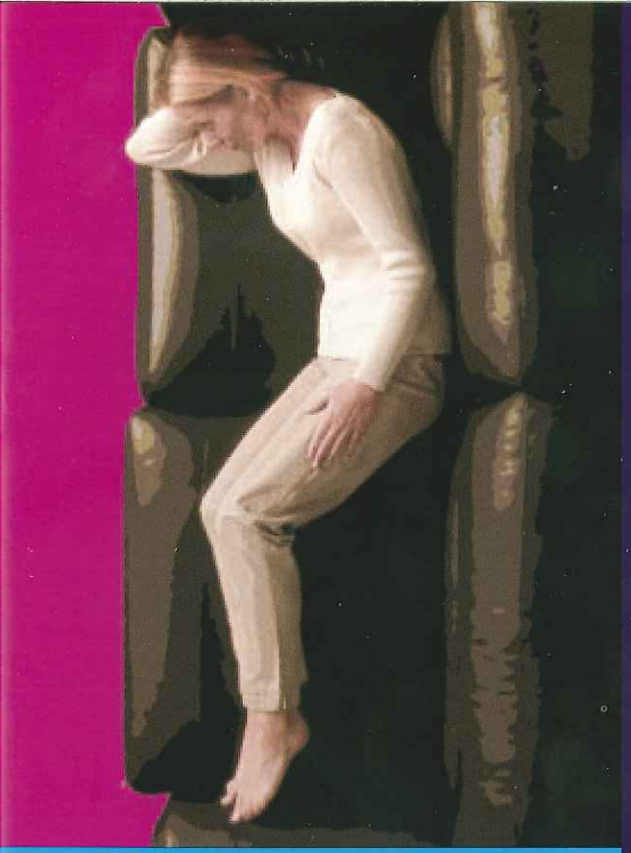

Primary Biliary Cholangitis

PBC for Healthcare Practitioners

pbc foundation

PBC Foundation (UK) Ltd
2 York Place
Edinburgh
EH1 3EP
UK
Tel: 0131 556 6811
Fax: 0131 556 8488
info@pbcfoundation.org.uk
www.pbcfoundation.org.uk

Introduction

Since its discovery in 1851, names for what we now know as PBC have included "Primary Biliary Cirrhosis", "Xanthomatous Biliary Cirrhosis" and even "Chronic Destructive non-Suppurative Cholangitis". As early as 1959, it was known that Primary Biliary Cirrhosis was not a medically accurate reflection of the disease. In order to address this, in June 2015, it was agreed internationally that PBC will henceforth be known as Primary Biliary Cholangitis.

The autoimmune liver disease, Primary Biliary Cholangitis (PBC), is relatively uncommon. As such, each primary health care practice may only come across a very small number of patients with this condition. This brief pamphlet, commissioned by the patient support charity, The PBC Foundation, is designed to give Healthcare Practitioners some background information about PBC so that they can provide the best care for these patients in conjunction with hospital consultant colleagues. PBC patients have their own information leaflet produced by The PBC Foundation.

The form of this pamphlet will be a series of questions with up-to-date answers. Both patients with PBC and a number of their Healthcare Practitioners have requested this information.

What Is PBC?

PBC is an autoimmune liver disease with unknown cause. As such, it is in a group of autoimmune diseases which include thyroid disease, some forms of diabetes, rheumatoid arthritis and Sjögrens Syndrome. PBC patients may also have one or more of these other autoimmune conditions.

In PBC, the immune 'attack' is upon smaller intrahepatic bile ducts, this ultimately leads to destruction of the bile ducts – a 'disappearing bile duct' syndrome – cholestasis and, in the latter stages of the disease, jaundice.

Like most other autoimmune diseases, PBC affects mostly women (in Britain, about nine to every man). Generally, it presents between ages thirty and fifty five although it may be diagnosed at any age in adults and is rarely, if ever, seen in children. There is no connection between PBC and either alcohol consumption, or any of the established hepatitis viruses.

Although the cause of PBC is unknown, present theories of aetiology circulate around the hypothesis that molecular mimicry is involved. It is hypothesised that in susceptible individuals – particularly women, possibly with some other genetic susceptibility traits – antibodies are formed against some common, normally non-pathogenic, environmental agent which becomes involved in an immune process pathogenic to the host. These are the antimitochondrial antibodies (see below) which, because of molecular mimicry, are directed against host proteins.

Upon What is the Diagnosis of PBC Based?

There are three investigations upon which the diagnosis of PBC is based.

