INTRODUCTION

Chronic liver diseases may affect cardiac functions in the absence of other heart disease. Cardiomyopathy induced liver disease is claimed to be the third cause of death in transplanted children after rejection and infection . This is named in literature cirrhotic cardiomyopathy and may aggravate the course during liver transplantation ***(Moaref et al., 2014)***. Cirrhosis may cause left ventricular (LV)hypertrophy, impaired diastolic relaxation, prolonged QTc interval, and an attenuated cardiovascular response to stressors ***(Gaskari rt al.,2006)***.

Cholecardia is a term proposed by ***Moreshwar et al. (2017)*** to describe a syndrome in which pathological levels of bile acids induce cardiomyopathy. The effect of cholestasis on cardiac performance is rarely explored in children with cholestatic liver disease.

Therefore, the evaluation of cardiac functions is very important in patients with hepatic injury.

AIM OF THE WORK

The aim of this work is to assess cardiac performance in choletatic patients in comparison to non cholestatic hepatic patients.

Chapter 1

CHOLESTASIS

Cholestasis results from impairment in the excretion of bile, which may be due to mechanical obstruction of bile flow or impairment of excretion of bile components into the bile canaliculus. When present, cholestasis warrants prompt diagnosis and treatment. The differential diagnosis of cholestasis beyond the neonatal period is broad and includes congenital and acquired etiologies. It is imperative that the clinician differentiates between intrahepatic and extrahepatic origin of cholestasis. Treatment may be supportive or curative and depends on the etiology. Recent literature shows that optimal nutritional and medical support also plays an integral role in the management of pediatric patients with chronic cholestasis ***(Khalaf et al., 2016).***

Clinico-Lab Definition

Cholestasis results from impairment in the excretion of bile and its constituents secondary to either mechanical obstruction or defective transmembrane transport; bilirubin, bile acids, and cholesterol in the blood and extrahepatic tissues. This accumulation results in the clinical findings of jaundice, scleral icterus, xanthomas, acholic stool and cholestatic pruritus ***(Suchy et al., 2014)***.

Cholestatic hyperbilirubinemia is defined as serum conjugated bilirubin greater than 1.0mg/dL (17.1 μmol/L) if the total bilirubin is less than 5.0 mg/dL (85.5 μmol/L), or greater than 20% of the total serum bilirubin if the total serum bilirubin is greater than 5.0 mg/dL (85.5 μmol/L) ***(Moyer et al., 2004)***

One sign of cholestasis is the manifestation of jaundice which refers to the yellow discoloration of the skin, sclera, mucous membranes, and body fluids. Jaundice is apparent when serum total bilirubin exceeds 2 to 3 mg/dL (34.2 to 51.3 μmol/L) in older children.

Pathophysiology

Bile formation and transport is regulated by distinct membrane transport systems. Genetic mutations in transporter genes or exposure to cholestatic injury result in reduced function. This results in impairment in the metabolism and excretion of bilirubin, bile acids, and cholesterol to re-circulate into the blood stream and levels are elevated in the serum ***(Wagner et al., 2009)***.

Bilirubin is a red flag found in the laboratory evaluation that can help the clinician identify cholestasis. Thus, understanding the metabolism of conjugated bilirubin is essential for deconstructing the complex mechanisms of cholestasis ***(Khalaf et al., 2016):***

Conjugation:

Unconjugated bilirubin, a precursor to conjugated bilirubin, is poorly water soluble, bound to albumin in the circulation, and a product of heme breakdown (**Fig.1)**. Bilirubin is dissociated from albumin and taken up by hepatocytes via the carrier bili- translocase at the sinusoidal junction. Within the hepatocyte, unconjugated bilirubin is bound to glutathione s-transferase and conjugated with glucuronic acid ***(Khalaf et al., 2016)***.

