Primary Biliary Cholangitis

pbc foundation

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PBC for Healthcare Practitioners

Introduction

Primary Biliary Cholangitis (PBC), previously known as Primary Biliary Cirrhosis, is an autoimmune condition, of unknown cause, that affects the liver. PBC can be classed as a common rare disease, with an estimated 22,000 patients in the UK. It affects mainly women, the ratio being 9:1 (female to male). PBC can affect adults at any age, most patients are diagnosed between the ages of 35 and 55 years.

In large-scale genetic studies, there have been several genetic risk factors identified. Understanding of these factors is still incomplete. Although PBC is not inherited, first degree relatives of those with PBC (especially females) do have a greater risk of developing PBC than the general population. It is currently believed that an environmental trigger starts the immune attack in PBC. There are ongoing studies on environmental risk factors but no one trigger factor has been identified. This, too, is an area where more research is needed.

In PBC, the autoimmune injury is focused on the biliary epithelial cells (BEC) of the small, interlobular bile ducts, causing a non-suppurative destructive cholangitis that can eventually lead to biliary cirrhosis. A proportion of cases will develop end-stage liver disease with attendant need for liver transplantation.

Up to 50% of PBC patients have at least one other autoimmune condition: Sjogren's Syndrome, Raynaud's syndrome, autoimmune thyroid disease, coeliac disease, and rheumatoid arthritis are among the more common conditions.

Diagnosing PBC

Up to 60% of PBC patients are asymptomatic at time of diagnosis. The diagnosis of PBC is made on the presence of at least two of the three following features:

Antimitochondrial Antibody (AMA) and Immunology In the UK, and many other countries, autoantibodies are detected by immunofluorescence. Around 90% of PBC patients have a positive AMA at a titre of >1:40.

Antinuclear antibodies can also be found in PBC but are also found in other liver diseases. However, those antibodies that give a rim-like pattern and multiple-dots are specific for PBC. It is important when considering patients with possible autoimmune liver disease to consider the pattern of antibody staining.

PBC is also characterised by disproportionate elevation of IgM.

Liver Biochemistry

PBC is a cholestatic liver disease in which there is disproportionate elevation of serum alkaline phosphatase (ALP) and -glutamyl transferase (GGT). There may also be moderate elevation of serum aminotransferases (ALT and AST). In patients with end-stage liver disease, the bilirubin is elevated and the prothrombin time (PT) may be prolonged. If hypersplenism is present, the platelet count may also be reduced.

Liver Biopsy

In cases of AMA-ve PBC or suspected PBC-AIH overlap, or where there is potential for the presence of a confounding additional form of liver disease, liver biopsy may be helpful in confirming or refuting the diagnosis and staging the degree of fibrosis (see below).

The characteristic histological lesion in PBC is non-suppurative destructive cholangitis, in which the bile duct is surrounded by an intense lymphocytic or granulomatous infiltrate and the biliary epithelium is infiltrated by individual lymphocytes. Other features include portal granulomas, interface hepatitis, ductular proliferation and cholate-stasis. Progressive destruction of bile ducts leads to ductopenia. Progressive fibrosis eventually leads to biliary cirrhosis.

Clinical Course

If PBC is left undiagnosed, or untreated, in many patients the liver disease will progress over many years to cirrhosis and to end-stage liver disease (ESLD) with the usual manifestations of chronic liver failure and portal hypertension. Clinical features of ESLD include jaundice, ascites, variceal haemorrhage and hepatic encephalopathy. PBC patients with cirrhosis also have increased risk of hepatocellular carcinoma (HCC). The clinical course is similar in men and women although itching is commoner in women and males are at greater risk of liver cancer.

Symptoms

Up to 60% of patients with PBC are asymptomatic at time of diagnosis, though most patients subsequently develop symptoms. The principal symptoms of PBC are often profound physical and mental fatigue and cholestatic pruritus. Systematic enquiry often reveals eye, mouth and vaginal dryness; persistent upper

abdominal pain; and some patients will have symptoms indicative of other autoimmune conditions (e.g. rheumatoid arthritis, thyroid disease, etc).

