SPECIAL ARTICLE

PRIMARY BILIARY CIRRHOSIS - CURRENT CONCEPTS AND TREATMENT

K M Fock

SINGAPORE MED J 1996; Vol 37: 20-23

Introduction

Primary biliary cirrhosis is a disease of unknown aetiology affecting primarily the small and medium-sized intrahepatic bile ducts as a non-suppurative destructive cholangitis leading to bile duct damage, fibrosis and ultimately cirrhosis. It was first described in 1851 by Addison and Gull[1]. Ahrens[2] termed the condition primary biliary cirrhosis although the term "chronic non-suppurative cholangitis"[3] appears to be a more accurate histological description. Primary biliary cirrhosis and primary sclerosing cholangitis belong to a group of "vanishing bile duct disorders" that manifest clinically as cholestatic liver disease.

Although the aetiology of primary biliary cirrhosis remains unknown, research in the past three decades has resulted in impressive advances in our understanding of its natural history, clinical spectrum and immunological abnormalities. The discovery of anti-mitochondrial antibodies has given us an important tool for diagnosis. Some progress has been made with regard to therapeutic interventions with new drug therapy and liver transplantation. The first definite step towards prolonging survival has been taken with the use of ursodeoxycholic acid, a therapeutic agent which promises to alter disease progression.

Epidemiology

Primary biliary cirrhosis is rare. It has been reported in all parts of the world although it appears to be more common in Europe and North America than in Africa and Asia. Estimates of incidence range from 3-9 per million per year[4-6]. Women are affected more than men (9:1) but the disease runs a similar course in both sexes. There is familial clustering, and primary biliary cirrhosis has been reported in sisters, twins, mothers and daughters[7]. There have been two reports of five cases of primary biliary cirrhosis in Singapore[8,9]. A further twelve cases are reported in the current issue of this journal[10].

Aetiology

Although the aetiology of PBC remains unknown, an autoimmune origin has been proposed[11]. Direct proof is lacking as it is not possible to transfer the disease by autoantibodies or T cells or to produce an animal model of the disease. However, indications in support of immunological destructive process include the presence of disease-specific autoantibodies and T cells, and the finding of activated T and B lymphocytes in the vicinity of bile ducts that express major histocompatibility complex (MHC) class II antigen. The destruction of bile ducts is similar to that seen in graft versus host disease and the association with other autoimmune diseases further supports an autoimmune aetiology.

The initial triggering event may be due to microbial infection (molecular mimicry) or aberrant surface expression of a true autoepitope.

Division of Gastroenterology
Department of Medicine
Toa Payoh Hospital
Toa Payoh Rise
Singapore 298202

K M Fock, MBBS, M Med (Int Med), FAMS, FRACP, FRCP (Edin)
Associate Professor

Clinical features

The clinical features of primary cirrhosis have been well described. Typically, the patient is a middle-aged woman with pruritus, jaundice, portal hypertension, and hepatosplenomegaly, in decreasing order of frequency. Christensen reported in 1980 that 47% of patients presented with pruritus, 12% with jaundice, and 6% with gastrointestinal haemorrhage[12]. In 5% of the patients the presenting symptoms were suggestive of vascular disease or autoimmune disease (such as arthritis, scleroderma, Raynaud's phenomenon). Fifty-two patients in that series of 236 presented with no symptoms referable to the hepatobiliary system. This group is called asymptomatic primary biliary cirrhosis. Increasing use of routine haematological screening of apparently healthy populations or patients with unrelated disorders has led to the recognition of a group of patients with only biochemical abnormalities. Typical of primary biliary cirrhosis is the elevation of alkaline phosphatase, gamma-glutamyltransferase and serum IgM. Alkaline phosphatase is almost always elevated in primary biliary cirrhosis and is of hepatobiliary origin as can be shown by concomitant elevation of 5'-nucleotidase and γ gamma-glutamyltransferase. Values of alkaline phosphatase at presentation are usually more than two times normal. However, patients with primary biliary cirrhosis can have normal alkaline phosphatase levels, and in some instances the serum IgM levels are never or hardly ever increased even in late stage disease. In these patients anti-mitochondrial antibody or liver biopsy provides the basis for diagnosis. The proportion of asymptomatic biliary cirrhosis is substantial. Epidemiological studies in a defined area in Sweden indicate that 50 percent of patients are asymptomatic at time of diagnosis[13]. Although on histology most of the asymptomatic patients had early disease, these patients do progress clinically and histologically. Mitchison found that thirty-five percent of asymptomatic patients become symptomatic and their survival was no different from those with symptomatic disease[14].