Excretion:

Conjugated bilirubin is excreted into bile canaliculi via an adenosine triphosphate dependent transporter known as multispecific organic anion transporter or multidrug resistantce-associated protein (MRP2). If there is any interruption of transport of bilirubin into the canaliculus, the conjugated bilirubin will recirculate into the serum, where it is detected on laboratory evaluation ***(Khalaf et al., 2016).***

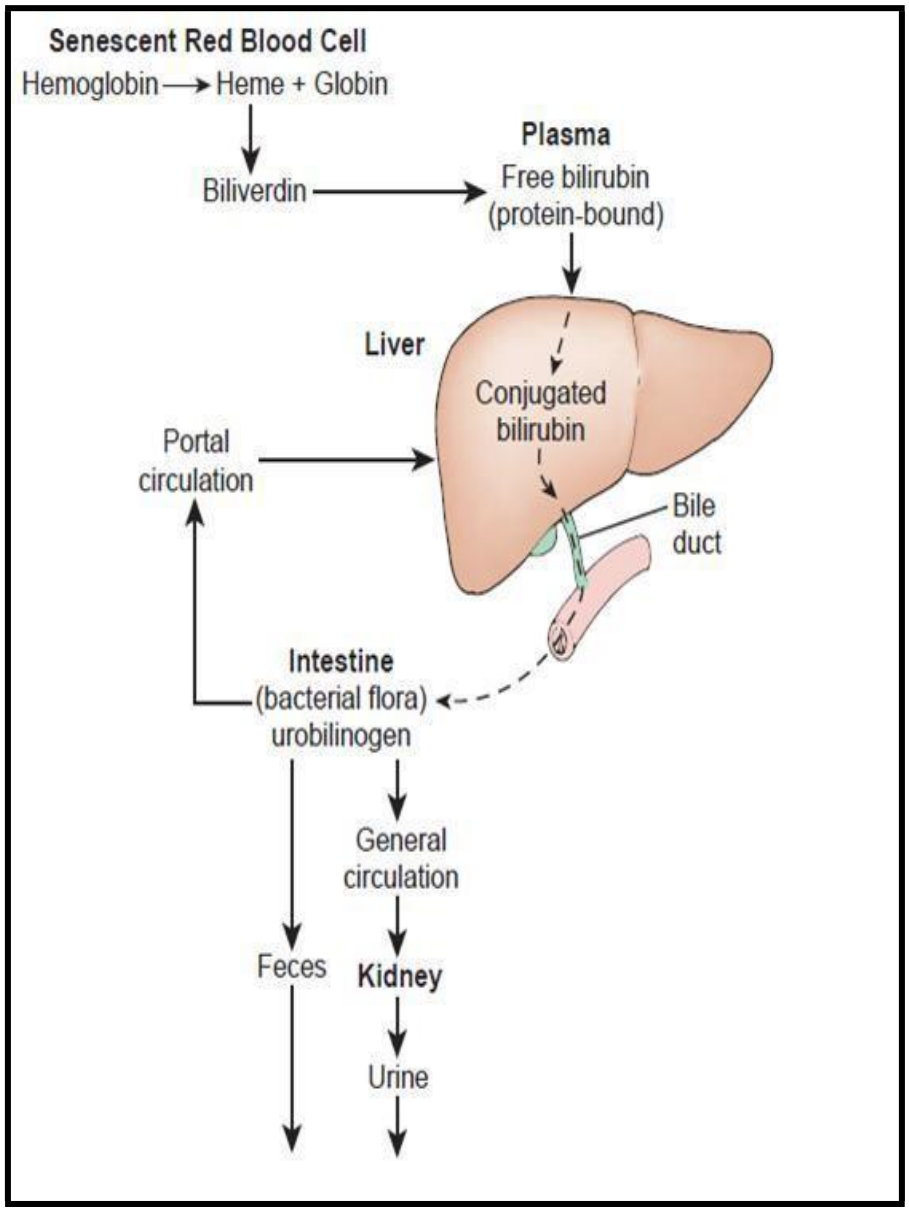

Figure (1): The process of bilirubin formation, circulation and elimination. ***(www.Biology-forums.com).***

Focused Differential Overview

The differential for cholestasis is broad and depends on the clinical presentation, physical findings and the chronicity of the disease. Causes of cholestasis among children and adolescent can be classified anatomically to extrahepatic, intrahepatic (**Fig. 2).**