Fatigue in PBC can be debilitating. There is a link between fatigue and impaired cognitive function which is currently being investigated. There is no treatment currently available for fatigue in PBC; a supportive and understanding clinical approach does improve patients' capacity to cope. In contrast to itching, fatigue does not significantly improve after liver transplantation. Up to 60% of PBC patients report fatigue as a symptom.

Pruritus can affect up to 70% of patients with PBC. As is the case with other cholestatic diseases (such as PSC, obstetric cholestasis, etc.), cholestatic pruritus in PBC can be severe, occasionally intractable, and can cause significant reduction in quality of life. However, most cases respond well to therapy.

Symptoms are often profound. They are often out of proportion to the severity of serological and histological findings.

Liver Biochemistry

Liver biochemistry tests give the best prognostic information. In early disease, serum alkaline phosphatase (ALP) and its response to treatment gives useful medium-to-long-term prognostic information. In advanced disease, a rise in bilirubin indicates a much shorter intervention-free prognosis. Biochemical response to treatment is key to clinical course and prognosis.

Patient risk can be measured using the UK-PBC Risk Score. This score uses serum bilirubin, AST or ALT and alkaline phosphatase to estimate survival. The score can be accessed on www.uk-pbc.com.

Estimation of the degree of fibrosis can usually be made reliably using non-invasive techniques such as Fibroscan, ultrasound, MRI, MRE (magnetic resonance elastography) and serological markers for fibrosis (such as the ELF - Enhanced Liver Fibrosis score).

Histology

Liver biopsy is now used much less frequently for the diagnosis and management of people with PBC. As discussed above, the diagnosis can confidently be made on the basis of clinical, biochemical and immunological grounds. Liver biopsy is usually reserved for when there is uncertainty about the diagnosis or for research.

Disease Management

Disease-modification

There is currently no cure for PBC. The standard of care for PBC is Ursodeoxycholic Acid (UDCA or Urso). UDCA is usually a lifelong medication. Recent guidelines from the European Association for the Study of the Liver suggest that all PBC patients should be treated with UDCA with 13-15mg/kg/day. UCDA is generally well tolerated. Some patients may experience weight gain, symptoms of abdominal discomfort, or increased/ decreased bowel frequency.

Up to 70% of PBC patients respond to UDCA. Several definitions of UDCA response have been published, incorporating changes in liver biochemistry, but irrespective of how it is defined, those who are UDCA-responders have a much greater liver transplant free survival than non-responders. UDCA response is measured 12 months after the start of weight-appropriate treatment with UDCA.

Recent data shows that early diagnosis and UDCA response is associated with a normal life expectancy. Those who do not meet a response criteria, Non-responders, should be referred to a specialist centre. Obeticholic acid, which has shown benefits in people with PBC, is licensed in some countries as a secondary therapy. In the UK, access to OCA is controlled by regional MDTs, hence referral is essential.

Symptom modification

Fatigue. There are currently no licensed therapies for PBC-related fatigue, though some patients with prominent daytime somnolence may benefit from modafinil (but this is not licensed for use in this condition).

Pruritus. In general, the first line of treatment is cholestyramine, a bile acid sequestrant that binds to bile acids, and other compounds, and prevents their re- absorption. Cholestyramine can be started at a dose of 4g twice daily and may be increased to 16g per day or even higher. Cholestyramine may bind to other medications and some vitamins and, for this reason, it should be taken separately from other medications by 2-4 hours. Experience shows cholestyramine to be most effective when taken just before and after breakfast.

Patients with pruritus who do not respond to cholestyramine may require specialist care. Second-line treatments for cholestatic pruritus include rifampicin, naltrexone, and sertraline. Please note that these drugs

are not licensed for use in this context and should be prescribed by those who are familiar with these agents, for patients with severe pruritus refractory to medical treatments, non-pharmacological therapies include nasobiliary drainage, phototherapy, plasmapheresis or extracorporeal albumin dialysis. Liver transplantation may be considered when the pruritus is intractable and severe.

Advanced Liver Disease Management

As with any form of progressive liver fibrotic disease, patients should be monitored for fibrosis progression and cirrhosis. There should be appropriate screening and surveillance for the complications of liver disease, especially portal hypertension (and consequent varices development) and liver cell cancer.

