Primary biliary cirrhosis (PBC)

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Primary biliary cirrhosis (PBC)

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What is primary biliary cirrhosis?

Primary biliary cirrhosis (PBC) is a chronic, progressive disease of the liver that is initially focal, i.e. it affects only certain regions of the liver, but over time progresses to affect the entire organ. It starts in the small bile ducts, which are destroyed by an inflammation. This results in retention of the bile produced in the liver and the deposition of toxic bile acids and other toxic compounds.

Because the inflammation is not caused by white blood cells and no pus is produced, the disease is also known as *non-suppurative destructive bile duct inflammation*. Its more common name, *primary biliary cirrhosis*, is due to the fact that the disease was formerly identified only in its terminal stage, which is characterized by cirrhosis. Today, early diagnosis is possible. The old name *primary biliary cirrhosis*, however, has been retained because of its established place in clinical practise. Because the blood or serum of patients with PBC contains so-called immune markers, which point to the presence of certain immunological reactions, and corresponding cells are found in the liver (see below), scientists speak of an autoimmune disease in which the cells of the immune system attack the body's own tissues.

Frequency of the disease and its duration

In 80–90% of cases, primary biliary cirrhosis affects women, males only in 10–20%. The disease very rarely strikes children but its frequency is higher than thought even a few years ago.

Untreated, patients with PBC have an average survival of 12 years, with a maximum of 20 years. The

medications currently available have resulted in a significant prolongation of the clinical course and the option of liver transplantation, which may ultimately be required, can result in a large proportion of patients being cured.

Staging

Current practice divides PBC into four stages (stages I–IV), although the exact length of the individual stages is unclear.

Stage I: In this stage, the inflammatory changes are restricted to the bile ducts (figure 1) and the immediately surrounding connective tissue (non-suppurative destruction of the bile ducts). The inflammatory cells involved at this stage are so-called immunocompetent cells, which, as mentioned above, attack the person's own liver. Cells of this type are also found in other immune diseases of the liver, for example in autoimmune hepatitis.

Stage II: This stage is characterized by increased formation of bile ducts (bile duct proliferation). These new bile ducts try to replace the destroyed ones. The inflammatory changes in the surrounding connective tissue consolidate and may spread to neighbouring liver tissue (figure 2).

Stage III: More and more bile ducts are now destroyed (bile duct rarefication). Adjacent hepatic tissue is increasingly affected by inflammatory change and an increase in connective tissue heralds the onset of cirrhosis (figure 3).

Stage IV: Connective tissue has increased further and has separated the remaining liver tissue into fields of different size. Because of the tendency of liver tissue to regenerate, regeneration nodes of varying size appear (figure 4). This makes the surface of the liver

