Primary biliary cirrhosis—presentation and diagnosis

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Presentation

Asymptomatic patients

The onset of primary biliary cirrhosis is insidious; an initial acute phase of the disease is uncommon. Patients are considered as asymptomatic if no symptoms can be attributed to their liver disease when it is first detected. The duration of the asymptomatic stage varies and may be more than 8 or 10 years. In a British study [3], 36% of the patients developed symptoms during a follow-up period of 6 years; in a Mayo Clinic study [4], 75% became symptomatic within 7.8 years. No predictors were found as to which of the patients would develop symptoms. The ratio between male and female patients was similar for both the symptomatic (20% male, 80% female) and the asymptomatic group, and there were no significant differences in age in all published investigations [5]. In asymptomatic patients, routine investigations as part of a health check or clinical examination because of an unrelated disorder usually show an increased alkaline phosphatase (AP) or gammaglutamyltranspeptidase (γ-GT), or the presence of antimitochondrial antibodies (AMA). At that time many of the AMA-positive but asymptomatic patients with normal biochemistry already have histological features consistent with PBC or typical findings of cholestasis [6]. Others may be referred to an internist because of osteoporosis or because of another associated extrahepatic disorder, as listed in Box 1 below.

Box 1:

Disorders associated with PBC

- Osteoporosis
- Arthropathy, arthritis
- Sjogren's syndrome (dry eyes and dry mouth)
- Raynaud's disease
- Scleroderma
- CREST syndrome or single components (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, teleangiectases)
Systemic lupus erythematosis
Glomerulonephritis
Hashimoto thyreoiditis
Keratoconjunctivitis sicca
Cutaneous disorders (lichen planus, pemphigoid, dermatomyositis)
Coeliac disease
Ulcerative colitis
Pulmonary fibrosis
Gallstones
Hepatocellular carcinoma
Myasthenia gravis

Because the onset of PBC is difficult to recognize, only a few data on the frequency of asymptomatic patients are available. According to an investigation on AMA-positive or negative patients, it has been shown that in Italy about 60% of AMA-positive patients were free of symptoms [7]. In a Swedish study, 46% of the patients were asymptomatic [8]. In an older American report 37% were without symptoms [9], and in a new one 20% were without symptoms [10]. Since 1974, when about 12% of the patients were asymptomatic, this figure has increased to 62% in 1982, likely due to the introduction of multiphasic biochemical screening of blood samples. Because in a larger study from the United Kingdom about 60% at presumed diagnosis of PBC were free of symptoms [11], one can assume that the prevalence of asymptomatic patients ranges from 20% to 80% (median 36.8%) (Table 1)[11–14]. Of course, these figures depend strongly on the attentiveness and care of the investigator.

<table>
<thead>
<tr>
<th>References</th>
<th>Frequency of asymptomatic patients</th>
<th>Hepatomegaly</th>
<th>Splenomegaly</th>
<th>Ascites</th>
<th>Edema</th>
</tr>
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<tbody>
<tr>
<td>Kepelman et al, 1981 [3]</td>
<td>37%</td>
<td>52%</td>
<td>26%</td>
<td>1.9%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Eriksson et al, 1984 [2]</td>
<td>48%</td>
<td>6%</td>
<td>6%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Ryding et al, 1985 [5]</td>
<td>20%</td>
<td>31%</td>
<td>15%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Mecklenburg et al, 1980 [6]</td>
<td>35%</td>
<td>4%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Math et al, 1984 [33]</td>
<td>13%</td>
<td>30%</td>
<td>12%</td>
<td>3%</td>
<td>14%</td>
</tr>
<tr>
<td>Ismaili et al, 1987 [7]</td>
<td>60%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>James et al, 1988 [11]</td>
<td>61%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leuschner et al (unpublished data), 1985</td>
<td>42%</td>
<td>38%</td>
<td>11%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Kim et al, 2000 [10]</td>
<td>30%</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>
The frequency of physical findings in asymptomatic patients ranges from 10% to 80% or even more. Hepatomegaly, for example, was found in 50% to 100% of patients in earlier studies [12,15,16] but in fewer than 10% [3,8] by other investigators. The liver is usually palpable below the costal margin and noted to be firm and smooth. Splenomegaly, which is never massive, has been noted in about 6% to 50% [9,17]. Splenomegaly is observed more often in patients with histological evidence of cirrhosis, but the presence of a large spleen does not necessarily indicate significant portal hypertension. Other physical findings, such as xanthelasma, xanthomata, and hyperpigmentation will be discussed later.

