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.

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Primary biliary cirrhosis (PBC) is considered to be an autoimmune disease as it is associated with serum anti-mitochondrial antibodies and abnormalities of the immune system. Although it is not thought to be an inherited disease, there have been a number of reports describing multiple cases of PBC occurring within a single family.¹⁻¹⁷ However, there has only been one recent systematic study of PBC frequency within families published as an abstract.¹⁸

Abnormalities of immune function have also been shown in family members of patients with PBC suggesting immunogenetic susceptibility. Unaffected family members have an increased frequency of anti-mitochondrial antibodies⁴ and abnormal T cell function.^{16, 19} The exact nature of the molecular basis for an inherited immunological susceptibility to PBC and its comparative importance to disease manifestation remains uncertain.

The evidence that environmental factors are important in the development of PBC is limited^{20, 21} but such factors could also be involved in its familial occurrence.

In this report, we describe a systematic study of 736 patients with PBC who attended and were reviewed over a period of 25 years in a single unit, carried out to determine both the prevalence and pattern of familial disease.

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 with an established diagnosis of PBC 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

Institute of Liver Studies, King's College Hospital and King's College School of Medicine & Dentistry, London

A M Brind
G P Bray
B C Portmann
Roger Williams

Correspondence to:
Professor Roger Williams,
CBE, King's College
Hospital, Bessemer Road,
London SE5 9PJ.

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TABLE I Clinical details of familial cases of primary biliary cirrhosis

Family	Presentation	Date	Age	Biopsy stage and date	Serum autoantibodies	Autoimmune disease	Follow up and outcome
1 Daughter*	Jaundice in pregnancy	1986	24	II 1989	AMA 1/320	Nil	Asymptomatic
Mother	Abdominal pain	1986	51	III 1987	AMA 1/320	Thyroid disease	Transplanted 1992
2 Daughter*	Abnormal LFTs	1988	51	I 1990	AMA 1/160	Nil	Asymptomatic
Mother	Abdominal pain	1961	51	IV 1972	AMA +	Thyroid disease	Died liver disease 1972
3 Daughter*	Jaundice in pregnancy	1985	25	III 1986	AMA 1/40	Nil	Transplanted 1991
Mother	Jaundice	1984	50	IV 1985	ANA 1/160	Nil	Transplanted and died 1987
4 Daughter*	Fatigue	1976	38	IV 1976	AMA +	Nil	Ascites and varices 1982
Mother	Variceal bleed	1988	73	IV 1988	AMA 1/640	Nil	Died variceal bleed 1988
5 Daughter*	Abnormal LFTs	1976	33	II 1984	AMA +	Coeliac disease	Varices 1990
Mother	Fatigue	1983	70	IV 1983	AMA 1/800	Nil	Died liver disease 1990
6 Daughter*	Variceal bleed	1976	43	IV 1976	SMA +	Nil	Died liver disease 1978
Mother	Variceal bleed	1971	69	IV 1971	AMA 1/320	Raynauds	Died liver disease 1971
7 Daughter	Abnormal LFTs	1989	54	II 1989	Not tested	Polyarthritis	Asymptomatic
Mother*	Variceal bleed	1991	81	No biopsy	AMA 1/1290	Thyroid disease	Died liver disease 1991
8 Daughter*	Jaundice in pregnancy	1985	29	III 1992	AMA 1/320	Nil	Mild symptoms
Mother	Fatigue and pruritus	1988	53	Incomplete details	AMA +	Nil	Mild symptoms

*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 $>250 \mu\text{M}$. This was at age 57 years in two cases and age 30 years in the third (six, three, and seven years after presentation respectively). Three 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 1.33% 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 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 DR8^{15 23} and we have 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 underlie 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 as 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).¹¹ 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

TABLE II Case reports of familial PBC

Walker <i>et al</i> 1972 ¹	2 Sisters
Klatskin <i>et al</i> 1972 ²	2 Sisters
Chohan <i>et al</i> 1973 ³	Twin sisters
Galbraith <i>et al</i> 1974 ⁴	Two brothers
Tong <i>et al</i> 1976 ⁵	Mother and daughter
Fagan <i>et al</i> 1977 ⁶	Mother and daughter
Douglas <i>et al</i> 1977 ⁷	Mother and daughter with coincident onset and disease in non-related carer
Jaup <i>et al</i> 1980 ⁸	Father and 4 daughters associated with hypergammaglobulinaemia
Kato <i>et al</i> 1981 ⁹	Father and daughter
Cales <i>et al</i> 1983 ¹⁰	2 Brothers with common HLA haplotype
James <i>et al</i> 1986 ¹¹	Father and daughters associated with IgA deficiency
Chiaranti <i>et al</i> 1987 ¹²	Mother and 2 daughters
Chalmers <i>et al</i> 1987 ¹³	2 Sisters associated with autoimmune thrombocytopenia
James and Myszor 1990 ¹⁴	2 Mother and daughter pairs
Manns <i>et al</i> 1991 ¹⁵	2 Sisters, mother and daughter with common HLA-1 haplotype
Tsuji <i>et al</i> 1962 ¹⁶	2 Sisters, brother and sister with similar T cell responsiveness
Harada <i>et al</i> 1992 ¹⁷	Brother and sister associated with polymyositis, Hashimoto's thyroiditis, and vasculitis

arthritis.²⁶ 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,²⁰ there have been reports of geographical and seasonal clustering of cases,²¹ and there is a report of PBC occurring in a non-related nurse of a patient with PBC.⁷ 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.²⁷ In some studies a high prevalence of *E coli* urinary tract infections has been found among patients with PBC.²⁸ 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.⁷

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.⁵

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