Anti-mitochondrial antibody

Antibodies to mitochondria were reported in patients with primary biliary cirrhosis in 1965[15]. Since then, the validity of this test has been confirmed repeatedly[16,17]. Circulating antibodies are found in 95% of patients with primary biliary cirrhosis[18]. They are, however, not confined to primary biliary cirrhosis, being detectable in 30% of patients with

autoimmune chronic active hepatitis and 30% with connective tissue disease. They are also present in the overlap syndrome of primary biliary cirrhosis and chronic active hepatitis as well as drug induced hepatitis. Interestingly, anti-mitochondrial antibodies (AMA) are found in patients with chronic graft versus host disease[19] and this suggests that both diseases may have a related pathogenetic background.

The antibodies are a heterogeneous group and can be subdivided further[16-18]. The M2 variant is specific for primary biliary cirrhosis. M9 is associated with early PBC, healthy relatives of sufferers of PBC and even normal people (10-15%). M8 is specific for PBC and is found only in those who are M2 positive. M3 is associated with drug reaction and pseudo-lupus syndrome, and M6 is seen in collagen vascular disease. Subtyping of these antibodies allows greater diagnostic accuracy for primary biliary cirrhosis. Although much research has gone into the molecular biology of the antigens that produce these antibodies, it is still uncertain whether AMAs are related to the pathogenesis of primary biliary cirrhosis.

Histology

The only hepatic lesion diagnostic of primary biliary cirrhosis is the injured septal or interlobular bile ducts which are usually less than 70-80 μm in diameter. Such ducts are not often seen on needle biopsy but are well represented in surgical biopsies. Granulomas have been found in all stages of the disease but are not specific for PBC, and other conditions with hepatic granuloma such as sarcoidosis need to be considered. As in other chronic cholestatic syndromes, copper can be seen in hepatocyctes and should not be confused with Wilson's disease. Histological staging of biliary cirrhosis employ one of three staging systems: that of Scheuer[20], Popper & Schuffner[21] or Ludwig[22]. Standardised histological staging is important in that serial evaluation can determine if drug therapy is effective in altering the progress of the disease.

Differential diagnosis

Three conditions enter into the differential diagnosis of PBC. Autoimmune cholangiopathy resembles PBC biochemically and histologically; however, AMAs are absent and antinuclear antibodies are present, and serum IgG (rather than IgM) is elevated. In this condition, liver function tests show a hepatitic picture and active hepatitis is seen on histology. In patients with AMAs there is an initial improvement in liver function tests (LFTs) with administration of steroids just as in chronic active hepatitis. The natural history, however, resembles classic primary biliary cirrhosis. Primary sclerosing cholangitis resembles PBC in initial presentation but can be differentiated by absence of AMAs, presence of ANCA (anti-neutrophil cytoplasmic antibody) as well as by cholangiography and histology. Cholestatic sarcoidosis can cause real diagnostic difficulty. It may not be possible to exclude it on the basis of clinical features, serum biochemistry, including serum angiotensin converting enzyme. However serum anti-mitochondrial antibody is negative.

Natural history

The course of the disease is protracted and comprises 4 phases[23]:

(a) a preclinical phase in which the patient is positive for anti-mitochondrial antibodies without hepatobiliary symptoms or LFT abnormality.
(b) an asymptomatic phase in which the patient has abnormalities of LFT without hepatobiliary symptoms, lasting from 1 to 20 years.
(c) symptomatic phase with mild or no jaundice lasting 1 to 10 years.
(d) terminal phase lasting a few months to 2 years.

