Prevalence and pattern of familial disease in primary biliary cirrhosis

A M Brind, G P Bray, B C Portmann, Roger Williams

Abstract

Susceptibility to primary biliary cirrhosis (PBC) may be partly inherited although instances of PBC within families are only infrequently described. The records of 736 patients with PBC seen over a 25 year period were examined to identify those with a positive family history. Ten patients originating from eight families were identified, giving a frequency of 1.33%. They comprised mother and daughter pairs; in two families both mother and daughter had been seen at our clinic. The daughters presented at an earlier age, median 36 years (range 24–54), than the mothers, 52 years (50–81). During follow up one daughter (45 years) and six mothers have died (range 53–81 years) and two mothers and one daughter have had a transplant aged 57, 57, and 30 years respectively. It is concluded that familial PBC is not rare, that it is related to maternally inherited factors, and that disease tends to present earlier in the second generation.

(Gut 1995; 36: 615–617)

Keywords: familial disease, primary biliary cirrhosis.

Methods

The case records of a total of 736 patients who were referred to and reviewed at the Institute of Liver Studies, King’s College Hospital from 1967 to 1992 were examined to identify those with a record of other cases of PBC within the family. The diagnosis of PBC was based on standard criteria (that is, positive anti-mitochondrial antibody, raised biliary enzymes, compatible clinical history, and liver histology). Details of presentation (mode, date, and age), autoantibodies, liver biopsy findings, follow up and outcome, presence of other diseases and family history of autoimmune disease were obtained wherever possible by interview or by informal postal questionnaire of the patients and affected family, as well as examining the case records held within our hospital and any other hospitals attended by the patient.

Results

In 10 (1.33%) of 736 patients there was a history of PBC in a family member and in two instances both affected family members had been seen at our clinic. Table I gives details of the patients, and the first patient to be seen. All had serum anti-mitochondrial antibody positivity and were mother and daughter pairs, all were white and originated from Britain. No record of affected but unrelated family members was found. All mothers and two of the daughters were cirrhotic at diagnosis; the histological stage of disease and the date of liver biopsy is shown. The daughters presented at an earlier age, median 36 years (range 24–54) than the mothers, median 52 years (range 50–81). All but three of the daughters had presented before their mothers.

Of the eight affected daughters, three were asymptomatic at presentation and were diagnosed because of the finding of abnormal liver function tests. Three others had presented with jaundice in pregnancy, one with tiredness, and one with bleeding oesophageal varices. All the mothers were symptomatic at presentation: two had tiredness, two abdominal pain, one jaundice, and three oesophageal varices. Although all the daughters had been raised by their mothers, at the time of presentation none of the daughters was living with her mother. There were records of associated thyroid disease in three patients and one had coeliac disease.

Median follow up for the daughters was 6.5 years (range 2–16) and for the mothers was 3.5 years (range 1 month–9 years). Mortality over this period comprised one daughter (aged 45 years) and six mothers, median age 72 years.
TABLE I  Clinical details of familial cases of primary biliary cirrhosis