Liver Transplantation

PBC is a well-established indication for liver transplantation (LT) and LT is an excellent treatment for PBC-related liver failure. LT may also be indicated for severe, refractory pruritus. PBC recurs after LT and recurrent PBC may be found in up to 50% of liver allografts at median 6.5 years post-LT. However, recurrent PBC very rarely causes graft failure. Outcomes are excellent with a 10 year survival in excess of 70%.

Co-morbidities

Hypercholesterolaemia: Some patients have markedly raised serum cholesterol. The increased cholesterol levels may be due to lipoprotein X and there is little evidence that those with PBC are at increased risk of cardiovascular complications. Treatment with statins and/or fibrates is usually safe in those with PBC and treatment should be considered on an individual basis.

Osteoporosis: Cholestatic liver disease contributes to osteoporosis, so consideration should be given to assessing bone mineral density (DEXA Scan). If osteoporosis (or osteopaenia) is present, treatment should be offered with lifestyle changes, use of calcium and vitamin D supplements, bisphosphonates and other interventions as appropriate.

General Health Measures

Tobacco smoking has been shown to increase the risk and rate of progression of liver fibrosis in PBC, therefore patients should be strongly encouraged not to smoke. There is probably no specific benefit from avoiding alcohol altogether but consumption should not exceed recommended levels (the current UK guidelines advise an upper limit of 14 units (140g) alcohol per week for both men and women). Patients should consume a

healthy balanced diet (there is no benefit from a low fat diet), engage in regular exercise and try to maintain a healthy body mass index (BMI). Those on long term cholestyramine and with prolonged cholestasis may be at risk of malabsorption of fat soluble vitamins A, D, E and K.

One in three PBC patients are affected by depression. Emotional, psychological and physical self-management have enormous impact upon daily living with PBC. Patients should be signposted to a patient support organisation, e.g., The PBC Foundation, and given support materials to help them in their daily lives.

Most people with PBC can take medication normally.

Variant forms of Primary Biliary Cholangitis

AMA-ve PBC

Approximately 5% of PBC patients have AMA-negative PBC, meaning that clinical, biochemical and histological features are characteristic of PBC but AMA cannot be detected in the serum using conventional techniques. Some patients have AMA detected by ELISA or immunoblotting and others have PBC-specific ANA. The clinical manifestations and natural history of AMA-negative and AMA-positive PBC appear to be the same.

Premature ductopenic variant

The premature ductopenic variant is an aggressive form of PBC characterised histologically by extreme ductopenia that is disproportionate to the extent of liver fibrosis. Owing to markedly decreased quality of life and the adverse effect of chronic severe cholestasis on nutritional status, liver transplantation is generally required within a few years of presentation.

PBC/AIH overlap syndrome

The term 'AIH/PBC overlap syndrome' is used to describe variant forms of PBC in which there are characteristics of both autoimmune hepatitis (AIH) and PBC. In approximately 8-10% of patients with a diagnosis of PBC, features of AIH co-exist. In addition to AIH/PBC overlap (in which patients have features of both disorders), it has also been reported that patients may present with a typical picture of PBC, which then evolves into a typical picture of AIH over a time frame of 6 months to 13 years. Treatment for those with overlap syndromes should be done in specialist units.

Research in PBC

The cause of PBC is not known; while some therapies reduce the rate of progression, they do not cure the condition. Some of the symptoms, especially fatigue, can be disabling and treatment is for many ineffective. UK-PBC is a consortium of patients, families, doctors, scientists and other healthcare professionals that coordinates research in PBC, which is ongoing.

Summary

PBC is a slowly progressive life-long disease which affects intra-hepatic bile ducts and may lead to cirrhosis

The main symptoms in PBC are lethargy and itching

Severity of symptoms does not correlate with severity of disease

Patients with PBC often have other autoimmune conditions

Ursodeoxycholic Acid is the standard of care, with a recommended dose of 13-15mg/kg/day and is a lifelong treatment

Liver transplantation is used for those with end-stage liver disease and is generally very successful

Those who do not respond to first-line therapies should be referred to specialist units

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