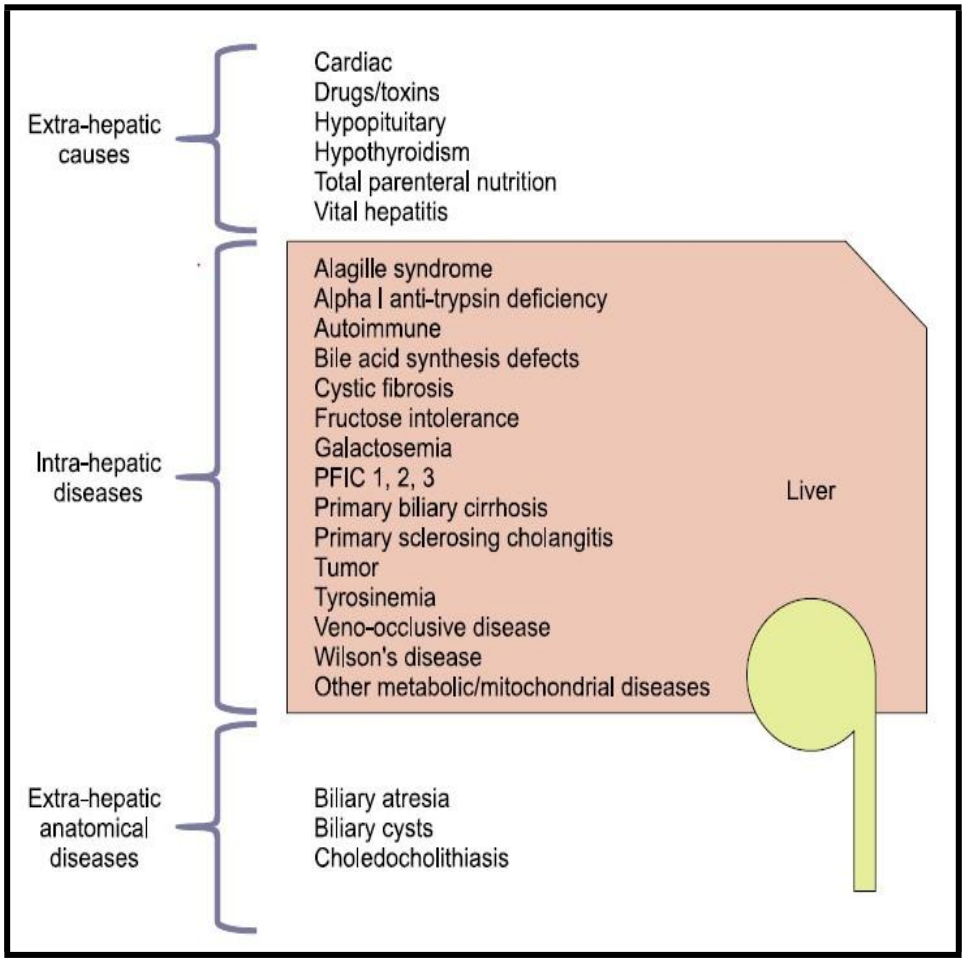

Figure (2): Expanded differential diagnosis of cholestatic disease in childhood (image courtesy of Sara Karjoo MD) ***(Khalaf et al., 2016).***
PFIC: progressive familial hepatocellular cholestasis.

Biliary atresia (BA) is the most frequent and severe cause of neonatal cholestasis. Biliary atresia is an ascending inflammatory process of the biliary tree leading to progressive obliterative scarring of the extra- hepatic and intrahepatic bile ducts, resulting in biliary cirrhosis and liver cell failure and death within 2-3 years. Only early surgical treatment can withhold biliary cirrhosis, that is why rapid identification of BA is crucial. In a few cases, it may be part of a syndrome and associated with other congenital malformations such as polysplenia (100%), situs inversus (50%), or cardiac anomalies (50%) and/or vascular malformations, e.g., preduodenal portal vein (60%) ***(Davenport et al., 2006).*** The incidence of BA is estimated to be from 1/14000 to 1/20000 live births in European countries, and 1/15000 live births in the US. It is most common in East Asian countries with up to 1/2700 live births in Taiwan ***(Harb and Thomas, 2007).*** Precise data as regards incidence in Egypt is unavailable in literature.