No spontaneous remission has been documented in PBC. In most patients the course is slowly progressive. However, in some patients complications or manifestations not related to the degree of cholestasis can occur. First, variceal bleeding which occurs generally as a terminal event can occur in some patients in the early stage of disease[24]. Second, ascites may develop[25]. Third, there is a risk of hepatocellular carcinoma that is relatively higher in male patients (present in 33% at autopsy) than in female patients (5% found at autopsy by population models)[26].

At least four prognostic models have been devised to determine the prognosis of patients with primary biliary cirrhosis[27-30] (Table I). In all models bilirubin has been included. These prognostic models are useful in determining the optimal timing of liver transplantation in patients.

Table I – Independent variables predictive of survival on which prognostic index formulae are based

Model	Factors considered
Christensen et al[27]	Age Bilirubin Albumin Histological cirrhosis Histological cholestasis
Dickson et al[28]	Age Bilirubin Albumin Prothrombin time Edema
Rydning et al[29]	Bilirubin Variceal bleeding
Bonsel et al[30]	Age Bilirubin Albumin Prothrombin time HBsAg status Neurological complication Varices Ascites Clinical jaundice

Treatment

The relatively slow progression of the disease makes drug trials difficult. Ultimately the end point of any drug trial for primary biliary cirrhosis should be either mortality or transplantation. Other variables such as symptoms, bilirubin or liver histology may be monitored, but the improvement of these variables does not necessarily mean that prognosis has been improved. Based on analysis of placebo patients in the various trial studies, it has been calculated that if a drug produces a 50% reduction in mortality, then more than 200 patients need to be followed up for five years to show such an effect with statistical confidence[31]. Primary biliary cirrhosis being uncommon, only multicentre trials could accumulate such numbers.

Definitive medical therapy for primary biliary cirrhosis has until recently been universally disappointing. The use of corticosteroids[32], azathioprine[27], D-penicillamine[33] and chlorambucil[34] has resulted only in marginal therapeutic success and, in the case of steroids, chlorambucil and

penicillamine have been associated with an unacceptable profile of adverse effects. Colchicine has produced more favourable results, but improvement in liver function tests has not been accompanied by improvement in symptoms, liver histology, survival or requirement for transplantation[35-37]. Cyclosporin has produced biochemical, symptomatic and histologic improvement. However, nephrotoxicity and hypertension limit the use of this drug[38].

Ursodeoxycholic acid (UDCA) was first used in 1989[39] and thereafter a number of uncontrolled trials were performed. To date, eleven controlled trials exist. Eight authors described symptomatic improvement in 30-60% of patients compared with 20% amongst controls[40]. Poupon demonstrated that the risk of treatment failure from hyperbilirubinaemia or clinical complications was three times higher in the placebo group than in the UDCA group treated for 2 years[41]. Liver histology seems to be positively influenced, but this remains to be statistically proven. Follow-up showed that the need for liver transplantation was reduced by UDCA[42]. A multicentre trial from Canada also showed that UDCA leads to an improvement in the serum markers of cholestasis[43]. This was supported by similar results from the Mayo Clinic[44].

What is the mode of action of UDCA in primary biliary cirrhosis? Recent investigations have shown that relatively high UDCA concentrations protect phospholipid membranes against damage by toxic bile ducts. This may result from its hydrophilic properties[45]. UDCA has also been shown to increase bile flow in animals and it may do the same in humans[46]. Finally UDCA may have immuno-modulating effects[47].

The experience with methotrexate is more limited. Two groups, Bergasa[48] and Kaplan[49], documented improvement in pruritus, liver function tests and liver histology. Toxicity from methotrexate includes interstitial pneumonitis and bone marrow suppression. Dose related hepatotoxicity has not been reported in the limited trials.