**Pattern at presentation of asymptomatic and symptomatic patients**

Symptomatic patients present with pruritus, fatigue, and abdominal pain as classical symptoms, and scratch marks, jaundice, hepato- and splenomegaly as uncharacteristic but frequent signs. As shown in Table 2, the prevalence of pruritus seems to have decreased between 1973 and 1989, possibly because more and more patients are being detected in the early stages I and II of the disease, but the complaint of fatigue seems to have increased. In the 1950s, about 80% of patients presented with jaundice; in 1989 only 3.8% so presented [18]. In former years, pruritus was described in more than 50% of the patients, but in recent studies in only 20%. Fatigue was not reported in a case series of 100 in 1973 [19] and now is reported in up to 81% [20], maybe because physicians became aware that lethargy was a typical symptom of primary biliary cirrhosis. In a more recent study, fatigue was reported to affect fewer patients [21]; however; the real figure for this rather subjective symptom is uncertain [22–24]. The use of a standard validated screening system may settle this issue (see Table 2).

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<tr>
<td>Jaundice</td>
<td>30%</td>
<td>12%</td>
<td>9%</td>
<td>16%</td>
<td>3%</td>
<td>11%</td>
<td>4%</td>
<td>4%</td>
<td>8%</td>
<td>25%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
<td>11%</td>
<td>4%</td>
<td>81%</td>
<td>81%</td>
<td>45%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>57%</td>
<td>47%</td>
<td>59%</td>
<td>18%</td>
<td>16%</td>
<td>35%</td>
<td>26%</td>
<td>--</td>
<td>--</td>
<td>49%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0%</td>
<td>7%</td>
<td>1%</td>
<td>1%</td>
<td>--</td>
<td>--</td>
<td>5%</td>
<td>8%</td>
<td>8%</td>
<td>45%</td>
</tr>
</tbody>
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(a) Double dash indicates information not provided.

Concerning the histological stage of asymptomatic and symptomatic patients, several authors have shown that 42–66% of asymptomatic patients are at an earlier stage, whereas symptomatic patients in 79% to 82% are at a later histological stage of the disease [25], although stage III or IV is still found at presentation in 34% to 57% of asymptomatic patients. There are probably no histological differences between symptomatic and asymptomatic patients.

**Fatigue**

Persistent fatigue is now the most common symptom in patients with primary biliary cirrhosis, occurring in about 20% to more than 80% [21,26]. Synonyms of fatigue are lethargy, exhaustion, malaise, or lassitude. Fatigue interferes with normal daily activities to the same degree as seen in patients with end-stage renal failure [27]. This means that
lethargy is a significant problem for most patients with PBC, and in almost 50% it is the predominant and worst symptom [28]. Fatigue was underestimated in previous years, although as early as in 1990 it was described as interfering with physical activity in 73% of the patients and with family life in 57% [20]. Physicians are unable to treat fatigue and even patients themselves overlook or ignore fatigability, because PBC is a disease of middle-aged women who may explain fatigue with growing older, and thus expect a decrease in physical activity.

In the United Kingdom it has been shown using the Fisk Fatigue Severity Score, developed to assess the impact of fatigue on the quality of life [29], that these scores were significantly higher in PBC patients than in chronic hospital-attending controls [26] or in age- and gender-matched healthy community controls [21]. Fatigue does not appear to be related to patients' age, gender, or relevant intercurrent disorders such as thyroid disease. No correlation between fatigue score and liver histology, histological stage of the disease, and the Childs-Pugh score was noted, and no association with liver function parameters such as serum bilirubin, albumin, or prothrombin time was found [21,26]. Interestingly, there was a weak correlation between fatigue and pruritus, which was not merely an effect of sleep disturbance, as has been shown by measuring sleep quality with polysomnography [30]. None of the patients in these studies had a history of encephalopathy, but all have shown a weak positive correlation between fatigue and depression or obsessive-compulsive disorder. A similar correlation was seen in the control group, however, likely because fatigue is often a component of depression. Further, there were no significant differences in patients treated or not treated with ursodeoxycholic acid and patients who had to be transplanted.