BA is classified into three types based on the most proximal level of biliary obstruction. BA type 1 has patency to the common bile duct. BA type 2 has patency to the common hepatic duct. BA type 3, the most common type occurring in greater than 90% of cases, results in complete occlusion of extrahepatic bile ducts up to the level of the porta hepatis.

The exact etiopathogenesis of BA is still unknown and is suggested to involve environmental, infectious, and genetic factors. Pre- or perinatal infections with rotavirus,

cytomegalovirus, and reovirus ***(Schilsky and Ala, 2010)*** were shown to infect and damage bile duct epithelia giving support to the hypothesis of a primary cholangiotropic viral infection as the initiating event of BA. In addition, alloimmune events mediated by liver infiltrating maternal effector T lymphocytes (microchimerism) have also been proposed to play a part in the pathogenesis of BA ***(Srivastava, 2014)***.

Biliary cysts, previously described as ***choledochal cysts***, can also present with cholestasis. Biliary cysts are cystic dilations that may occur throughout the biliary tree. They are divided into five different types depending on the location, number of cystic dilations, and involvement of the pancreaticobiliary junction**.** Incidence of biliary cysts has been reported at up to 1 in 1,000 births in select Asian countries, and is higher among Europeans and North Americans ***(O'Neill, 1992).***

Many mechanisms have been proposed for the pathogenesis of congenital and acquired biliary cysts. The majority of patients present before the age of 10 years of age, usually with a triad of abdominal pain, jaundice, and a palpable mass ***(Shah et al., 2009).*** Cysts can also be incidental findings on abdominal imaging. Biliary cysts are associated with a number of complications, including cholelithiasis, ductal strictures, cholangitis, and even cholangio- carcinoma. These complications present with a cholestatic pattern of serum liver tests.

Sclerosing cholangitis is characterized by a varying degree of stenotic and focally dilated intrahepatic bile ducts with rarification of segmental branches ***(Girard et al., 2012).*** Liver transplantation is the only treatment option.

In a few neonatal to infantile cases, it is associated with ichthyosis, and hence termed as neonatal ichthyosis and sclerosing cholangitis (NISCH) syndrome ***(Grosse et al., 2012)***.

Progressive familial hepatocellular cholestasis (PFIC) is a collection of inherited disorders that lead to progressive liver failure secondary to impaired bile formation and secretion.

This conglomerate of diseases often presents in infancy and childhood with intractable pruritus, coagulopathy, and other signs and symptoms of end stage liver disease. While prevalence is unknown, the estimated incidence is about 1 in 50,000 to 1 in 100,000 births.

Three broad types of PFIC have been described with an autosomal recessive mode of inheritance. Type I presents with unremitting cholestasis, pruritus, and jaundice prior to one year of age ***(Srivastava, 2014).***