Conventional treatment of pruritus has relied on cholestyramine, phenobarbitone and more recently ursodeoxycholic acid. The antibiotic rifampicin has been recently evaluated in several trials[50,51]. Complete relief of pruritus was noted in 79% of patients in one study[50] and in another study a response was evident within 7 days of therapy[51]. Long term treatment was associated with significant side effects in about 10% of patients, and careful monitoring is needed. Overall, these findings are encouraging, and bigger trials are needed to define the role of rifampicin.

Liver transplantation has dramatically improved the prognosis of PBC. In a large series of 161 patients transplanted by the Pittsburgh group the actuarial survival after transplant was 75% at 1 year and 70% at 5 years[52]. Ninety percent of patients were able to return to part-time employment. Patients who undergo transplantation have a marked improvement in quality of life, as both hepatic and extrahepatic manifestations resolve with transplantation.

Whether or not primary biliary cirrhosis recurs after liver transplantation remains a controversial issue. Recurrence of biliary cirrhosis has been reported by Hubscher[53] and Wong[54]. Gouw however was unable to detect any recurrence of disease in a review of 19 transplanted patients[55]. Nevertheless, the persistence of anti-mitochondrial antibodies after liver transplantation would suggest that recurrence is possible although the rate of recurrence may be low.

In conclusion, the last three decades have seen tremendous progress in our understanding of primary biliary cirrhosis as an immunological disorder of the liver and at last we are within sight of prolonging the survival and improving the quality of life of patients with PBC with effective treatment.

References

1. Addison T, Gull W. On a certain affection of the skin - vitiligoidea - a plana βtuberose. Guy's Hosp Rep 1951; 1:265.
2. Ahrens EH Jr, Payre MA, Kunkel HG, Eisenmenger WJ, Blondheim SH. Primary biliary cirrhosis. Medicine (Baltimore) 1950; 29:299.
3. Rubin E, Schaffner F, Popper H. Primary biliary cirrhosis: chronic non-suppurative destructive cholangitis. Am J Path 1965; 46:387.
4. Danielsson A, Boqvist L, Uddenfeldt P. Epidemiology of primary biliary cirrhosis in the northern part of Sweden. Hepatology 1990; 11:458-64.
5. Myszor M, James OFW. The epidemiology of primary biliary cirrhosis in northeast England: an increasingly common disease? Q J Med 1990; 75:377-385.
6. Witt-Sullivan H, Heathcote J, Cauch K, Blerdis L, Gheut C, Katz A, et al. The demography of primary biliary cirrhosis in Ontario, Canada. Hepatology 1990; 12:98-105.
7. Mitchison HC, Malcolm AJ, Bassendine MF, Jaines OF. Metabolic bone disease in primary biliary cirrhosis at presentation. Gastroenterology 1988; 94:463.
8. Lim KP, Ho KT, Gwee HM, Chan HC. Primary biliary cirrhosis in a Chinese female. Med J Aust 1979; 2:364-5.
9. Chong R, Ng HS, Seah CS. Primary biliary cirrhosis. A description of four cases. Singapore Med J 1988; 28:68-71.
10. Yap I, Wee A, Tay HH, Guan R, Kang JY. Primary biliary cirrhosis - an uncommon disease in Singapore. Singapore Med J 1996; 37:48-50.
11. Bjorkland A, Totterman TH. Is primary biliary cirrhosis an autoimmune disease? Scand J Gastroenterol 1994; 29 Suppl 204:32-9.
12. Christensen E, Crowe J, Doniach D, Popper H, Ranek L, Rodeis J. Clinical pattern and course of disease in primary biliary cirrhosis based on an analysis of 236 patients. Gastroenterology 1980; 78:236-47.
13. Lofgren J, Jarnerot G, Danielsson D, Hemdol I. Incidence of biliary cirrhosis in a defined population in Sweden. Scand J Gastroenterol 1985; 20:647-50.
14. Mitchison HC, Lucey M, Kelly P, Neuberger J, Williams R, James OFW. Symptom development and prognosis in primary biliary cirrhosis. Gastroenterology 1990; 99:778-84.
15. Walker JG, Doniach D, Roitt IM, Sherlock S. Serological tests in the diagnosis of primary biliary cirrhosis. Lancet 1965; i :827.
16. Bassendine MF, Yeaman SJ. Serological markers of primary biliary cirrhosis: Diagnosis, prognosis and subsets. Hepatology 1992; 15:545-8.
17. Gershwin ME, Coppel RL, Mackay IR. Primary biliary cirrhosis and mitochondrial autoantigen - insight from molecular biology. Hepatology 1988; 8:147.
18. Berg PA, Klein R. Antimitochondrial antibodies in primary biliary cirrhosis and other disease: Definition and clinical relevance. Dig Dis 1992; 10:85-101.
19. Siegert W, Stemerowicz R, Hopf-U. Antimitochondrial antibodies in patients with chronic graft versus host disease. Bone Marrow Transplant 1992; 10:24-7.
20. Scheuer PJ. Liver biopsy interpretation. 2nd Edition. Baltimore: Williams & Williams, 1973.
21. Popper H, Schaffner F. eds. Non suppurative destruction chronic cholangitis and chronic hepatitis. In: Progress in liver disease, Vol 3. New York: Giune & Strattan, 1970:336.
22. Ludwig J, Dickson ER, McDonald GSH. Staging of chronic non-suppurative destructive cholangitis (syndrome of PBC). Virchows Arch A Path Anat Histol 1978; 379:103-12.
23. Vireling JM. Primary biliary cirrhosis. In: Zakim D, Boyer TD. eds. Hepatology a textbook of liver disease, 2nd ed. USA: WB Saunders 1990: 1158-205.
24. Lebrec D, Sicot C, Benhamon JP. Portal hypertension and primary biliary cirrhosis. Digestion 1976; 14:220-6.

