Are increased individual susceptibility and environmental factors both necessary for the development of primary biliary cirrhosis?

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Summary and conclusions

A daughter, her mother, and an unrelated close friend developed primary biliary cirrhosis (PBC). The mother and the close friend nursed the daughter through her terminal illness and presented with PBC within 21 months after her death. Half of the asymptomatic first-degree relatives in the two families had serum autoantibodies, including one with antimitochondrial antibody, suggesting some genetic susceptibility to abnormal immune reactions.

It is concluded that some environmental factor may be present in PBC, perhaps in addition to a genetic susceptibility to that factor.

Introduction

Primary biliary cirrhosis (PBC) is a chronic disease in which immunological abnormalities, particularly autoantibodies in the blood, almost always occur.^{1,2} Autoantibodies and increased serum immunoglobulin concentrations also occur in asymptomatic relatives of patients with PBC,^{3,4} suggesting that genetic factors may be important. Attempts to identify other genetic factors have, however, been unsuccessful,^{5,6} and reports of familial PBC are infrequent.^{2,7-10} We describe a mother and an unrelated friend who developed PBC after nursing the daughter who died of the disease. Other, healthy members of both families had serum autoantibodies. Unknown environmental factors may be important in causing PBC in genetically susceptible people.

Case reports

Case 1—A 40-year-old woman presented in June 1970 with pruritus for nine years and pale stools and dark urine for six months. She denied alcohol abuse. Examination showed slight icterus and numerous scratch marks. Serum bilirubin concentration was 30 $\mu\text{mol/l}$ (1.8 mg/100 ml), alanine aminotransferase activity 70 U/l (normal 10-40), and alkaline phosphatase activity 260 U/l (normal 40-100). Prothrombin time, plasma albumin concentration, and full blood count were normal. Hepatitis B surface antigen was not detected. Oral cholecystography and a drip-infusion cholangiogram showed a normal gall bladder and common bile duct. The initial antimitochondrial antibody (AMA) test was negative, and a percutaneous liver biopsy specimen showed normal liver architecture with a lymphocytic portal tract infiltration. Cholestyramine gave some relief. Three months later itching recurred and she became jaundiced. Two AMA tests were positive. Open liver biopsy showed portal tract fibrosis with a dense chronic inflammatory cell infiltrate and several granulomas. PBC was diagnosed. Her itch responded only transiently to increasing amounts of cholestyramine and thereafter worsened relentlessly. Two years later cervical myelotomy reduced touch sensation without

relieving the itch. In April 1974 brain-stem spinothalamic tractotomy led to hemiplegia, and she died two weeks later. During the last two years she developed deep jaundice, finger clubbing, xanthomas, and hepatosplenomegaly. A further liver biopsy specimen showed advanced biliary destruction. During the last two years she was bedridden and nursed at home by her mother (case 2) and a close friend (case 3).

Case 2—The mother of case 1, a 74-year-old woman, presented with generalised itch in September 1974, five months after the death of her daughter. Examination showed generalised pigmentation and a palpable liver. Senile pruritus was diagnosed. Eight months later the pruritus worsened and the plasma alkaline phosphatase activity (liver origin) was 461 U/l. Plasma bilirubin concentration, alanine aminotransferase activity, and albumin concentration were normal, and hepatitis B surface antigen was not detected. Laparotomy was performed. The gall bladder contained small faceted stones, the extrahepatic bile ducts were normal, and cholecystectomy was carried out. The liver looked cirrhotic, and a wedge biopsy specimen showed severe chronic inflammatory cell infiltration of the portal triads and granulomas. The AMA test was strongly positive, and PBC was diagnosed. Cholestyramine relieved the itch. She subsequently developed jaundice, osteoporosis, and ascites. In July 1978 she died of acute myocardial infarction. Her tissue type was HLA-AW 32/A9/B12/B18.

Case 3—A 43-year-old woman, a close, lifelong friend and near neighbour, nursed the first patient daily throughout the last two years of her illness. She washed her and helped with bedpans during the terminal stages. Two months after the death of case 1 she became tired and suffered right hypochondrial discomfort. An oral cholecystogram showed gall stones, and in May 1975 cholecystectomy was performed. The liver looked normal and an operative cholangiogram was normal. Liver function tests were normal. Eight months later she presented with generalised itch, but no clinical abnormality was found. Plasma bilirubin concentration was 20 $\mu\text{mol/l}$ (1.2 mg/100 ml), alanine aminotransferase activity 99 U/l, and alkaline phosphatase activity (liver origin) 465 U/l. Hepatitis B surface antigen was not detected. Percutaneous transhepatic cholangiography showed no abnormality, and the smooth-muscle and AMA tests were positive. Cholestyramine and aluminium hydroxide relieved her itch. A liver biopsy specimen showed fibrosis and a chronic inflammatory cell infiltration of the portal triads. PBC was diagnosed. Her tissue type was HLA-A2/A9/B5/BW15.