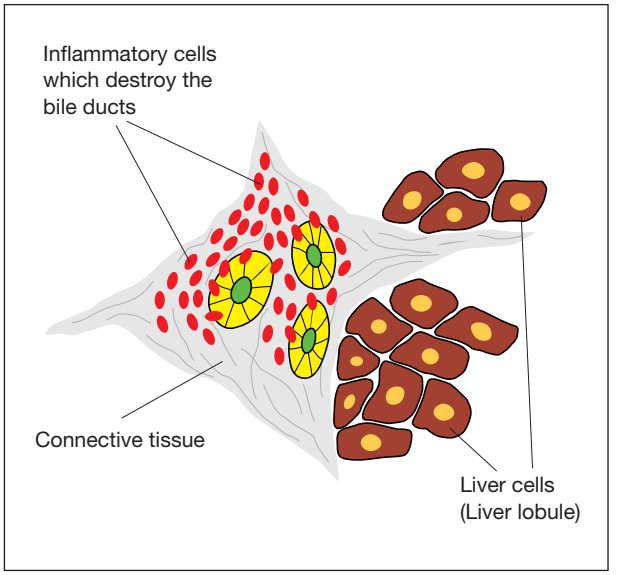

Figure 1: PBC stage I

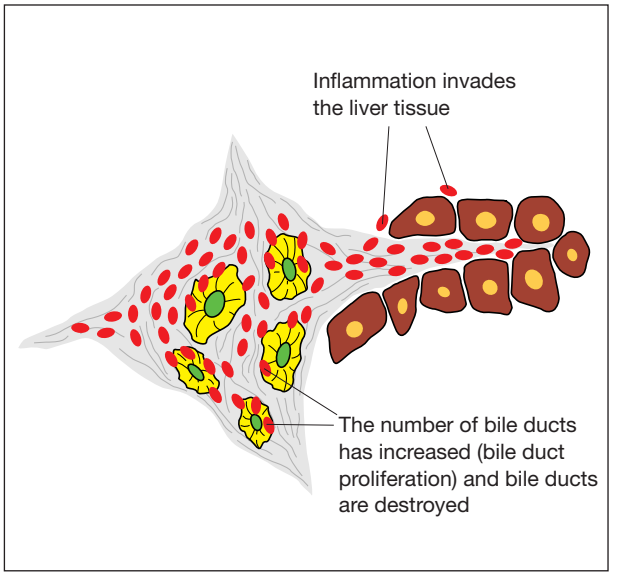

Figure 2: PBC stage II

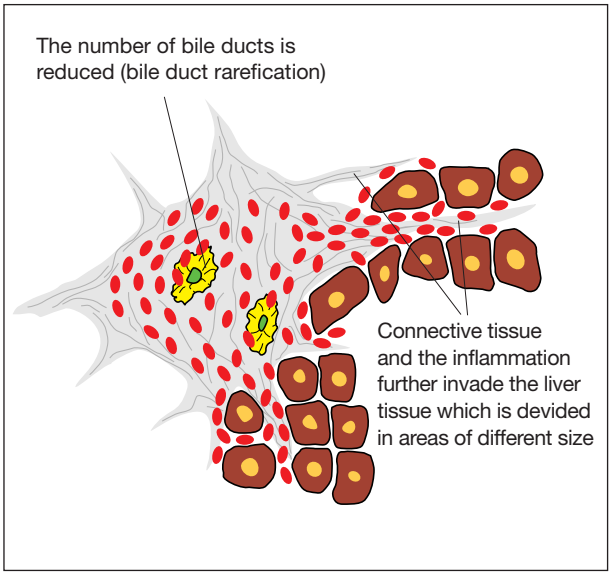

Figure 3: PBC stage III

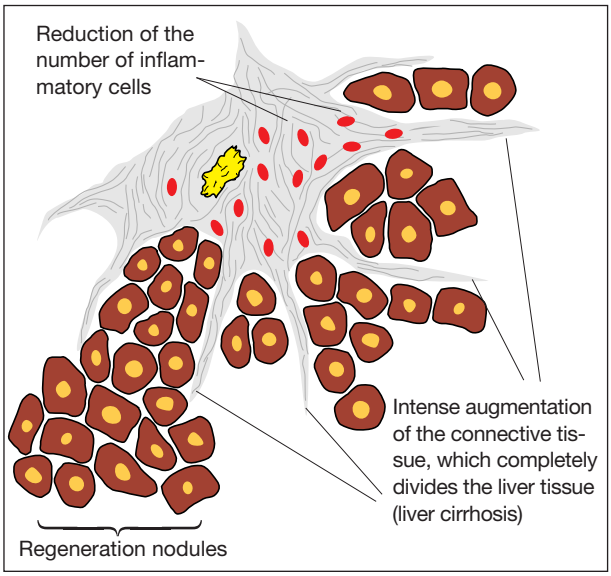

Figure 4: PBC stage IV

bumpy. The bile ducts continue to disappear and inflammatory cells in the surrounding connective tissue have become fewer. We have now reached complete cirrhosis (PBC). Since in complete liver cirrhosis not only bile ducts have changed their course in the liver but also blood and lymph vessels, blood and lymph can be accumulated and esophageal varices and ascites will develop.

How does one recognize primary biliary cirrhosis?

