Presentation and mortality of primary biliary cirrhosis in older patients

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Abstract

Objectives: many patients with primary biliary cirrhosis present for the first time aged over 65, but it is unclear whether the disease is different in older patients. We have examined presentation and mortality in relation to age at which primary biliary cirrhosis was first suspected clinically.

Design: we identified 1023 patients from our regional primary biliary cirrhosis database with definite or probable primary biliary cirrhosis (689 definite); 397 (39%) presented aged ≥65. Definite primary biliary cirrhosis was defined as a positive antimitochondrial antibody titre ≥1/40, abnormal liver enzymes and compatible/diagnostic histology; probable as the presence of two of these indications.

Results: there was no difference in presenting clinical features between the older and younger groups. Older patients were significantly less likely than younger to have had liver biopsy (50% vs 78%; P < 0.001). The 1023 patients had been followed for 8561 patient years. Follow-up was shorter (5.9 ± 4 vs 9.8 ± 5.5 years; P < 0.001) in the older group because of higher cumulative mortality (59% vs 33%; P < 0.001). Liver-related deaths were significantly commoner in the older group (18% vs 13%; P < 0.05). The mortality ratio for liver deaths (liver deaths per year of follow-up) was 2.4 times higher in the older group (0.031 vs 0.013).

Conclusions: patients with primary biliary cirrhosis who are over and under 65 have similar features on presentation. The annual risk of liver death is 2.4 times higher in those presenting over 65, reaffirming the importance of age as an independent prognostic factor in an unselected primary biliary cirrhosis population.

Keywords: autoimmune disease, elderly, liver, primary biliary cirrhosis

Introduction

Primary biliary cirrhosis (PBC) is an autoimmune liver disease typically presenting in middle-aged women with progressive cholestatic jaundice [1]. It was thought to be a rare disease, often leading to death from liver failure. However, in recent years perception of the condition has changed. PBC is now often diagnosed at an asymptomatic stage, through the detection of either abnormal serum liver biochemistry or autoantibodies. The changing clinical spectrum of PBC results partly from earlier diagnosis and partly from the recognition of antimitochondrial antibody (AMA) as a marker for the disease [2, 3].

Several large series from tertiary referral centres have shown that the mean age of diagnosis is now between 55 and 60 years [4], implying that many patients are over 65 on first presentation. When prognostic markers for PBC have been examined using multivariate analysis, old age is always an adverse risk factor [5]. Furthermore, the dynamic model from the Mayo Clinic has confirmed that increasing age continues to have an independent and adverse effect on prognosis, implying that the disease course in elderly subjects may be more rapid [6]. Conversely, other studies have speculated as to whether PBC is a more benign disease in elderly patients or the same disease presenting later in life [7, 8].

We have examined the features of PBC in patients presenting for the first time at the age of 65 years or over and compared them to features seen in younger subjects. We have also examined mortality, to determine whether or not advanced age carries an adverse prognosis in PBC.

Methods

Patients in whom a diagnosis of PBC has been considered in North-East England have been entered
into a PBC database. This was established to carry out an epidemiological study of PBC in a stable population, resident in a defined geographical area in northern England (defined by post code) between January 1987 and December 1994.

The case-finding methodology for this study has been described previously [9]. Briefly, we (i) included all PBC patients attending the liver clinic at Freeman Hospital, Newcastle, (ii) sought patients from all gastroenterologists in the region, (iii) used the Regional Hospital Information System to identify all patients with biliary cirrhosis (ICD-9 codes 571–6) from the 13 hospitals in the region, (iv) examined autoimmune antibody profiles carried out in the region between 1987 and 1994 and identified those with positive AMA titre $\geq 1:40$ (209,000 profiles examined—85% of all profiles carried out), and (v) obtained death certificates for patients who died of biliary cirrhosis in the region (ICD-9 codes 571–6) from the Office of National Statistics.

In the present study, we also included patients who had been excluded from the epidemiological study because they lived outside the strictly defined study area (but still within the North-East) or because they had died before 1 January 1987 or been diagnosed after 31 December 1994. Thus, this case series includes both patients in the epidemiological study [9] and all other patients from North-East England in whom a diagnosis of PBC was considered between 1968 and December 1995.

We examined retrospectively the hospital case records of all patients in whom a diagnosis of PBC was considered. In the patients with no known case records we approached the family general practitioner for information on the patient ($n = 20$). We invited these patients (by post), to attend the PBC clinic where we took their history, examined them and carried out blood tests.