FIG 2—Family tree of case 3 showing antibodies detected in relatives. A=Antimitochondrial. SM=Smooth muscle. Mi=Microsomal. T=Thyroglobulin. Sk=Skeletal muscle. P=Parietal cell. Figures are ages of subjects (years).

case 3 was the sole relative with AMA. Her liver function tests showed only a minimal increase in alkaline phosphatase activity (111 U/l; normal 40-100 U/l), which was of liver origin. The husband of case 3 had thyroglobulin antibody. There was no history of liver disease in either family, and all relatives except the one mentioned above had normal plasma bilirubin concentrations and alanine aminotransferase and alkaline phosphatase activities.

Discussion

PBC is a chronic disease in which autoantibodies, particularly AMA,¹ are almost always found in the blood. Abnormal cellular immune responses also occur.² Family studies show an increased prevalence of AMA and other autoantibodies and increased serum immunoglobulin concentrations in 7-16% of asymptomatic relatives.³⁻⁴ AMA in particular, which occurs in less than 1% of the general population,¹¹ has been found in 7% of asymptomatic relatives of patients with PBC.³ Otherwise healthy people who have AMA in the blood do not necessarily, however, have liver disease.¹¹ This suggests that patients with PBC may share a genetic predisposition to unusual immune reactions that allow other, undefined factors to lead to PBC. Further evidence for the importance of genetic factors in PBC would be obtained by finding the disease in more than one family member. There are few such reports; PBC has occurred in sisters,⁷⁻⁸ twins,⁹ and mothers and daughters.²⁻¹⁰ This paucity of reports would be explained if PBC in the relatives of patients was often asymptomatic.¹² If this were so, it certainly did not apply in these two families, as all asymptomatic relatives apart from the

mother of case 3 had normal liver function values. On the other hand, attempts to obtain evidence for the importance of genetic factors in PBC from the study of ABO and rhesus blood groups and histocompatibility antigens have not been successful.⁵⁻⁶ It therefore seems that whatever the role of genetic factors in abnormal immune reactions in PBC may be, other factors may also be important.

Fagan *et al*¹⁰ described PBC in a mother and daughter. They had lived together for a long time and had presented with PBC within five years of one another, suggesting that recent interaction of environmental and genetic factors had produced the disease. Other reports of familial PBC do not comment on such associations, but related patients have often presented within three years of one another.²⁻⁹ In our study the elderly mother and unrelated friend of the daughter presented with PBC within six years after the clinical onset of the daughter's illness and within two years of close and personal contact with her. It seems reasonable to suggest that some common environmental factor shared at the time of their close physical relationship may have been important in producing the disease. In addition other members of both families studied showed the ability to produce autoantibodies. As PBC may be asymptomatic for a long time,¹² we accept that our experience may be explained by coincidence. On the other hand, taken in conjunction with other reports, our experience supports the view that PBC may result from the exposure of a genetically susceptible person to a particular environmental factor.

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ONE HUNDRED YEARS AGO Dr Ostmann relates the following case in the *Vierteljahrsschrift für Gerichtliche Medizin*. Madame S, who had been married about five months, was suddenly seized with rigors, headache, and vomiting. For about a week, she had been exposed to ill-treatment by her husband, but she had continued her daily work without appearing to suffer from any particular illness. She died suddenly without having experienced any abdominal pain, and without any symptom indicative of abortion. The body was examined twenty-four hours after death. There was a dark discoloration about the abdomen, which was greatly distended. There was no sanguineous discharge from the genital organs; but, at the time of raising the body to place it in a coffin, it was found that a foetus, with its umbilical cord and placenta, had escaped from the vagina. There were no marks of violence on the skin, nor any appearances of wounds or other injuries internally or externally. Putrefaction was far advanced. Between the labia and the inner surfaces of the thighs, there was a knuckle of intestine about eight inches long, as well as a membranous sac. The mucous membrane of the vagina was of a reddish-brown colour, and at the upper end the canal was laid open, but there was no effused blood. The uterus was

found in the membranous sac above described. It was of a dark colour; its walls were thin and soft; and its inner surface had a dirty red colour; at the point of insertion of the placenta, it was of a brownish red. The foetus presented nothing unusual in appearance. The genital organs were carefully examined. There was no mark of wounding or other mechanical injury upon them, and there was no effused blood. On these facts, the experts who examined the body came to the conclusion that abortion had taken place after the death of the woman. They concluded that if it had taken place during life, there would have been copious haemorrhage. Putrefaction had taken place with great rapidity; the gases evolved had accumulated in large quantity in the intestines and the cavity of the abdomen. The pressure produced by these cases had caused an expulsion of the foetus, followed by that of the uterus and intestine. According to the observations of Hoffmann, the pressure produced by the gases evolved in putrefaction is sufficiently great to lead to a rupture of the genital organs and the extrusion of the intestines. The rapid putrefaction of the body had caused in this case, by gaseous pressure, an annular rupture of the uterus and the expulsion of this organ. (*British Medical Journal*, 1879.)