The first symptom of PBC is often pruritus (itching), which can be mild but may be moderate or even severe, and which is most noticeable at night. Most often affected are the arms, back and legs. Pruritus can increase in the warmth (for example in the bed) or in dry air (heating period). Patients may also experience significant fatigue or reduction in performance as a first sign of the disease (table 1). More rarely, there may be yellowish grey subcutaneous deposits of fat, called xanthelasmata in the nasal region of the eyelids, though these more commonly do not appear until later in the course of the disease.

PBC may manifest itself for the first time following pregnancy. In these cases, patients may have experienced gestational cholestasis (reduced outflow of bile) during the last three months prior to delivery, which, however, resolves after the birth. Not longer afterwards, however, the same symptoms (especially pruritus) recur. These cases of recurrent symptoms following delivery are mostly due to PBC, as is easily demonstrated using laboratory data (see below).

Table 1

Characteristics of PBC

- Females are most commonly affected, less often males
- First disease manifestation following pregnancy
- Pruritus (itching of arms, legs, back)
- Tiredness, fatigue, reduced performance
- Sometimes xanthelasmata (subcutaneous fat deposits in the eyelids)

How does your physician diagnose PBC?

In the past, PBC was difficult to diagnose. Because it was typically first diagnosed in an advanced stage, it received the name “primary biliary cirrhosis”. Today, simple blood tests can confirm the diagnosis in earlier stages (stage I and II), when patients have not yet developed cirrhosis.

Physical examination

In early disease stages, the physician typically finds no changes on physical examination. There is no jaundice (yellow discoloration of the skin and eyes caused by increase in serum bilirubin) and the liver and spleen are not enlarged. Ultrasound of the liver returns normal findings or, if abnormal, are of the type associated with fatty degeneration (steatosis). In a more advanced stage, the liver may be enlarged, followed later by signs of cirrhosis (see table 4). At ultrasound, the liver surface is wavy or bumpy, due to scar tissue the liver itself shrinks and decreases in size over time, and because a reverse blood flow exists spleen size increases. Since similar alterations can be found in patients in whom liver cirrhosis developed of different reasons all findings are not typical for PBC alone.

Laboratory tests, ultrasound tomography

Even at an early stage there are typical changes on laboratory examinations of the blood. Almost 100% of patients show elevation of so-called **a**nti**m**itochondrial **a**ntibodies (AMA) in the blood. AMAs are antibodies that circulate in the blood and are directed at the mitochondria, cell organelles in which the energy metabolism of liver and bile duct epithelial cells is located. AMAs, although they are not the cause of

PBC, nor are they responsible for the severity of the disease, are strong evidence for the diagnosis (table 2). In addition, there are increased blood levels of enzymes such as alkaline phosphatase (AP) and γ-glutamyltranspeptidase (GGT or γGT), which indicate inflammatory changes of the bile ducts and cholestasis. Also characteristic for the disease is an increase in blood levels of a protein called immunoglobulin M (IgM). If these parameters in the blood are increased and if repeated examinations document the presence of AMAs, the diagnosis of PBC can be considered confirmed, even when the patient has no symptoms. Levels of other liver enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and glutamate-dehydrogenase (GLDH), which indicate inflammatory changes in the liver, may be slightly elevated. This is due to the fact that the inflammation primarily affects the bile ducts, not the liver tissue itself.

In more advanced disease stages (stages III and IV), there is hardly any further change in laboratory parameters. Thus, laboratory values by themselves say little about the stage of the disease. In late stages, liver function gradually declines, resulting in a drop in the protein (albumin) concentration of the blood and in

Table 2

Characteristic laboratory findings in PBC

- Elevated alkaline phosphatase (AP) and γ-glutamyltranspeptidase (GGT, γGT)
- Slight increase of the transaminases (AST and ALT)
- Often significant increase in immunoglobulin M (IgM)
- Evidence of antimitochondrial antibodies (AMA)

clotting factors. Bilirubin, the main pigment of the bile, however, increases and patients develop jaundice. At the beginning only in the eyes, lateron all over the skin. Because bilirubin is not excreted by bile but by urine the urine is dark while the stool is getting light.