The Antimitochondrial Antibody (AMA)

These antibodies, usually detected by indirect immunofluorescence, are now known to be directed against a group of enzymes – the pyruvate dehydrogenase complex – normally found on the inner mitochondrial membrane of almost all animal cells. These antibodies are very disease specific, but are neither tissue, nor species, specific. They are present in around ninety percent of patients with PBC. It has been shown that individuals with a consistent strongly positive antimitochondrial antibody in the serum at a titre of <1:40, but who have normal liver function tests, have a high probability of having abnormal liver histology suggestive of early PBC. Over eighty percent of these individuals will develop biochemical and clinical features of the disease. The AMA is routinely measured in most immunology laboratories in the United Kingdom as part of an 'autoantibody' screen, along with thyroid antibodies, rheumatoid factor and antinuclear antibodies.

Liver Function Tests

Patients with PBC have abnormal liver function tests, usually the alkaline phosphatase is more raised than the transaminases. Serum bilirubin is elevated late in the disease. Liver synthetic function is preserved until late in the disease, so serum albumin and clotting are usually normal. Immunoglobins show raised serum IgM, often IgG.

Liver Biopsy

The classical lesion of PBC is an immune attack upon intrahepatic bile ducts with aggregates of lymphocytes, sometimes with non-caseating granulomas, near bile ducts. As the disease progresses, there is piecemeal necrosis of liver cells extending from portal tracts together with portal fibrosis.

This leads to a combination of disappearing bile ducts and, ultimately, cirrhosis. The pathological process can be uneven within the liver. Liver biopsy is very helpful for staging the disease.

The staging of the liver disease is assessed by the clinical, serological, image findings and liver histology. Liver ultrasound may be used to exclude concomitant gallstone disease, particularly in patients with abdominal discomfort. Furthermore, use of Fibroscan and serological markers of fibrosis will also give useful and non-invasive help in determining the degree of fibrosis. In practice, if a middle-aged female has positive antimitochondrial antibodies and is found to have raised serum alkaline phosphatase, then the likelihood is extremely high that she has Primary Biliary Cholangitis, even in the absence of any symptoms related to liver disease. If, during the investigation of any other disease, a patient is found to have positive antimitochondrial antibodies, then liver function tests should be checked and specific clinical enquiries should be made of the patient concerning the possibility of PBC symptoms (see below).

What Is The Clinical Course?

This may be divided into three – asymptomatic, symptomatic and complicated.

Asymptomatic Phase

With the immunological and biochemical screening and with increasing awareness of PBC, up to half of PBC patients are asymptomatic of liver disease at time of diagnosis. Long term follow-up studies suggest that about half of these initially asymptomatic patients (but with positive AMA and abnormal Liver Function Tests (LFTs)) will develop typical symptoms within five years. It is impossible to predict, at the outset, which patients will develop symptoms and the speed of the clinical course in an individual.

Symptomatic Phase

The principal symptoms of PBC are often profound physical and mental lethargy, together with pruritis. The physical and mental lethargy can also occur in other liver diseases – for example, Hepatitis C. It is so marked that a number of individuals with PBC have been initially thought to have ME.

The mental and physical lethargy can be out of proportion to the severity of the histological and biochemical findings. Pruritis is characteristic of all chronic cholestatic liver diseases. It can be particularly prolonged and severe in PBC. It is often made worse by hot baths, or showers and somewhat improved by sunbathing.

Other complaints often seen in PBC are non-specific, but persistent right upper abdominal pain and dryness of eyes and mouth (like Sjögrens Syndrome).

Complications

The complications of PBC are as for any other end stage cirrhosis. These are portal hypertension, leading to bleeding varices, or ascites and liver cell failure leading to encephalopathy, often with prolonged persistent jaundice. About five to ten percent of PBC patients still present for the first time to medical attention with these end stage complications.

What Are The Likely Presenting Symptoms?

These are often profound, persistent, mental and physical lethargy, weakness and pruritis. Systematic enquiry often reveals dry eyes and mouth, or persistent upper abdominal pain. Some patients have symptoms suggestive of other autoimmune diseases – for example, rheumatoid arthritis, or the symptoms of hypo, or hyper, thyroidism and are found by chance to have antimitochondrial antibodies and abnormal liver blood tests. Some patients with PBC have unexplained weight loss, possibly with malabsorption of fat. It is hypothesised that some of these patients have a 'dry gland' syndrome, including insufficient pancreatic secretion. In addition, a small proportion may also have Coeliac disease. Among post-menopausal females, symptoms and signs of osteoporosis may occur since chronic cholestasis (as occurs in PBC) may accelerate naturally occurring post-menopausal osteoporosis.

On examination, patients with more advanced disease have persisting jaundice, together with dark pigmentation of the skin, particularly the trunk. The reason for the pigmentation is unclear. A few patients have marked hypercholesterolaemia with xanthomas and xanthelasmata around the eyes and, occasionally, elsewhere. A small proportion of patients present with the signs and symptoms of portal hypertension – particularly ascites, or marked bleeding from oesophageal varices.