Fatigue is also associated with chronic autoimmune hepatitis, chronic hepatitis-C, alcoholic liver disease, and nonalcoholic steatohepatitis (NASH) [21,31,32], but the fatigue score is higher in PBC.

**Pruritus**

Pruritus is one of the most common symptoms, seen in 20% to 60% of jaundiced patients with PBC [33] (see Table 2), which means that in jaundiced patients it is almost as common as fatigue. Taking all PBC patients together, 80% will experience pruritus during the course of the disease [34]. Pruritus is most often present in the absence of jaundice in PBC and develops in 50% to 60% of PBC patients [19]; it precedes jaundice in more than 90% by months or years. Jaundice develops later during the course of the disease, is persistent, and is associated with a poor prognosis. Pruritus may first occur during pregnancy, and therefore may be mistaken for pruritus of idiopathic cholestasis of pregnancy. In the postpartum period, pruritus of pregnancy resolves rapidly, whereas pruritus due to PBC persists, worsens, or recurs after a short interval. As mentioned above, pruritus is correlated with fatigue [26], not caused by sleep disturbance. Other symptoms such as abdominal pain, weight loss, nausea, vomiting, and anorexia often accompany pruritus.

The onset of pruritus usually is insidious. It can be localized or generalized and often commences in the perianal and genital region or on plantar and palmar surfaces. Itching is usually worse in the evening and at night, enhanced in warm weather, in bed, under a belt, or in woolen socks. It increases during the winter and is associated with dry skin. In some patients, pruritus is exacerbated during pregnancy and hormone replacement therapy. Pruritus in PBC is not effectively eased by scratching.
Pruritus may occur at any point in the course of the disease, but it may also subside spontaneously, mostly during the late stages of the disease. Intractable pruritus may lead patients to contemplate suicide. Severe pruritus unresponsive to treatment is an indication for liver transplantation [35,36]. Because the degree of pruritus does not correlate with routine biochemical indices, bilirubin, or cholestasis indices, indication for liver transplantation is exclusively determined by the subjective feeling of the patient when medical treatment fails.

Pruritus does not originate from primary pruritic skin lesions, but local, secondary lesions such as excoriations or prurigo nodularis due to scratching may develop. Finally, a rough and thickened skin with hyperpigmentation as a consequence of chronic scratching and due to increased deposition of melanine becomes apparent [37]. There may be a paler so-called “butterfly” area over the back that is inaccessible to scratching. Therefore, patients may initially be referred to a dermatologist or even a psychiatrist. Pruritus does not correlate with the existence of xanthomata or xanthelasma.

**Jaundice**

Jaundice characterizes the later stages of the disease, although it may be the initial symptom in about 10% of patients, usually in association with pregnancy or the intake of contraceptives or other estrogen-based medication [9,13,18]. In the 1950s, about 80% of the patients were yellow at first presentation. In the later phase of the disease, jaundice is seen in 50% to 60% of symptomatic patients, but in fewer than 10% of asymptomatic patients [38]. Accordingly, serum bilirubin in the jaundiced patients has increased to 48 ?mol/l (2.8 mg/dl) with a range of 3.2 to 493 ?mol/l (0.2–29 mg/dl). As can be seen in Table 2, jaundice seems not to be correlated with pruritus, being observed 2 to 7 times more often than jaundice. In severe cholestasis, steatorrhea with fecal fat excretion up to 70 g per day has been reported [39]. Despite the high losses of fat-soluble vitamins A, D, E, and K, only 1% to 2% of the patients experience night blindness. Due to vitamin K-deficiency, prothrombin time may be prolonged, with an increased tendency to bleeding after trivial trauma.

Jaundice slowly increases as a consequence of progressive hepatic bile-duct destruction, and it usually precedes other clinical manifestations such as ascites, bleeding esophageal varices, or encephalopathy. When jaundice is established, it parallels the increase of skin pigmentation and hepatomegaly. Within 5 years of presentation with symptomatic PBC, 20% or more patients will be icteric [22].