The date a presumed diagnosis of PBC (i.e. date of ‘presentation’) was made was the time at which two of the following three diagnostic criteria were first fulfilled and recorded in case records: (i) positive AMA titre (1:40), (ii) abnormal ‘liver function tests’ (LFT—i.e. bilirubin, serum transaminases, alkaline phosphatase) and (iii) compatible/diagnostic liver histology for PBC. Despite the presence of at least two of the diagnostic criteria entered in the case records, the diagnosis of PBC may not have been considered by the physician responsible for the patient at that time.

From the regional database, we identified individuals with definite or probable PBC. A definite diagnosis was defined as the presence of all three diagnostic criteria. Probable PBC was defined as two of the three criteria [10].

We describe those aged $\geq 65$ at the time of presumed diagnosis as the ‘older’ group, and those aged $<65$ as the ‘younger’ group.

We recorded clinical, biochemical and liver histology data for all subjects on the regional PBC database. As biochemical and serological results are from different laboratories and reference ranges may vary, we expressed data as a ratio of the normal range. All liver biopsies were reviewed by one of two histopathologists and classified according to current histological criteria into ‘early’ (Scheuer stage I/II) and ‘advanced’ (Scheuer stage III/IV) [11].

Results are expressed as mean (SD) or median. We performed comparisons with the Student’s unpaired
test for parametric variables and the \( \chi^2 \) test and Mann–Whitney \( U \) test where appropriate. A statistically significant result is when \( P < 0.05 \).

We obtained ethical permission for the collection of data and development of the database from the joint Newcastle hospitals/University ethical committee and all other ethical committees in the study region. All subjects gave informed consent for inclusion.

Results

Presentation

From the regional database we identified 1023 individuals with definite or probable PBC presenting between 1968 and 1995. Three hundred and ninety-seven presented at or after the age of 65; 626 presented before the age of 65 (Table 1).

Six hundred and eighty-nine (67%) had definite PBC. Of the 334 with probable PBC, 297 (89%) were AMA-positive with abnormal LFT but had not had the diagnosis confirmed by liver biopsy, 23 (7%) were AMA-negative but with compatible biopsy and abnormal LFT (‘autoimmune cholangiopathy’ — regarded as clinically indistinguishable from PBC [12]) and 14 (4%) were AMA-positive and had compatible liver histology but normal LFT (these patients have an \( \geq 80\% \) chance of progressing to classical disease [13]).

There was no significant difference in the proportions of those presenting with no symptoms or complications of liver disease at the time of presumed diagnosis in the older compared to the younger group (Figure 1). However, significantly more of the younger group had non-specific minor symptoms of PBC (24.5% versus 16.5%).

Investigations

There were no significant differences in the markers of disease severity at presentation (serum albumin and bilirubin) between those who had presented before or after the age of 65 in either the definite PBC group or the probable PBC group. Neither were there any significant difference in serum alkaline phosphatase concentrations or transaminase between the age groups at presumed diagnosis (Table 2).

The older patients were significantly less likely to have had the diagnosis confirmed histologically than the younger group (\( P < 0.001 \)). Of the 689 who had had liver biopsy, staging details were available in 491 (71%). In those in whom a biopsy was performed (132/200: 66% of biopsies in those over 65 at the time of presentation, 359/489: 73% of biopsies in the younger group), the frequency of advanced histological disease (i.e. stage III/IV) was significantly higher in those patients presenting over 65 than in younger patients (\( P < 0.01 \)). In those who had liver biopsy, when grouped according to age at first presentation, the ratio of the number of those with cirrhotic to precirrhotic disease increased with advancing age (Figure 2).

Notwithstanding the lower proportion of patients receiving biopsies in the older group, patients over 65

Table 2. Levels of biochemical markers in subjects presenting with definite or probable primary biliary cirrhosis for the first time before or after the age of 65

<table>
<thead>
<tr>
<th>Mean ratio of abnormal result (SD)**, by age at presentation</th>
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<tbody>
<tr>
<td>( \geq 65 ) years</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Bilirubin</td>
</tr>
<tr>
<td>Definite</td>
</tr>
<tr>
<td>Probable</td>
</tr>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>Transaminase</td>
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</tbody>
</table>

**Expressed as a ratio to normal: abnormal bilirubin, alkaline phosphatase, transaminases >1, albumin <1.

**Ratios are significantly higher in those with a definite diagnosis compared with those with a probable diagnosis (\( P < 0.05 \)).