Ultrasound examination now reveals a liver surface that is irregular. There is also evidence of disturbed blood supply to the liver (collateral circulation), accumulation of fluid in the abdominal cavity (ascites) and sometimes of an enlarged spleen.

Laboratory tests should, depending on the severity of the disease, be obtained every 4–12 weeks, with follow-up ultrasound examinations every 4–8 months.

Tissue samples from the liver (liver biopsy)

Sampling of tissue obtained by ultrasound-guided puncture of the liver is done only at the time of first diagnosis for histological confirmation. Although it is currently a matter of discussion whether, given the highly reliable nature of the available laboratory tests, liver biopsy is necessary at all, the fact that PBC is a disease requiring life-long treatment and possibly liver transplantation underscores the importance of confirming the diagnosis by histological examination of the tissue. Once the diagnosis has been confirmed, further biopsies are not required unless there is suspicion of hepatocellular carcinoma. For liver biopsy, the patient is usually admitted to the hospital for one and a half days to monitor for complications, such as bleeding or bile leakage, which, however, are extremely rare. Liver puncture can also be done on an outpatient basis in cases in which timely access to medical care in the case of complications is assured.

What is the clinical course of PBC?

Common symptoms

In its earlier stages, PBC usually causes no typical complaints. Pruritus (see above), which in some patients may occur early and long before a final diagnosis of PBC is made, may in some cases not occur until later, even sometimes for the first time in a terminal disease stage. Typical for PBC is tiredness, fatigue, and a drop in productivity.

Associated "rheumatic" disorders

Some patients report symptoms affecting the joints and muscles. These are called associated rheumatic symptoms. Also considered a rheumatic disease is the so-called Hashimoto thyroiditis. In this disease, the body produces antibodies against thyroid tissue, which is gradually destroyed. Another disorder in which autoimmunological cases have been discussed is the so-called Sicca syndrome. It is characterized by reduction in the secretions of the large glands, such as the tearr, vaginal and salivary glands and the pancreas (table 3).

Table 3

Important associated disorders in patients with PBC

- Associated rheumatic disorders
  Joint complaints
  Hashimoto thyroiditis
  Sicca syndrome
- Osteoporosis
- Vitamin deficiency
- Skin changes typical for cirrhosis (see table 4)
- Hepatocellular carcinoma

Loss of bone mineral density (osteoporosis)

Osteoporosis, which is a loss of bone mass, occurs early in patients with PBC. Why this occurs in these patients is unknown. Because PBC most commonly affects women and because women not infrequently suffer from osteoporosis following menopause, it is sometimes not possible to distinguish between these two forms. The extent of osteoporosis can be measured radiologically (DEXA scan). In some cases, patients require treatment with medication.

Fatty stools (steatorrhea), vitamin deficiency syndromes

Sicca syndrome results in dry mucous membranes (e.g in the eyes) and is also associated with reduced production of enzymes by the pancreas which are required for digestion of fats. Fat cannot be cleaved by enzymes in the gut and is excreted via the stool (steatorrhea). In this case, the fat content of the stool is increased (steatorrhea). Because bile acids are necessary for the absorption of fats and fat-soluble vitamins (vitamins A, D, E and K in the gut), cholestasis in the liver resulting in a deficiency of bile acids in the bowel together with Sicca syndrome contributes to fatty stools and vitamin deficiencies. A deficiency of vitamin A results in night blindness; vitamin D deficiency promotes development of osteoporosis, while reduced levels of vitamin K is associated with disorders of blood coagulation. In most patients, however, vitamin deficiency syndromes are not significant and may be mild, so that the above-mentioned symptoms do not develop and no treatment as a rule is required.

Skin changes

We have already mentioned the xanthelasmata, or subcutaneous deposits of fat in the eyelids. Small fatty tumors, called xanthomata, may also develop on the hands, feet or buttocks. As PBC progresses from its early to late stages, the classical signs of liver cirrhosis develop (table 4). On the skin, there may be star-shaped lesions called spider naevi. The colour of the lips and tongue may become darker (lipstick-lips) and the skin appears thinner, especially on the face and brow.