**Other features of the clinical pattern**

**Xanthomata**

Xanthoma are seen in about 15% to 50% of patients [14,22,40], but represent the first finding in less than 1% [22]. In symptomatic patients, both xanthomata and xanthelasma are seen more often than in asymptomatic patients (11%). Xanthomata may be eruptive, tuberose, or planar, and first appear in the palms. They are most prominent on knees and elbows, over the neck and trunk, and under the breasts. Tuberose xanthomata develop on extensor surfaces of the extremities, especially on knuckles and the Achilles tendon. In a few patients, the development of xanthomatous neuropathy has been described [41]. Patients then complain of numbness and tingling in hands and feet, pain in the fingers and toes.
Xanthomata have been described as being associated with serum cholesterol concentrations of 600 to 800 mg/dl, especially with high density lipoprotein (HDL), but this has not been corroborated by more modern studies [19]. Attempts to diminish xanthomata or xanthelasma by low-fat diet, clofibrate or plasmapheresis were without any success or even were detrimental [42]. Xanthomata resolve slowly as liver function deteriorates during disease progression. Xantheasma are common and present as yellowish plaques in the skin of the eye lids, commonly near the internal canthus. When xantheasma are removed surgically, they very often recur within a few months.

As in all chronic liver diseases uncharacteristic abdominal pain in the right upper quadrant is an nonspecific symptom, seen in about 7% to 10% of patients with primary biliary cirrhosis [18,19,22]. Because gallbladder stones have been described in about 30% of the patients [43], commonly pigment and not cholesterol stones, epigastric pain could originate from the gallbladder, but most of the gallbladder stones are asymptomatic. In many patients, abdominal pain resolves spontaneously.

**Portal hypertension**

Portal hypertension is a common complication of PBC, but fewer than 50% of the patients present with variceal bleeding or ascites. In some patients with PBC, liver disease is first recognized when hemorrhage occurs, mostly because in these cases the disease has progressed quiescently. But hemorrhage does not necessarily imply complete liver cirrhosis, as presinusoidal blockage of the blood flow by nodular hyperplasia may also induce portal hypertension [44,45]. In probably 25% to 50% of PBC patients, esophageal varices are due to hyperplastic nodules [46,47]. Portal hypertension can be present in the absence of varices and is only accurately measured by determination of the wedged hepatic vein pressure [48]. The progression of portal hypertension is not well documented. In an older study with 265 PBC patients, 31% developed new varices over a 7-year follow-up period [49]. By the end of the first year, 16% already had varices, by the end of the third year, 31% did. Forty-eight percent of those with documented varices had episodes of hemorrhage over the same period. In another study, it was shown that varices develop in 25% within 2 years and 75% with 4 years [50]. From these data, it can be concluded that portal hypertension is a common finding in patients with primary biliary cirrhosis, but is rarely severe.

In some patients, portal vein thrombosis has been reported more often than in cirrhosis of any other etiology. Spider naevi are less frequent and less prominent than in postnecrotic or alcohol cirrhosis.

**Osteopenia and osteoporosis**

Osteopenia and osteoporosis remain unrecognized in many patients. The World Health Organization defines osteopenia as a bone mineral density 2.5 standard deviations below the young normal mean (T score) (T-values from −1 SD to −2.5 SD) and of osteoporosis as >−2.5 SD. The postmenopausal frequency of osteoporosis in PBC is unknown.

In patients with advanced PBC, liver disease predominates until pre-existing osteopenia and osteoporosis presents with severe pain in ribs or in the back due to fractures. Despite the high incidence of osteopenia [51], clinical symptomatology related to bone...
disease is less common when the disease is mild. Severe acute pain occurs at fracture sites, and yet some patients may lose height without any acute bone pain [52]. Fractures commonly occur at the ribs and vertebra, especially if patients have been treated with prolonged corticosteroid therapy, and rarely at the long bones of the extremities or the pelvis.

The risk of developing osteoporosis in patients with stage III or IV is said to be fivefold higher than in stage I or II [53]; in the latter, bone mineral density is similar to the expected density in the normal population. Factors indicating the presence of osteoporosis in PBC patients are advanced age, lower body mass index, and more advanced histological stage. The only independent variable correlating with the rate of bone loss was bilirubin in the Menon study—in contradiction to an earlier study [54].