Is There A Familial Risk Of PBC?

There is an increased familial incidence of PBC – particularly between mothers and daughters. The exact size of this risk is unknown, but it is unlikely to be more than two percent although genetic factors do play a part. At present, screening of relatives of patients with PBC, even daughters, is not necessary, or advised, unless relatives have symptoms, or laboratory findings, which could be attributed to PBC.

How Common Is PBC?

This varies in different parts of the world. Recent studies in the United Kingdom suggest that, at least in some places, the prevalence may be as high as two hundred and fifty per million of the population, or one in a thousand women over the age of forty. A recent estimate is of twenty thousand patients in the UK. As many as thirty to forty percent of these may be asymptomatic. About nine out of ten sufferers are women.

What Specific Treatment Is Currently Available?

There is no 'cure' for PBC at present. The only licenced treatment at a dose of 10-15mg per kilo per day is with the bile acid, ursodeoxycholic acid (Ursofalk). Systematic analysis of the results of controlled trials of ursodeoxycholic acid in PBC suggest that there is some slowing of the clinical course of the disease, although little benefit to symptoms. Ursodeoxycholic acid treatment is surprisingly free of adverse effects. No consensus exists as to whether patients known to have PBC, but who are asymptomatic, should be treated with ursodeoxycholic acid and, if so, for how long. Current treatment cost is just over £1,000 per year.

Because of the 'immune' nature of the disease, a number of immunosuppresant regimes have received clinical trials in the past twenty years. The majority of these have either shown no benefit, or unacceptable side effects, or both. A number of controlled trials of, for example, other bile acids, corticosteroids and other treatments, are currently underway – usually in conjunction with ursodeoxycholic acid. Because of the unpredictable clinical course of the disease, treatment and trials are difficult to interpret and advising individual patients about whether to take treatment is difficult. Some patients may remain asymptomatic for twenty years, while others can go from asymptomatic to complicated (portal hypertension), even death, from liver disease within a year or two. Furthermore, the severe symptoms of tiredness and lethargy, sometimes pruritis, can be out of all proportion with the underlying histological, or biomedical, abnormalities. These symptoms do not necessarily respond to ursodeoxycholic acid, or other treatments currently under investigation. Whatever else it may do, ursodeoxycholic acid improves LFTs in the vast majority of patients.

As for other end state liver diseases, transplantation is now a widely accepted option. It is one of the commonest indications for transplantation. Current results for liver transplant for PBC are better than for any other major disease group. Up to ninety percent of patients transplanted for PBC should be alive after one year, eighty percent after five years, with good quality of life. The timing of transplantation is difficult. As with other liver diseases, it is a combination of assessment of prognosis without transplantation (length of life) and severity of symptoms (quality of life). This assessment should be made in one of the UK Liver Transplant Centres. All centres are very happy to receive referrals for initial consideration and advice, usually from consultant colleagues from any DGH.

What Treatments Are Available For Other Features Of PBC?

Pruritus:

This is best treated initially with Cholestyramine (Questran). Over half of patients with pruritus respond to this treatment which interrupts the entrohepatic circulation, possibly affecting bile acid metabolism, which may be associated with pruritis. Cholestyramine may cause dose-related diarrhoea. Cholestyramine binds bile acids and other medications, hence should not be given at the same time as ursodeoxycholic acid, or other regular medication. Second line treatments include Rifampicin, Naltrexone and other agents. Note that these agents may be hepatotoxic and have significant side-effects and should be used under expert guidance. Dry skin is a prominent feature of the pruritis, so liberal use of skin moisturisers is strongly recommended.

Hypercholesterolaemia:

Some patients have markedly raised serum cholesterol. As with other patients this can and should be treated – preferably with a fibrate or statin but it must be remembered that the increased cholesterol levels may be due to lipoprotein X and there is little evidence of an increased risk of cardiovascular complications.

Osteoporosis:

Since PBC occurs most frequently in post-menopausal women and cholestatic liver disease may contribute to osteoporosis, consideration should be given to assessing bone mineral density (DEXA Scan). If osteoporosis is present, treatment is as for any other patient with osteoporosis.

Prescribing for patients with PBC:

In general, liver function is well preserved until late in its clinical course. This means that most medications can be given in a normal fashion. Because PBC is a cholestatic disorder, sex hormones should not be given without a strong indication. Paracetamol is usually safe in all stages but should not be given at more than 3g/day. Other drugs should be used as with other liver diseases.

The PBC Foundation (UK) Ltd is a Scottish Registered Charity, Number SC025619
Registered Company Number: 207493

Revised August 2015