Table 4

Signs of liver cirrhosis (due to PBC, PSC and other causes)

- Skin changes
  Spider naevi (dilated small blood vessels)
  Lipstick or lacquer lips (degeneration of lip skin, darkening of the red colour of the lips)
  Red tongue (degeneration of the epithelium of the tongue)
  Thinning of the skin (disturbance of the nutrition of the skin with degeneration)
- Ascites (fluid in the abdominal cavity)
- Edema (swelling of the legs)
- Black and blue marks after very minor injuries (tendency to bleed)
- Loss of body hair (chest and abdomen) in males
- Signs that are not observable by the patient:
  Esophageal varices (varicose veins in the esophagus)
  Reduced brain function (hepatic encephalopathy)

Complications of complete cirrhosis

The complete or near-complete transformation of the liver into scar tissue results in a significant reduction in blood flow through the organ. Instead, the blood flows through so-called collateral pathways that bypass the liver. These include varices of the esophagus, which may bleed profusely. There may also be accumulation of fluid in the abdominal cavity (ascites) and brain function may also be affected (hepatic encephalopathy), which can further complicate the clinical picture. In the terminal stage about 3% of patients develop hepatocellular carcinoma.

How does one treat PBC?

As late as 1985, PBC was considered an untreatable disease. Today, this disease is amenable to both treatment with drugs and with liver transplantation.

Drug treatment

Treatment with medication begins as soon as the diagnosis is confirmed, regardless of disease stage. Treatment consists in the administration of ursodeoxycholic acid (UDCA), a bile acid that normally occurs in only small amounts in humans. The daily UDCA dose is 13–15 mg per kilogram of body weight. UDCA should be taken in two to three doses per day, treatment should not be interrupted. Interruption of therapy results in a renewed worsening (rebound effect) in laboratory values (table 5). Recent studies have shown that in some patients a combination of UDCA with a cortisone preparation (prednisone, budesonide) or, at least initially, with the immunosuppressant medication, azathioprine, is superior to the effects of UDCA alone. Further data are needed before this combination can be recommended as standard therapy. In

Table 5

Drug therapy of PBC

- Ursodeoxycholic acid (UDCA): 13–15 mg per kilogram of body weight daily
- Therapy starts immediately after the diagnosis is confirmed
- Duration of therapy: life long or until liver transplantation
- If response to UDCA is inadequate, combination with cortisone, budesonide or azathioprine (still being tested in studies)

patients who do not respond sufficiently to UDCA alone a combination therapy should be initiated already now. Combination therapy should only be started in patients with the early stages I or II of PBC.

Results and side effects of therapy

In infrequent cases, UDCA is associated with diarrhoea. As a rule, however, the drug is taken without any side effects. Many patients have been treated with UDCA over a period of 12–22 years without any need to interrupt or discontinue the drug due to side effects.

As an effect of treatment during the first six months the liver enzymes γGT and GLDH drop by up to 80%, followed by improvements in AP and IgM by 30–60% and finally of the inflammation parameters, AST and ALT. Only the concentrations of AMAs remain unchanged. In 30% of patients with relatively low initial concentrations, value return to normal after three to five years of therapy, while in the remaining 70% they improve significantly but never completely return to normal.

It has been shown that therapy with UDCA improves not only the laboratory values but also histological findings. The development of esophageal varices is slowed, the need for liver transplantation is delayed and patients' life expectancy is improved.

Less clear is the effect of UDCA on symptoms such as fatigue and pruritus, which may sometimes become intolerable (table 6). The treatment of these two symptoms has been shown to be especially difficult, requiring much patience and endurance from both physician and patient. It appears to be the case that patients with mild cholestasis (slight elevation of AP and GGT, but normal bilirubin) are more often free of complaints than are patients with high values.