Although most reports indicate that osteoporosis is associated with primary biliary cirrhosis, recent studies applying a more sophisticated stratification of patients questioned this observation [55–57]. The authors showed that osteoporosis was no more prevalent in patients with PBC than would have been expected in a normal population of comparable age and gender. These differences may be explained by differences in severity of PBC.

Osteomalacia was common in patients when they presented with late stage PBC [58,59], being due to vitamin D deficiency as a consequence of intestinal malabsorption. Because patients are nowadays diagnosed earlier with mild cholestasis and without steatorrhea, osteomalacia in PBC is no longer seen [60,61].

**Hepatocellular carcinoma (HCC)**

The presence of liver cirrhosis is a risk for the development of hepatocellular carcinoma (HCC). Previous studies suggested that cirrhotic PBC is a relatively rare precursor of the development of HCC [62,63]. In a study of 273 patients identified with histologically confirmed stage III or IV PBC, 16 cases (5.9%) developed hepatocellular carcinoma during a period of 20 years [64]. The incidence was significantly higher in males (20%) than in females (4.1%). Because HCC probably develops several years after cirrhosis has been present and no prospective models exist, careful screening for HCC may be appropriate in those with cirrhosis. In a recent Japanese study of 396 patients, HCC developed in 3.5% within an observation time of 6 months to 22 years. Independent risk factors for the development of HCC were advanced age, male gender, and a history of blood transfusion [65]. Whether a superinfection with hepatitis C virus plays an important role in the development of HCC in PBC patients with cirrhosis remains unanswered [66].

**Ulcerative colitis**

The association of primary biliary cirrhosis with ulcerative colitis is very rare and only few case reports have been published [67–69]. Diarrhea in patients with PBC is more often due to pancreatic hyposecretion in sicca syndrome or celiac disease, which is discussed further below.

**Different presentation in males and females**

The question of whether male and female patients with PBC present with different features has been investigated in only in a few studies [40,70]. In the smaller study [70], with
30 age-matched women and men, the authors found no differences. In the second study from England [40], stage of the disease, serum bilirubin, alkaline phosphatase, gastrointestinal bleeding, ascites, hepatomegaly and splenomegaly, and xanthomata were identical in men and women (Table 3). When symptoms and signs were compared at diagnosis, pruritus was present significantly more often in women. When female patients were stratified into pre- and postmenopausal patients, pruritus was more marked in the premenopausal group. Hyperpigmentation related to pruritus was also recorded, significantly less frequently in males. The number of patients without any liver-related symptoms and signs was equal in both groups. Of the associated extrahepatic diseases, only Sjogren's disease was seen significantly more commonly in women, whereas scleroderma, Raynaud's phenomenon, or autoimmune thyroiditis were the same in both sexes.

<table>
<thead>
<tr>
<th>Physical signs [41]</th>
<th>Men</th>
<th>Women</th>
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<tr>
<td>Hepatomegaly</td>
<td>88%</td>
<td>95%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>51%</td>
<td>56%</td>
</tr>
<tr>
<td>Ascites</td>
<td>14%</td>
<td>10%</td>
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<tr>
<td>Xanthomata</td>
<td>8%</td>
<td>18%</td>
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<tr>
<th>Liver-related symptoms [41]</th>
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<tr>
<td>Pruritus</td>
<td>45%</td>
<td>68%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>44%</td>
<td>53%</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>23%</td>
<td>15%</td>
</tr>
<tr>
<td>No symptoms</td>
<td>23%</td>
<td>12%</td>
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<th>Laboratory data [41]</th>
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<tr>
<td>Bilirubin</td>
<td>44 μmol/l</td>
<td>33 μmol/l</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>645 U/l</td>
<td>640 U/l</td>
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<tr>
<td>I, II</td>
<td>41%</td>
<td>42%</td>
</tr>
<tr>
<td>III, IV</td>
<td>59%</td>
<td>58%</td>
</tr>
<tr>
<td>Hepatocellular cancer [66]</td>
<td>20%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Data on extrahepatic complications are not given; will be treated later.