Figure 2. The ratio of the numbers of individuals with advanced/early primary biliary cirrhosis (cirrhotic/precirrhotic) by age at first presentation.
Table 3. Histological stage in those who had liver biopsy after presenting with primary biliary cirrhosis for the first time before (n = 489) or after (n = 200) the age of 65

<table>
<thead>
<tr>
<th>Age at first presentation</th>
<th>≥65 years</th>
<th>&lt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (and %) of subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (stage I/II)</td>
<td>48 (36)</td>
<td>182 (51)</td>
</tr>
<tr>
<td>Advanced (stage III/IV)</td>
<td>84 (64)*</td>
<td>177 (49)</td>
</tr>
<tr>
<td>Median time from presumptive to</td>
<td>3 (0–138)</td>
<td>4 (0–195)</td>
</tr>
<tr>
<td>histological diagnosis,</td>
<td>months (range)</td>
<td></td>
</tr>
</tbody>
</table>

*aSignificantly more than in the younger group.

Table 4. Deaths and liver-related mortality ratios* in those presenting with primary biliary cirrhosis primary before or after the age of 65, and in those who had had liver transplantation (none of whom were in the older group)

<table>
<thead>
<tr>
<th>Age at first presentation</th>
<th>≥65 years</th>
<th>&lt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. in group</td>
<td>355</td>
<td>42</td>
</tr>
<tr>
<td>No. (and %) of deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>209 (59)</td>
<td>25 (60)</td>
</tr>
<tr>
<td>Liver-related (A)</td>
<td>67 (19)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Years of follow-up (B)</td>
<td>2012</td>
<td>209</td>
</tr>
<tr>
<td>Liver-related mortality ratio (A/B)</td>
<td>0.033</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*Number of liver-related deaths/total number of years at risk (i.e. sum of years of follow-up).

Discussion

Presentation

The two previous studies of PBC in older people have involved small numbers of patients and incomplete follow-up data. The study of Hislop et al. [7] included only seven patients presenting over 70, with mean follow-up of 25 months. Lehmann et al. [8] examined 35 patients who were over 65 at presentation, with mean follow-up around 55 months. In our case series, we examined the presentation of PBC in 1023 patients, 39% of whom were aged 65 or over at the time of presumed diagnosis. We confirm that PBC does not appear to be a ‘different’ disease in elderly people as symptoms at first presentation are neither more nor less severe in younger than older individuals.

Investigations

Biochemical measures of severity did not differ between older and younger groups. Fewer of those aged ≥65 had a definitive diagnosis of PBC (i.e. had had liver biopsy). It may be argued that making a definite diagnosis of PBC in an elderly patient is of little benefit, particularly as there is no treatment of proven benefit for PBC (although ursodeoxycholic acid delays the development of oesophageal varices even in those with stage IV disease [14]). Liver biopsy is a relatively safe procedure in older patients, with no greater mortality than in younger individuals [15].

In our study, we were surprised to find no delay from the time of clinical suspicion to definitive diagnosis in older people who did have a liver biopsy. Perhaps biopsy was performed in older patients with
more severe disease, but there was no significant difference in the markers of severity (serum albumin and bilirubin) between older and younger subjects who had liver biopsy. In most instances in which patients (particularly older patients) did not have liver biopsy, it was thought by the responsible clinician that biopsy would not add to the management of their patient. The frequency of advanced-stage disease (Scheuer stage III/IV) where biopsy was performed was significantly higher in those presenting for the first time over the age of 65. This increased proportion of those with ‘advanced’ disease with advancing age could suggest either that these individuals are presenting later in the same disease or that there is a reduced willingness to consider liver biopsy in those over 65.

Mortality
It is not surprising that overall mortality was higher in the older group (59% versus 33%) since there are more deaths in the older group from non-liver-related causes. However, we have confirmed other studies that examined independent prognostic variables in smaller groups: in over 1000 PBC patients whom we followed for 8561 years, the liver-related mortality ratio was over twice as great in women presenting over age 65 (3%/year) than in those presenting below that age (1.3%/year). There is little clinical evidence to support the idea that this was because older patients had presented with more advanced disease. As with many other diseases, the ability of the ageing organism to withstand the severe stress of advanced liver disease and possible age-related impaired homeostasis may be responsible [16].

Key points
• Almost 40% of subjects with primary biliary cirrhosis present for the first time at or after the age of 65.
• Primary biliary cirrhosis should be included in the differential diagnosis in older people with abnormal liver blood tests.
• The mortality ratio is higher in individuals who present for the first time when they are over 65.

References

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