<table>
<thead>
<tr>
<th>Family</th>
<th>Presentation</th>
<th>Date</th>
<th>Age</th>
<th>Biopsy stage and date</th>
<th>Serum autoantibodies</th>
<th>Autoimmune disease</th>
<th>Follow up and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Daughter*</td>
<td>Jaundice in pregnancy</td>
<td>1986</td>
<td>26</td>
<td>II 1989</td>
<td>AMA 1/320</td>
<td>Nil</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Mother</td>
<td>Abdominal pain</td>
<td>1986</td>
<td>51</td>
<td>I 1987</td>
<td>AMA 1/320</td>
<td>Thyroid disease</td>
<td>Transplanted 1992</td>
</tr>
<tr>
<td>2 Daughter*</td>
<td>Abnormal LFT's</td>
<td>1988</td>
<td>51</td>
<td>I 1990</td>
<td>AMA 1/160</td>
<td>Nil</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Mother</td>
<td>Abdominal pain</td>
<td>1961</td>
<td>51</td>
<td>II 1972</td>
<td>AMA 1/10</td>
<td>Thyroid disease</td>
<td>Died liver disease 1972</td>
</tr>
<tr>
<td>Mother</td>
<td>Abdominal pain</td>
<td>1967</td>
<td>50</td>
<td>IV 1987</td>
<td>AMA 1/640</td>
<td>Nil</td>
<td>Transplanted and died 1987</td>
</tr>
<tr>
<td>4 Daughter*</td>
<td>Jaundice</td>
<td>1984</td>
<td>50</td>
<td>IV 1990</td>
<td>AMA 1/460</td>
<td>Nil</td>
<td>Ascites and varices 1982</td>
</tr>
<tr>
<td>Mother</td>
<td>Fatigue</td>
<td>1976</td>
<td>38</td>
<td>IV 1976</td>
<td>AMA 1/460</td>
<td>Nil</td>
<td>Died variceal bleed 1988</td>
</tr>
<tr>
<td>5 Daughter*</td>
<td>Abnormal LFT's</td>
<td>1976</td>
<td>33</td>
<td>II 1984</td>
<td>AMA 1/20</td>
<td>Coeliac disease</td>
<td>Varices 1990</td>
</tr>
<tr>
<td>Mother</td>
<td>Fatigue</td>
<td>1983</td>
<td>70</td>
<td>IV 1983</td>
<td>AMA 1/800</td>
<td>Nil</td>
<td>Died liver disease 1990</td>
</tr>
<tr>
<td>2 Daughter*</td>
<td>Variceal bleed</td>
<td>1985</td>
<td>50</td>
<td>IV 1985</td>
<td>SMA 1/20</td>
<td>Nil</td>
<td>Died liver disease 1978</td>
</tr>
<tr>
<td>Mother</td>
<td>Variceal bleed</td>
<td>1976</td>
<td>43</td>
<td>III 1976</td>
<td>AMA 1/320</td>
<td>Nil</td>
<td>Died liver disease 1971</td>
</tr>
<tr>
<td>7 Daughter*</td>
<td>Abnormal LFT's</td>
<td>1989</td>
<td>54</td>
<td>II 1989</td>
<td>AMA 1/1290</td>
<td>Polyarthritis</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Mother</td>
<td>Variceal bleed</td>
<td>1981</td>
<td>91</td>
<td>No biopsy</td>
<td>AMA 1/320</td>
<td>Thyroid disease</td>
<td>Died liver disease 1991</td>
</tr>
<tr>
<td>8 Daughter*</td>
<td>Jaundice in pregnancy</td>
<td>1985</td>
<td>29</td>
<td>III 1992</td>
<td>AMA 1/800</td>
<td>Nil</td>
<td>Mild symptoms</td>
</tr>
<tr>
<td>Mother</td>
<td>Fatigue and pruritus</td>
<td>1988</td>
<td>53</td>
<td>Incomplete</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*First case seen. LFTs=liver function tests, AMA=anti-mitochondrial antibodies.

(range 53–81). Two mothers and one daughter have had a transplant because of deterioration in liver function with serum bilirubin rising to >250 μM. This was at age 57 years in two cases and age 30 years in the third (six, three, and seven years after presentation respectively). The daughters remained virtually asymptomatic over the follow up period, one has mild symptoms, and three daughters have bled from oesophageal varices.

Discussion
Familial primary biliary cirrhosis is not rare—although the frequency of 1-3.3% recorded in our series is, however, less than the 5-5% (22 of 405) reported in the one previous study, which was carried out in New York.18 Our figure for prevalence may be an underestimate as ascertainment depended on the index case being aware of the medical history of their relatives and a record of this appearing in the case notes. It is unlikely that the discrepancy between the two studies results from differences in the criteria used for diagnosis, 38 patients with undiagnosed liver disease are mentioned in the other report but are not included in their calculation of PBC prevalence. We were strict in excluding cases where a diagnosis of PBC was not definite and many of our cases were followed up for a considerable period. Our series does not include any families with more than two affected members whereas seven such families are described in the other study. In that report, it was suggested that the occurrence of multiple family members with PBC might result from increased penetrance of the disease or an increased awareness of the disease in the affected family. The higher prevalence recorded in the other group may be because of greater disease awareness and more frequent screening for disease in their population, or result from a real difference in the comparative importance of familial factors in the aetiology of PBC in these two parts of the world.