**AMA-negative PBC and overlap syndrome of PBC with autoimmune hepatitis**

There are no unequivocal definitions of the overlap syndrome (OLS) between PBC and autoimmune hepatitis and of AMA-negative PBC, also called autoimmune cholangitis (AIC). In the autoimmune hepatitis/PBC OLS, biochemical, serological, or histological findings of the two diseases are present in the one patient. In adult patients, this overlap syndrome is seen in about 8% to 10% [71–73].

Patients with OLS usually present with no specific symptoms, so it is not possible to differentiate those with autoimmune hepatitis from those with primary biliary cirrhosis based on symptoms. Patients may be of either gender; more commonly they are women (as usual in
autoimmune hepatitis and PBC) and of younger age. Recently, however, the first case of an autoimmune hepatitis/PBC overlap syndrome in a child has been reported [74]. This patient presented all features of an autoimmune hepatitis and none of primary biliary cirrhosis, except antimitochondrial antibodies. Due to the small number of patients with OLS and AIC, no one has enough experience and observations on the clinical presentation of these patients, except that patients with an overlap syndrome seem to have less often pruritus [72]. Further aspects of the overlap syndromes will be discussed within this issue.

In 5% to 10% of patients with PBC, AMA are not detectable using standard techniques. This variant is called AMA-negative primary biliary cirrhosis, second variant of the AIH/PBC OLS, or autoimmune cholangitis [71]. As has been shown by several investigators, AMA-negative PBC patients are indistinguishable from AMA-positive patients regarding symptoms and the presence of other autoimmune disorders and complications [74]. The largest study is from Italy [7] and reports on 297 patients, of which 30 (10%) were AMA-negative. At the initial visit, there were no differences between the two groups for gender, patients' age, percentage of asymptomatic patients, number of major complications of cirrhosis, duration of the disease, anti-HCV, HBs-Ag, and HBc-antibodies.

In conclusion, patients with an autoimmune hepatitis/PBC overlap syndrome and with autoimmune cholangitis clinically cannot be distinguished from classic PBC. Only more detailed laboratory (including immunogenetic tests) and histological investigations allow differentiation.

Diagnosis of primary biliary cirrhosis

Since antimitochondrial antibodies (AMA) were introduced into diagnostic procedures for primary biliary liver diseases, diagnosis has become easy [15]. In addition, a more comprehensive recognition of typical characteristics as well as epidemiological studies have allowed definition of the incidence and prevalence of PBC over the last 20 years.

The classic diagnostic triad for PBC consists of increased enzymes indicative of cholestasis (ie, alkaline phosphatase), positive antimitochondrial antibodies, and diagnostic liver histology. Some patients do not present with all three criteria, however, but only with positive testing for AMA, and compatible or diagnostic liver histology, but with normal liver enzymes. These patients were named “probable” PBC patients by a group from the United Kingdom, whereas the triad was referred to as “definite” PBC [11,25]. Finally, there is one group which is only positive for AMA without any other characteristics for PBC (Table 4). For patients with “probable” PBC, the authors have shown [6] that at least 80% of these patients ultimately will develop abnormal liver function tests and eventually 75% will present with classic symptoms of liver disease [25]. This includes patients with a so-called “AMA-negative PBC” or “autoimmune cholangitis” [71].
It is of interest that none of the diagnostic groups mentioned in Table 4 includes any clinical symptoms. Because symptoms such as pain in the upper abdominal quadrant, or findings such as jaundice, ascites, variceal hemorrhage, and so on are common to all chronic liver diseases, especially in the late stages, only pruritus, mental and physical fatigue, and xanthomata or xanthelasma in a middle-aged woman suggest PBC as the diagnosis (Table 5). Because up to 60% of patients with PBC may be asymptomatic, in 43% of patients diagnosis will not even be considered [25], showing that the real number of patients with PBC is underestimated.

