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
    - Trombocytopenia 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.

- Rifamipicin 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