Treatment of osteoporosis, steatorrhea and vitamin deficiencies

Osteoporosis, which develops at an early disease stage, can today be treated very effectively with bisphosphonates. In women with postmenopausal osteoporosis, bisphosphonates resulted in prevention of bone loss and even in restoration of bone mass. This effect has not yet been proven in patients with PBC but is considered very likely. For this reason, these drugs are also used in patients with PBC. Treatment with vitamin D and calcium is also effective. In all cases patients should maintain a regular, balanced Western diet and get plenty of outdoor exercise, which also helps prevent osteoporosis (table 7). Female sex hormones (estrogens) also prevent osteoporosis. Because estrogens, however, also promote cholestasis, their use in PBC is controversial.

Table 6

Treatment of pruritus

- Ursodeoxycholic acid (UDCA)
- Colestyramine or
- Colestipol or
- Opiate antagonists or
- Combination of the above treatments

Table 7

Treatment of osteoporosis in PBC

- Adequate physical exercise outdoors
- Well-balanced diet
- Bisphosphonates and/or calcium and vitamin D
- Estrogens (in females)

Fatty stools, which occur less frequently, can be combated by reducing the fat content of the diet to 40–50 grams daily. If this is not sufficient, patients can be given enzyme-containing medications. If these, in turn, do not produce the desired effect, patients are advised to prepare their food with modified, easily absorbable fat such as Ceres margarine. These modified fats do not require to pancreatic enzymes to be broken down before they are absorbed in the small bowel.

If patients experience vitamin deficiencies, regular injections of the fat-soluble vitamins A, D, E and K are recommended, but unfortunately these drugs are no longer available. Because they are injected into muscle, they cannot be lost with fatty stools.

Liver transplantation

As the disease progresses and liver function cannot be maintained, or if there are complications or itching becomes unbearable, liver transplantation represents the most effective option. Although transplantation of the liver is one of the most major operations in modern medicine, the technique has become very refined and is very effective. Following liver transplantation, patients undergo follow-up treatment with the long-term goal of preventing rejection of the transplanted organ. This treatment consists of administration of so-called immunosuppressants (table 8), which many physicians give in combination with UDCA.

Following transplantation, PBC may recur in a small number of patients in the transplanted liver or they may develop a different type of liver damage (e. g. rejection, changes in blood vessels). In these cases, patients are treated with medications as long as possible but in some cases a second liver transplantation may be necessary.

Table 8

Immunosuppressive therapy options following liver transplantation

- Cortisone preparations (e. g. prednisolone or prednisone)
- Cyclosporin A
- Tacrolimus
- Azathioprine
- Mycophenolate Mofetil
- Combination of the above medications

Is primary biliary cirrhosis related to autoimmune hepatitis?

Indeed, there is a small proportion of patients with PBC whose laboratory parameters and findings from microscopic analysis of liver tissue point equally to PBC and to autoimmune hepatitis. Other patients, who suffered initially from PBC, later showed signs of increasing inflammation, and finally they showed signs of both PBC and chronic autoimmune hepatitis. Such cases of mixed disease are called “overlap syndromes”.

The small number of patients with overlap syndrome may respond to a combination of UDCA (13–15 mg per kilogram of body weight per day) and a low-dose cortisone preparation, possibly in combination with the immunosuppressant azathioprine.

Summary

- Primary biliary cirrhosis (PBC) is a chronic inflammatory autoimmune disease of the liver.
- Beginning at the small bile ducts and gradually extending to the liver tissue, PBC leads ultimately to liver cirrhosis.
- The average survival of untreated patients is 12–20 years from first diagnosis.
- Because of improvements in laboratory diagnostics, PBC can today be identified in an early disease stage.
- Drug therapy consists in life-long administration of ursodeoxycholic acid (UDCA) beginning immediately after confirmation of diagnosis.
- UDCA improves liver enzyme values and histological findings, postpones the need for liver transplantation and extends life expectancy.
- Liver transplantation remains as an option when therapy with medications is no longer effective.
- Results of liver transplantation are very good and are steadily improving.

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