### Laboratory tests

The most important laboratory finding is the presence of antimitochondrial antibodies (Table 6). If a negative result is obtained but the disease is suspected, the test should be redone in another laboratory. In clinical practice, AMA can be detected by immunofluorescence, enzyme-linked immunosorbent assay (ELISA), or immunoblotting. The specificity of AMA in the presence of cholestasis is such an impressive predictor value that in patients with AMA titers $>1:40$ the liver histology is compatible with PBC in more than 97% [25]. Thus for the diagnosis of PBC, the sensitivity of AMA is 98% and specificity 96%.
AMA are routinely found in 85% to 90% of the patients, but in 10% to 15% they are not. The most important subtype of AMA for patients with PBC is M<sub>2</sub>, directed against the pyruvate dehydrogenase complex (PDC-E2), located in the inner mitochondrial membrane of bile duct endothelial cells. Other subtypes such as M<sub>4</sub>, M<sub>8</sub> and M<sub>9</sub>, located in different places of the mitochondrion, were believed to be prognostic [75], but a further study by the same authors does not support this finding. The AMA status probably does not affect treatment with ursodeoxycholic acid or liver transplantation [76].

Antimitochondrial antibodies may be detectable many years before any symptoms or biochemical features are present. Most of these patients have abnormal liver histology [77]. A decade later, nearly 80% will have developed symptoms and 83% cholestatic liver tests. These data show that almost all those who test positive for antimitochondrial antibodies will develop to PBC patients within 10 to 15 years [6].

It is of interest for the clinician that the titer of AMA does not correlate with clinical disease and that there is no correlation with disease progression [78]. After liver transplantation, AMA titers decrease but will return to pretransplant levels after a couple of months. Although after transplantation PBC recurs in only 20% of the patients, nearly 100% of transplanted patients are AMA positive [79]. Whether the standard treatment of PBC with ursodeoxycholic acid (UDCA) influences AMA titers is uncertain [76]. In one study from Japan [80], AMA disappeared in the serum in 20% of the treated patients with AMA titers between 1:40 and 1:80, but there was no evidence that this was associated with a therapeutic response. In our own 162 patients with PBC, AMA never disappeared, although some patients were treated for more than 20 years.

In patients who are AMA negative, other disease-specific antibodies can be detected. Antibodies against the nuclear core protein gp210 (ANA) are found in 10% to 40% of patients who are AMA positive and in about 50% of AMA-negative patients. The specificity for PBC is over 99% and the antibody may have prognostic significance [81]. The antibody against the nuclear pore protein p62 is present in about 25%, and the antibody against the protein of an inner nuclear membrane is found in fewer than 1%. That means in the 10% to 15% AMA-negative patients the detection of specific antinuclear antibodies closes the gap.
The liver enzyme pattern of PBC is classically cholestatic (see Table 6). Alkaline phosphatase (AP) and gammaglutamyl transpeptidase (GGT) levels are usually elevated to a greater degree than levels of AST and ALT. AP reaches a plateau early in the course of the disease and, like GGT, fluctuates within 20% to 30% of its concentration thereafter. AP usually ranges from concentrations slightly above the upper normal limit to 1500 or 2000 U/l, GGT to 300 or 500 U/l (10 or more times the upper limit of normal). Concentrations of alkaline phosphatase and GGT are not related to the rate of progression or the stage of the disease, which means they are not of prognostic value. Also, the concentration of immunoglobulin M (IgM) is elevated in almost all patients and ranges from 1.5 to 10 fold of the upper limit of normal. Like AP and GGT, IgM also does not correlate with the stage or the progression of the disease or AMA titers. Transaminases, gammaglobulins, serum albumin, and serum bile salt levels are of little help in establishing the diagnosis. In all cholestatic liver diseases, bile salts are increased in the serum. Serum lipids may be strikingly elevated, although patients with early PBC tend to have normal values or only mild elevations. In early disease, the HDL is high and only as the disease progresses do levels of LDL rise.

Bilirubin rises in all patients in the end stage of the disease. Bilirubin is a useful prognostic factor [82] that seems to be superior to all other prognostic models. Life expectancy is about 25 months when bilirubin is ≥6 mg% (≥102 ?mol/l) and less than 20 months when bilirubin exceeds 10 mg% (>170 ?mol/l).

Little attention has been paid to the relationship between laboratory data and liver histology. In one study [83], it has been shown that IgM levels in PBC patients were associated with intralobular bile duct lesions, whereas bile duct paucity was highly associated with serum GGT. Unexpectedly, the strongest link of liver fibrosis was with total gammaglobulins and immunoglobulin G (IgG). These interesting data have to be corroborated in further studies.