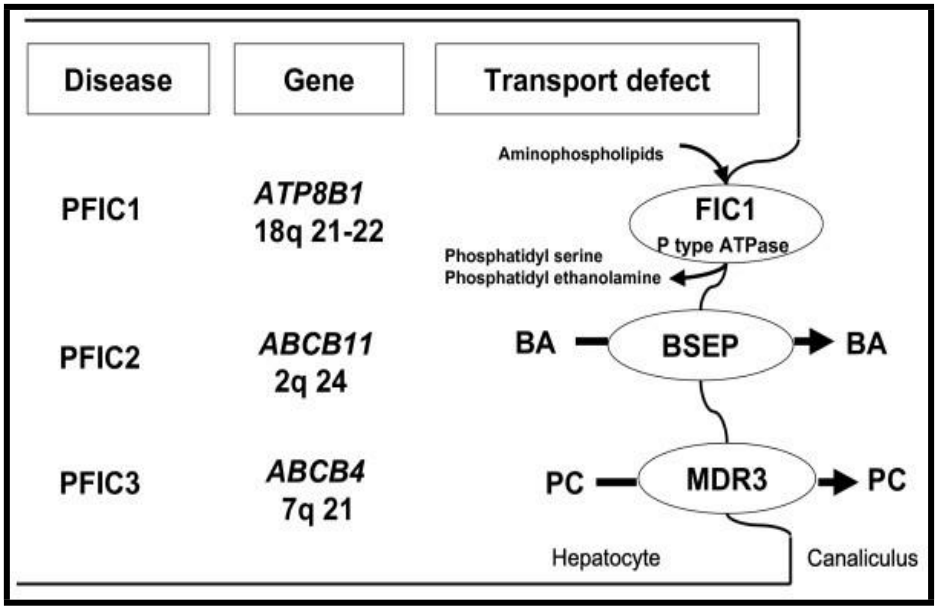

Figure (3): (PFIC): Types, related genes, and transport defects.
BA: bile acid; PC: phosphatidylcholine.

Of note, serum gamma glutamyltransferase (GGT) level is typically normal in PFIC type I, normal in type II, and elevated in type III. *MDR3* gene abnormality is seen in PFIC type III, which leads to abnormal secretion of phospholipids. The bile acids therefore accumulate and act as detergents to remove the GGT protein from the connecting glycosyl phosphatidyl inositol that anchors it to the bile canalicular membrane. The GGT protein then circulates into the serum and is elevated on laboratory in patients with PFIC III.

Patients with PFIC often progress to cirrhosis and resultant liver failure ***(Jansen and Müller, 1998).***

Table (1): Characteristic features of the types of PFIC

	PFIC 1	***PFIC 2***	***PFIC 3***
Transmission and Age of onset	AR, Neonates	AR, Neonates	AR, 1 month - 20 years
Gene and Chromosome	ATP8B1/F1C1, Ch 18q21-q22	ABCB11/BSEP, ch 2q24	ABCB4/MDR3,ch 7q21
Function of hereditary defect	Aminophospholipid translocase	Bile acid secretion	Phosphatidylcholine Secretion
Pruritis	Severe	Severe	moderate
GGT activity	Normal	normal	High
Serum ALT	Mildly elevated	> 5 × normal	> 5 × normal
Serum AFP	Normal	elevated	Normal
Serum Primary Bile Acid (PBA) concentration	Very high	Very high	High
Albumin	Low	Usually normal	Normal
Liver biopsy Histology	Minimal giant cell transformation, intracanalicular cholestasis, no ductal proliferation, minimal inflammation Late fibrosis	Giant cell transformation, intracanalicular cholestasis, no ductular proliferation, moderate inflammation, fibrosis	Giant cell transformation, intracanalicular cholestatis, ductular proliferation, moderate inflammation, marked fibrosis
Electron microscopy	Coarsely granular bile Loss of microvilli, swollen microvilli	Amorphous filamentous bile Loss of microvilli	Presence of cholesterol crystals Loss of microvilli
Immunohistochemistry	BSEP positive MDR3 positive GGT negative	BSEP negative MDR3 positive GGT negative to weakly positive	BSEP positive MDR3 negative GGT positive

BSEP: bile salt export protein; MDR3: multidrug resistance protein; GGTL: gamma glutamyl transpeptidase; ALT: alkaline tranferase; AFP: alpha fetoprotein ***(Amer and Hajira, 2014).***

Wilson's disease is an autosomal recessive copper storage disease linked to mutations on the *ATP7B*gene, with a prevalence of approximately 1 in 30,000 ***(Schilsky and Ala, 2010).***

The disease hallmark is decreased incorporation of copper into ceruloplasmin and resultant decrease of copper excretion in the bile. As a result, copper accumulates principally in the liver and brain, causing progressive hepatic and neuropsychiatric disturbances ***(Ranucci et al., 2014).***

While copper accumulation starts at birth, symptoms rarely present before five years of age. Approximately, 40-60% of patients present with symptoms during the second decade of life. Symptoms are often non-specific and will require a high degree of suspicion by the clinician. In the pediatric population, a patient will present more often with hepatic abnormalities because the central nervous system appears to be affected at a later time period ***(Khalaf et al., 2016).***