The familial predisposition that undoubtedly exists in PBC may have a genetic or environmental background. Published reports afford considerable evidence for a genetic predisposition. Thus there are the reports of HLA associations: with C4B2,22 C4A-Q0,15 and DR815.23 This has been found in other studies carried out in this Institute that 11% of patients have the HLA DR8-DQB1*0402 haplotype.23 There have also been reports of associations with a restriction fragment polymorphism within the tumour necrosis factor gene24 and the B related transcript gene.25 These genotypic associations may underly the phenotypic findings of abnormal lymphocyte function in families with PBC.16 None of our cases of familial PBC was associated with a well defined immune disorder, unlike those previously described in association with IgA deficiency11 or hypergammaglobulinaemia.8

Table II gives a summary of previous reports of familial cases of PBC. All our cases were female, which is consistent with the female preponderance in PBC, although affected male family members have been reported. Inheritance was maternal in all other reported cases where it is possible to deduce inheritance; the one exception was in the family with associated hypergammaglobulinaemia (father and daughters).1 If the inherited predisposition to PBC is truly maternal it might involve mitochondrial DNA, which is always maternally inherited or be related to non-inherited maternal HLA antigens, which have been implicated in the familial predisposition to rheumatoid arthritis.26
arthritis. Inherited familial predisposition to PBC is more likely, however, to be complex and polygenic involving the interaction of a number of genes. With respect to an environmental basis for the familial occurrence of PBC, epidemiological studies have linked development of PBC to the reservoir supplying drinking water, there have been reports of geographical and seasonal clustering of cases, and there is a report of PBC occurring in a non-related nurse of a patient with PBC. One suggestion is that an agent may be bacterial — that is, *Escherichia coli* — as there is cross reactivity between *E coli* antigens and anti-mitochondrial antibodies. In some studies a high prevalence of *E coli* urinary tract infections has been found among patients with PBC. Whatever the nature of the agent it has always been apparent that there is a long incubation period between the exposure and manifestation of the disease. All our family pairs spent a considerable period of their lives together but presented at different stages of the disease and at different times and had not been living together for some time in the immediate past. Four pairs of mothers and daughters presented within five years of each other but the second case to present was not always at a more advanced stage of the disease. Indeed the daughter in pair no 2 presented 17 years after her mother and with stage I disease. It is noteworthy that we did not find any case of PBC occurring in non-related family members. The case of PBC in a close contact of a patient did have a family history of autoimmune disease.

In this series all the daughters presented at a younger age than their mothers. This may be partly because of increased awareness of the disease and the greater availability of screening nowadays leading to more being found with asymptomatic disease at an earlier age. Many of the daughters, however, presented either before their mothers or had a more rapid disease progression. The daughter who had a transplant and the daughter who has died were younger than any of the mothers at death or transplantation. In addition, the other three daughters with symptomatic disease became symptomatic at a younger age than their respective mothers. Interestingly, Tong et al found the same phenomenon, where the daughter was more severely affected than her mother.

20 Triger DR. Primary biliary cirrhosis, an epidemiological study. *BMJ* 1980; 281: 775.
Prevalence and pattern of familial disease in primary biliary cirrhosis.

A M Brind, G P Bray, B C Portmann and R Williams

Gut 1995 36: 615-617
doi: 10.1136/gut.36.4.615

Updated information and services can be found at:
http://gut.bmj.com/content/36/4/615

Email alerting service

These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections
Pancreas and biliary tract (1949)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/