Laboratory tests typical for the overlap syndrome with autoimmune hepatitis will be discussed in another article in this issue.

**Imaging procedures**

Imaging procedures such as ultrasonography, computed tomography (CT), or magnetic resonance tomography (MRT) are not diagnostic. They may help in staging the liver disease by demonstrating signs of portal hypertension or an irregular shape of the liver and by excluding liver tumors, intrahepatic gallstones, or parasites.

The issue of whether liver histology is mandatory to make a confident diagnosis can be questioned. Though diagnosis of PBC in most patients can be established with a high degree of specificity by less invasive laboratory investigations, in some cases histology may be helpful, and in all patients it is desirable, if only to assess prognosis, and in a few cases to exclude other diseases with or without immune-mediated bile duct lesions such as primary sclerosing cholangitis, overlap syndromes, sarcoidosis, drug reactions, and so on. Once a definitive diagnosis of PBC has been established, further liver biopsies are not necessary.

There are four staging systems that have been used in the histological assessment of PBC [84]. All four agree that stage I is characterized by bile duct damage or portal inflammation. Stage IV is defined by the presence of liver cirrhosis. In stage II and III the
criteria vary, although all of them describe bile duct proliferation, periportal hepatitis, bridging necrosis, fibrosis, and scarring, but all in varying degree. A simplified system based only on the amount of scar tissue [84] would be in line with a staging concept developed for chronic hepatitis, where grading is performed by necroinflammatory features. In stage I of the simplified system there is no fibrosis visible; in stage II periportal fibrosis exists; in stage III, bridging fibrosis; and in stage IV, liver cirrhosis (Table 7).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Scheuer 1967</th>
<th>Gotto 1970</th>
<th>Ludwig et al 1978</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Bile duct lesion</td>
<td>Cholangitis</td>
<td>Portal hepatitis</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Ductular proliferation</td>
<td>Ductular proliferation</td>
<td>Periportal hepatitis</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Scarring</td>
<td>Precirrhotic stage</td>
<td>Bridging necrosis and/or fibrosis</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

Summary

Primary biliary cirrhosis is predominantly seen in middle-aged women. Typical symptoms are fatigue, pruritus, and abdominal pain. Jaundice develops in the end-stage disease. At presentation, about 40% of the patients are asymptomatic, but 30% to 50% already have hepatomegaly, and 15% present with splenomegaly. Even patients with fully developed liver cirrhosis may be free of symptoms. Abnormal physical signs and advanced histological stage are more frequent in symptomatic than in asymptomatic patients. Fatigue, pruritus, and Sjogren's syndrome are more common in women than men, but other signs and symptoms do not differ in the two sexes. PBC is associated with a large variety of other diseases, like arthropathy, CREST syndrome, autoimmune thyroiditis, and so on, which in addition will or will not produce symptoms. Hepatocellular carcinoma is a rare complication in women, but more frequent in men.

Diagnosis can be established by the triad antimitochondrial antibodies (AMA), cholestatic indices, and liver histology, diagnostic or compatible with PBC. When AMA are not detected, then antinuclear antibodies (autoantibodies against gp 210 and others) can be detected in 50% of AMA-negative patients. AMA titers do not correlate with the course of the disease nor histological progression. After liver transplantation, AMA recur in nearly 100%. The liver enzyme pattern in PBC patients is cholestatic; alkaline phosphatase and gammaglutamyltransferase increase to 10 or more times the upper limit of normal. The amount of enzymes does not correlate with disease progression or stage of the disease. The only prognostic factor in PBC is serum bilirubin.

AMA-negative patients account for about 10% to 15%. Routine biochemical tests are not different fromAMA-positive patients, but usually higher ANA, SMA, and IgG concentrations are detected. Histologically, it is PBC. The overlap-syndrome, autoimmune hepatitis-PBC presents with the histological features of autoimmune hepatitis and PBC, with AMA, ANA, or SMA.

Imaging procedures are not helpful for the diagnosis of PBC, except for liver histology. Histologically, four different stages can be assessed, ranging from florid bile duct lesions,
ductular proliferation, and fibrosis to liver cirrhosis. Liver histology is of interest for the assessment of the diagnosis and for staging of the disease.

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