### Primary Biliary Cirrhosis

#### Definition of primary biliary cirrhosis
- An autoimmune condition in which progressive destruction of the bile ducts eventually leads to cirrhosis.

#### Epidemiology of primary biliary cirrhosis
- Prevalence ≤ 4 in 100,000
- Males:Females = 1:9
- Peak incidence around 50 years
- Commonest in northern Europeans, least common in Africans.

#### Aetiology of primary biliary cirrhosis
- A combination of genetic predisposition and environmental triggers
  - Various studies have suggested an association with urinary tract infections, cigarette smoking and reproductive hormone use.

#### Presentations of primary biliary cirrhosis
- **History**
  - Asymptomatic (often diagnosed after incidental finding of abnormal liver function tests)
  - Fatigue and lethargy
  - Pruritus
  - Abnormal bleeding or bruising
  - Pale stool or dark urine
- **Examination**
  - Jaundice
  - Xanthelasma and tendon xanthomata
  - Hepatosplenomegaly
  - Features of chronic liver disease
    - Palmar erythema; Dupuytren’s contracture; gynaecomastia; spider naevi; cachexia; ascites
  - Ecchymoses
  - Features of other autoimmune diseases (e.g. diabetes, thyroid disorders, hypoadrenalism, vitiligo)

#### Differential diagnosis of primary biliary cirrhosis
- Other causes of chronic liver disease (see chronic liver disease section)
Investigations and diagnosis of primary biliary cirrhosis

- **Blood tests:**
  - Liver function tests
    - Raised ALP and GGT with mildly elevated transaminases initially. In later disease the bilirubin starts to rise.
  - Clotting
    - Elevated prothrombin time
  - Full blood count
    - Thrombocytopenia if cirrhosis present
  - Serum lipids
    - Cholesterol, LDL and HDL all significantly raised
  - Full liver screen of blood tests to rule out other causes of liver disease (see chronic liver disease section)

- **Autoimmune screen:**
  - Serum antimitochondrial M2 antibodies (95% sensitive, 98% specific)
  - Elevated serum immunoglobulins, especially IgM

- **Radiology**
  - Ultrasound liver to look for focal liver lesions, portal/hepatic vein thrombosis, extrinsic causes of biliary duct compression.
  - Magnetic resonance cholangiopancreatography (MRCP) gives a more detailed view of the biliary tree and does not have the associated morbidity of ERCP.
  - CT abdomen
    - This is more likely to be performed if an extrahepatic cause of cholestasis is suspected.

- **Liver biopsy**
  - For histological staging of cirrhosis or in cases where the diagnosis is unclear.

**Recommended diagnostic criteria** (American Association of Liver Diseases Practice Guidelines (AASLD) 2009):

- A diagnosis of PBC can be made if two of the following three criteria are met:
  - Biochemical evidence of cholestasis (i.e. elevation of alkaline phosphatase)
  - Presence of antimitochondrial antibodies
  - Histology showing non-suppurative cholangitis and destruction of interlobular bile ducts

**Chronic management of primary biliary cirrhosis**

- **Ursodeoxycholic acid (UDCA) 13-15mg/kg/day in usually two divided doses**
  - Can be used in any patient with PBC and abnormal liver biochemistry.
  - Can significantly improve liver biochemistry and reduce the need for liver transplantation and overall mortality.
  - However, has no effect on pruritus, fatigue or associated bone disease

- **Steroids and other immunosuppressive agents**
  - Prednisolone has been shown to significantly improve liver biochemistry, however, it makes bone disease much worse and thus is not recommended long-term
  - Steroid-sparing immunosuppressant drugs have not been shown to be effective in PBC

- **Anti-pruritics**
  - Cholestyramine: 4g per dose up to 16g/day given 2-4 hours apart from UDCA.
- Rifampicin at a dose of 150mg once or twice daily but needs careful monitoring of liver function tests.
  - Opiate agonists such as Naltrexone at a starting dose of 50mg daily
- Vitamins ADEK and calcium replacement
  - Calcium 1g and vitamin D 800 IU daily
- Bisphosphonates for patients at high risk of osteoporosis or T score < 2.5
- Orthotopic liver transplantation
  - Is indicated in patients with end-stage disease
  - Patients should be referred when the bilirubin level is > 100 micromls/litre or earlier if debilitating symptoms.
  - Up to 20-25% of patients will have disease recurrence at 10 years post-transplant.

**Further management of primary biliary cirrhosis**
- Patients with PBC are at risk of all the complications of chronic liver disease and these should be managed as laid out in the chronic liver disease section.

**Complications and associations of primary biliary cirrhosis**
- Osteoporosis
- Malabsorption of fats and fat-soluble vitamins can lead to osteomalacia and coagulopathies
- Liver cirrhosis and its complications (see chronic liver disease and decompensated liver disease)
- Renal tubular acidosis
- Associated conditions
  - Hypothyroidism (seen in up to 20%) of patients
  - Rheumatoid arthritis; Systemic sclerosis; Sjogren’s syndrome; Sicca syndrome

**Prognosis of primary biliary cirrhosis**
- Reports of this are variable. Some studies suggest that asymptomatic patients have a 50-70% 10 year survival whereas median survival from onset of symptoms is 5-8 years.
- The serum bilirubin level is a marker of prognosis

**Common questions concerning primary biliary cirrhosis:**
- What is the hallmark autoantibody associated with PBC?
  - Antimitochondrial M2 Ab
- What is the male:female ratio?
  - Highly female preponderance with a ratio of 1:9