Choledocholithiasis, the presence of one or more gallstones lodged in the common bile duct, results in cholestasis. One study reviewed a single center's experience with pediatric gallstones and reported that 72% of the stones were pigmented, 17% were cholesterol stones, and 11%were of unknown composition ***(Stringer et al., 2003).***

While the cause and associated conditions vary among different age groups within the pediatric population, total parenteral nutrition administration, abdominal surgery, hemolytic disease, and hepatobiliary disease were common causes across age groups from birth until 11years of age. Although no specific gene has been linked to symptomatic gallstone disease in the pediatric population, rates of disease prevalence among twin studies revealed an increased concordance rate among monozygotic twins ***(Katsika et al. 2005).***

Cholestasis caused by choledocholithiasis is often transient and may resolve spontaneously with stone passage or with the help of therapeutic endoscopic retrograde cholangio-pancreatography (ERCP) (Fig. 4) ***(Khalaf et al., 2016).***

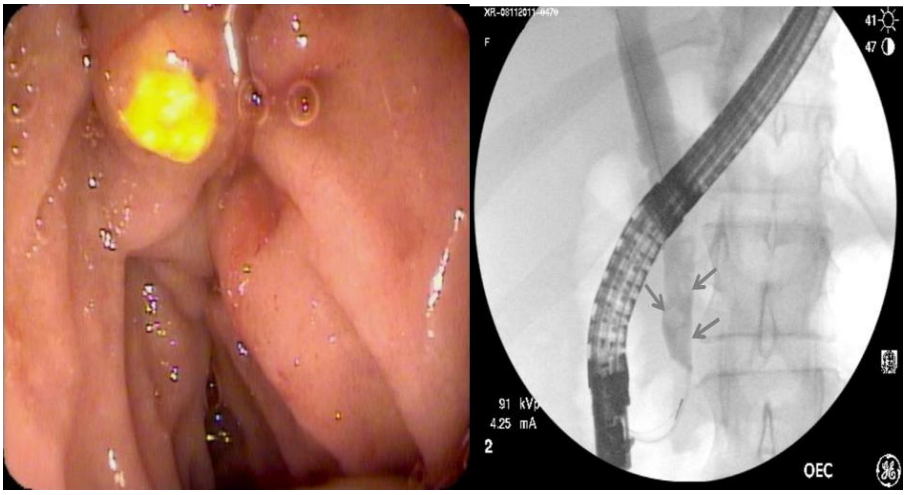

Figure (4): a,b: ERCP. **a:** Endoscopic view of impacted distal common bile duct stone protruding from the ampulla of Vater (image courtesy of David Troendle MD. **b:** Fluoroscopic cholangiogram showing multiple choledocholithiasis (arrows) in a dilated common bile duct (＞11 mm) (image courtesy of David Troendle MD*) (**Keil et al., 2010).***

Atypical causes of cholestasis

Benign Recurrent Intrahepatic Cholestasis

Originally described by ***Summerskill and Walshe***, benign recurrent intrahepatic cholestasis (BRIC) is a rare genetic disorder characterized by repeated episodes of severe pruritus and jaundice lasting from weeks to months.

The pathophysiology of BRIC is not well understood. It is an autosomal-recessive disease with incomplete penetrance secondary to a mutation in the *ATP8B1* gene located on chromosome 18. It encodes for the FIC1 protein, an aminophospholipid flippase ***(de Pagter et al., 1976).***

Pruritus is commonly the prodromal symptom of each attack, followed by jaundice several weeks later. Patients may also present with malaise, anorexia, nausea, vomiting, steatorrhea, malabsorption, and weight loss ***(Luketic and Shiffman, 2004)***.

Laboratory studies show a rise in the serum ALP level following the onset of pruritus. It is subsequently followed by a rise in serum conjugated bilirubin level, while serum GGT, AST, ALT levels remain normal or only mildly elevated ***(EASL, 2009)***.

No specific treatment is available for preventing or reducing the duration of attacks. Treatment is primarily focused on symptomatic relief until spontaneous resolution of each