25. Gores GJ, Wiesner RH, Dickson ER, Zimmeister AR, Jorgensen RA, Langworthy A. Prospective evaluation of csophageal varices in primary biliary cirrhosis: development, natural history and influence on survival. Gastroenterology 1989; 96:552-9.

26. Melia WM, Johnson PJ, Neuberger J, Zamar S, Portmann BC, Williams R. Hepatocellular carcinoma in primary biliary cirrhosis: detection by alpha foetoprotein estimation. Gastroenterology 1984; 87:660-3.

27. Christensen E, Neuberger J, Crowe J, Altman DG, Popper H, Portmann B, et al. Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis: trial results of an international trial. Gastroenterology 1985; 89:1084-91.

28. Dickson ER, Grambsch DM, Fleming TR, Fischer LD, Langsworthy A. Prognosis in primary biliary cirrhosis: model for decision making. Hepatology 1989; 10:1-7.

29. Rydning A, Schrumpf E, Abdelnoor M, Elgio K, Jenssen E. Factors of prognostic importance in primary biliary cirrhosis. Scand J Gastroenterol 1990; 25:119-26.

30. Bonsel GJ, Klompmaker IJ, Van't Veer F, Hadberna JBF, Sloof MJH. Use of prognostic models for assessment of valve of liver transplantation in primary biliary cirrhosis. Lancet 1990; 335:443-7.

31. Neuberger J, Lombard M, Golbraith R. Primary biliary cirrhosis. Gut 1991 Sep; suppl: S73-8.

32. Combes B. Prednisolone for primary biliary cirrhosis - good news, bad news. Hepatology 1989; 10:511-3.

33. James O. D-penicillamine for primary biliary cirrhosis. Gut 1985; 26:109-13.

34. Hoofnagle J, Davis G, Schafer DF, Peters M, Avigan MI, Pappas SC, et al. Randomised trial of chlorambucil for primary biliary cirrhosis. Gastroenterology 1986; 91:1327-34.

35. Kaplan MM, Alling DW, Zimmerman HJ, Wolfe HJ, Sepersky RA, Hirsch GS, et al. A prospective study of colchicine for primary biliary cirrhosis. N Engl J Med 1986; 315:1448-54.

36. Bodenheimer H, Schafner F, Pezzallo J. Evaluation of colchine in primary biliary cirrhosis. Gastroenterology 1988; 85:124-9.

