Introduction:
It is an autosomal recessive liver disorder characterized by neonatal cholestasis that progresses to hepatic fibrosis, cirrhosis, and end-stage liver disease usually by first decade, caused by defects in the transport of bile acids(1). Few patients have survived into the third decade of life without treatment (2). It is classified as Low GGTP PFIC (PFIC -1 and PFIC- 2) and High GGTP PFIC (PFIC-3). Low GGTP PFIC is the commonest cause with high GGTP PFIC only 20 cases reported in the world so far. Low-GGT progressive familial intrahepatic cholestasis has been reported in all races. Males and females are equally affected.

Pathophysiology And Classification (1-5):

**PFIC type 1:** Initially described in Amish population, the condition was originally named Byler disease and is caused by mutation in the ATP8B1 gene on chromosome 18 q 21-22.

**PFIC type 2:** Caused by mutation in a liver-specific ATP-binding cassette transporter gene (ABCB11) on chromosome 2q24. Patients tend to present as acute hepatic failure as compared to PFIC -1

**PFIC type 3:** caused by mutation in the class III multidrug resistance P-glycoprotein Gene (ABCB4) on chromosome 7q21. It is quite fatal and patients develop cirrhosis within a year of presentation.

PFIC1 and PFIC2 are associated with mildly elevated or normal serum levels of gamma-glutamyltransferase (GGT1), whereas PFIC3 is associated with high serum GGT1 levels and liver histology that shows bile stasis, portal inflammation and ductular proliferation in an early stage(1). Later fibrosis sets in.

There is a defect in canalicular bile acid transport with primary retention of hydrophobic bile salts as the mechanism of disease in patients with low-GGT progressive familial intrahepatic cholestasis with defect in bile excretion. This leads to elevated total serum bile acid concentrations (ie, usually >200 mmol/L compared to normal concentrations of <10 mmol/L). Total biliary bile acid concentrations are low (ie, 0.1-0.3 mmol/L, compared with normal concentrations of >20 mmol/L) and with a predominance of cholic acid conjugates.

Clinical Features (1,4):
PFIC morbidity is the result of chronic cholestasis. Cholestasis starts in early infancy and leads to fat malabsorption, fat soluble vitamin deficiency and growth failure. The dominant feature is pruritus, often occurs out of proportion to the level of jaundice, which is often low grade and can wax and wane. The pruritus is very disabling and usually does not respond to medical therapies. Most patients have debilitating pruritus; most of the remainder have constant itching without treatment. As many as one third have choledolithiasis. These patients do not have xanthomas.

Laboratory findings:
Serum bilirubin levels are elevated with increase in direct bilirubin levels in virtually all patients with PFIC. Total serum bile salt concentration is elevated. Total serum cholesterol level is within reference ranges. Serum alkaline phosphatase is elevated. Serum gamma-glutamyl transferase (GGT) levels are within reference ranges or low in low-GGT progressive familial intrahepatic cholestasis. These levels are elevated in patients with high-GGT progressive familial intrahepatic cholestasis. On liver biopsy, in
patients with low-GGT progressive familial intrahepatic cholestasis, hepatocellular and canalicular cholestasis, giant cell formation and ballooned hepatocytes are seen. With advanced disease, bile duct paucity and fibrosis sets in.

Treatment
Cholestyramine and Ursodeoxycholic acid (UDCA) have been used with variable effects. Cholestyramine is a nonabsorbable anion exchange resin, which binds bile acids and cholesterol and eliminates them in faeces. Dose: 250 mg/kg/day in divided doses(3). It helps to decrease pruritis. UDCA – A tertiary nontoxic hydrophilic bile acid, which replaces hepatotoxic bile acid and has cytoprotective effect, by inhibiting bile acid –induced hepatotoxic damage. Dose: 10-20 mg/kg/day(3).

Diet rich in medium chain triglycerides (MCT) and administration of fat soluble vitamins in 10 times RDA is needed.

For refractory pruritis, surgery in form of partial cutaneous biliary diversion (diverts gallbladder bile to a cutaneous ostomy) may be needed. Alternate internal diversion by self emptying distal ileal diversion helps. Liver transplantation is indicated in patients with decompensated cirrhosis or with a failed diversion with debilitating pruritis. Survival rates after transplantation are excellent. Liver transplantation is the only effective treatment of high-GGT progressive familial intrahepatic cholestasis.

Prognosis:
All forms of progressive familial intrahepatic cholestasis are lethal in childhood unless treated. Low-GGT progressive familial intrahepatic cholestasis can be rapidly progressive and result in cirrhosis during infancy, or it may progress relatively slowly well into adolescence and cause minimal scarring. Few patients have survived into the third decade of life without treatment. Patients with high-GGT progressive familial intrahepatic cholestasis manifest severe progressive intrahepatic cholestasis in the first year and progress toward hepatic failure in the first few years of life.

PFIC remains an unidentified condition and India and diagnosis may aid in early management. Genetic studies are recommended to identify the disease. Prenatal counselling can also be done if genetic mutation is identified in the parent case.

References:
(1).OMIM – result of CHOLESTASIS, PROGRESSIVE FAMILIAL INTRAHEPATIC, 1, 2, 3. dated 20/02/2010.
(5) Sheila Sherlock and James Dooley; Cholestasis: Diseases of the liver and hepatobiliary system; 11th edition; page 234.