population is not in the lower global range, as previously reported [6,14], but rather is similar to many countries [13,20,21], other than the USA [7], the UK [6] and Sweden [22]. We do not know if our results reflect a real increase in the prevalence of PBC or simply better case-finding methods in a well-defined population, which reduces the likelihood of missed cases.

The issue of the prevalence of PBC in immigrant groups was recently addressed in the state of Victoria, Australia [13]. The authors found a significant increase in the overall prevalence of PBC compared to a previous study from the same state. In addition, they found significantly higher prevalence rates in the three largest immigrant groups in comparison to patients born in Victoria. Since Israel is a relatively new pan-ethnic country this type of analysis is of particular interest and importance. Our analysis of prevalence rates in the main immigrant Jewish groups (East European and North African) in southern Israel showed that although the immigrants comprise 45.4% of the region's population, they represented 70% of our study cohort. The relatively high prevalence rates in these immigrant groups remained so even when they were adjusted for age. Similar to the findings in the Australian study [13], the prevalence rate in Israeli-born patients (including prevalence corrected for age) was significantly lower than the corresponding rates in immigrant groups.

There is no precise epidemiologic data on the prevalence of PBC in Africa, but it is thought to be one of the lowest in the world. We found a prevalence rate of 177 cases per million in former North African Jews who immigrated to Israel between 1950 and 1960. This figure is even higher when corrected for age (older than 40) with a prevalence of 700 cases per million. The prevalence of PBC in women older than 40 years in Britain was reported to be 939.8 cases per million, but only 344.2 cases per million for those born in the UK [6]. The corresponding rate for Australian-born women older than 40 is 160.3 cases per million [13]. The cause of this striking disparity may be unidentified environmental factors.

Ursodeoxycholic acid is the most commonly used treatment throughout the world for PBC [23], despite the troubling results of a recent meta-analysis of its efficacy in terms of survival, quality of life, histology and portal hypertension [24]. Our entire cohort was on UCDA (average dose 12–15 mg/kg/day). A few patients (10%) were taking colchicine even though there is

UCDA = ursodeoxycholic acid

scarce support for this treatment in the literature [23,25]. None of our patients was on immunomodulator therapy (methotrexate or mycophenolate mofetil), possibly because of limited evidence of any effectiveness for those treatments [23].

In summary, using multiple case-finding methods in southern Israel we found a larger overall prevalence of PBC in the population than initially reported, with a rate that approaches the prevalence of PBC as reported in some European countries. PBC is much more prevalent among Jews than Arabs. The prevalence of PBC in immigrants is higher than in those born in Israel. The present data may still underestimate the true prevalence of PBC since there may be asymptomatic PBC patients with undiagnosed PBC. Only a prospective epidemiologic assessment with multiple case-finding methods can determine the real prevalence and incidence rates for PBC in Israel.

Acknowledgment. The authors thank the following individuals for their contribution to this study: Michal Carmiel MD, Tel Aviv Sourasky Medical Center; Yaron Ilan MD, Hadassah University Hospital; Ziv Ben-Ari MD, Rabin Hospital; Doron Zamir MD, Barzilai Hospital; and Ignacio Sztarkier MD, Soroka University Hospital.

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Even the best of friends cannot attend each other's funeral

Anonymous

Reader, suppose you were an idiot and suppose you were in the government. I repeat myself.

Mark Twain (1935-1910), American writer