37. Zifiari A, Schaffner F. Long term follow up of patients with primary biliary cirrhosis in colchicine therapy. Hepatology 1991; 14:990-3.

38. Lombard M, Portmann B, Neuberger J, Williams R. Cyclosporin a treatment in primary biliary cirrhosis: results of a long term placebo controlled trial. Gastroenterology 1993; 104:519-26.

39. David R, Kurtz W, Strohm WD, Leuschner U. Die Wirkeung von ursodeoxychol - saure bei chronischen leberkrankheiten 2. Gastroenterology 1985; 23:420.

40. Leuschner U. Ursodeoxycholic acid therapy in primary biliary cirrhosis. Scand J Gastroenterol 1994; 29 Suppl 204:40-6.

41. Poupon R, Chretien Y, Poupon RE, Ballet F, Calmus Y, Darnis F. Is ursodeoxycholic acid an effective treatment of primary biliary cirrhosis? Lancet 1987; 1:814-6.

42. Poupon RE, Poupon R, Balkau and the UDCA-PBC study group. Ursodiol for the long term treatment of primary biliary cirrhosis. N Engl J Med 1994; 330:1342-7.

43. Heathcote EJ, Caush-Dudek K, Walker V, Bailey R, Blendis LM, Ghent CN, et al. The Canadian Multicentre doublc blind randomiscd controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1994; 19:1149-56.

44. Linder KD, Dickson ER, Baldus WP, Jorgenen RA, Ludwig J, Murtaugh PA, et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. Gastroenterology 1994; 106:1284-90.

45. Herman DM, Pandak WM, Hylemm PB, Vlahcevic ZR. Conjugates of ursodeoxycholate protect against toxicity of more hydrophobic bile salts: in vitrio studies in rat hepatocytes and human erythrocytes. Hepatology 1990; 12:486-91.

46.Dumont M, Erlinger S, Uchman S. Hypercholeresis induced by ursodeoxycholic acid and ketolithocholic acid in the rat: possible role bicarbonate transport. Gastroenterology 1980; 79:82-9.

47. Calmus Y, Gane P, Rouger P, Poupon R. Hepatic expression of class I and class II major histocompatibility complex molecules in primary biliary cirrhosis: effect of ursodeoxycholic acid. Hepatology 1990; 12:12-5.

48. Bergasa NV, Hoofnagle JH, Axiotis CA, Rabin L, Park Y, Jones EA, et al. Oral methotrexate for primary biliary cirrhosis: preliminary report. Gastroenterology 1991; 100:A720.

49. Kaplan M, Knox T. Methotrexate for biliary cirrhosis. Gastroenterology 1992; 102:18-24.

50. Podesta A, Lopez P, Terg R, Vallamil F, Flores D, Mastai R, et al. Treatment of pruritus of primary biliary cirrhosis with rifampicin. Dig Dis Sci 1991; 36:216-20.

51. Baschs L, Pares A, Elena M, Piera C, Rhodes J. Effects of long term rifampicin administration in primary biliary cirrhosis. Gastroenterology 1992; 102:2077-80.

52. Markus BH, Dickson ER, Grambsch PM, Fleming TR, Mazzaferro V, Klintmalm GB, et al. Efficacy of liver transplantation in patients with primary biliary cirrhosis. N Engl J Med 1989; 320:1709-13.

53. Hubscher SG, Elias E, Buckels JA, Mayer AD, McMaster D, Neuberger JM. Primary biliary cirrhosis: Histological evidence of disease recurrence after liver transplantation. J Hepatol 1993; 18:173-84.

54. Wong PY, Portmann B, O'Grady JG, Devlin JJ, Heqorty JE, Tan KC, et al. Recurrence of primary biliary cirrhosis after liver transplantation following FK 506-based immunosuppression. J Hepatol 1993; 17:284-7.

55. Gouw AS, Haagsma EB, Manns M, Klompmaker IJ, Slooff MJ, Gerber MA. Is there recurrence of primary biliary cirrhosis after liver transplantation? A clinicopathologic study in long-term survivors. J Hepatol 1994; 20:500-7.