# Cholestatic Disorders of Infancy: a Descriptive Study in the Pediatric Hepatology Unit at Cairo University Children's Hospital

*Thesis*

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بِسمِ الله الرحمنِ الرحيمِ

# وقُلْ رب زِدنِي علْما

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# ABSTRACT

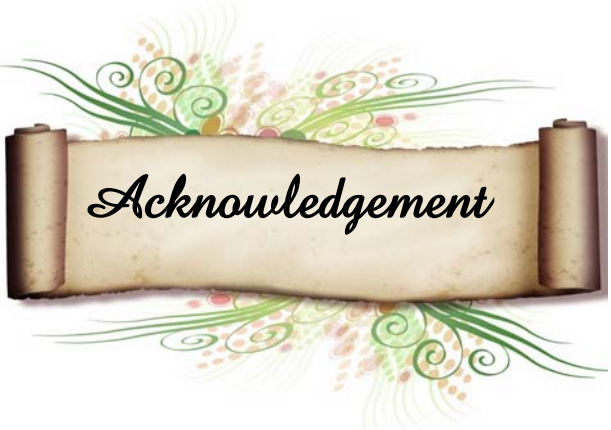
This a descriptive study of the clinical profile of patient presenting with cholestatic disorders of infancy through reviewing the medial record of the Pediatric Hepatology Unit at Cairo University Children's Hospital during the period from June 2009 to June 2010.

In our study 134 infants suffering from cholestasis presented at age from (4-270) days to our medical attention.

Jaundice was the most frequent symptom, representing (97%) of all symptom, biopsy was done for 98 cases in which the neonatal Hepatitis was the most frequent diagnosis (36.6%).

EHBA was the most common diagnosis (28.4%) of cases.

**Key words:** cholestasis, infant, jaundice

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# List of Abbreviations

| | | |
|---|---|---|
| AAT | : | Alpha-1-antitrypsin deficiency |
| AGS | : | Algaille syndrome |
| ALT | : | Alanine amino trasnferase |
| ASBT | : | Apical sodium bile acid transporter |
| AST | : | Aspartate aminotrasferase |
| BA | : | Biliary atresia |
| BASM | : | Biliary atresia splenic malformation syndrome |
| BRIC | : | Benign recurrent intrahepatic cholestasis |
| BSEP | : | Bile salt export pump |
| CC | : | Choledochal cyst |
| CFTR | : | Cystic fibrosis transmembrane conductance regulator |
| CMV | : | Cytomegalovirus |
| CSF | : | Cerebrospinal fluid |
| DNA | : | Deoxy riboneuclic acid |
| EHBA | : | Extrahepatic billiary atersia |
| ERCR | : | Endoscopic retrograde cholangiopancreatography |
| ESCLD | : | End-stage cholestatic liver disease |
| GGT | : | Gamma glutamyl traspeptidase |
| HBsAg | : | Hepatitis B surface antigen |
| HBV | : | Hepatitis B virus |
| HCV | : | Hepatitis C virus |
| HHV | : | Human herpes virus |
| HIV | : | Human immunodeficiency virus |
| HPV | : | Human papilloma virus |
| LDLT | : | Liver donor liver transplantation |
| MCTs | : | Medium chain triglycerides |
| MDR | : | Multidrug resistance |
| MRC | : | Magentic resonance cholangiography |
| NH | : | Neonatal hepatitis |
| NP | : | Niemann-pick disease |
| PC | : | Prothrombin concentration |
| PCR | : | Polymerase chain reaction |
| PFIC | : | Progressive familial intrahepatic cholestasis |
| PT | : | Prothrombin time |

| | | |
|---|---|---|
| RNA | : | Riboneuclic acid |
| SLT | : | Splitliver transplantation |
| TC sign | : | Triangular cord sign |
| TORCH | : | Toxoplasma Rubella Cytomegalovirus and herpes |
| UDCA | : | Ursodeoxycholic acid |
| VDRL | : | Venereal disease research laboratory |

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# INTRODUCTION

Bile secretion is a complex metabolic process, dependent on multiple structural and functional components in hepatocytes and bile duct cells. Its primary functions are to eliminate potentially toxic lipophilic compounds from the body, to excrete cholesterol, and to facilitate the digestion and absorption of lipids and lipid-soluble vitamins in the intestine ***(Boyer and Nathanson, 1999)***.

Cholestasis may be defined physiologically as measurable decrease in bile flow, pathologically as the histological presence of bile in liver cells and biliary system and clinically as the accumulation in blood and extra hepatic tissue of substance normally exerted in bile (e.g. bilirubin, bile acid and cholesterol) ***(Suchy, 2007)***.

Causes of neonatal cholestasis are long and diverse but the responses of newborn liver, either physiological or anatomical, are limited. This is because the ability of the developing liver of responding in the face of a varity of insulate are limited ***(Balistreri, 1985)***.

Thus infant with neonatal cholestasis usually present with variable degrees of jaundice, dark urine, pale stools and enlarged liver, all of which are non specific features of neonatal cholestasis ***(McLin et al., 2004)***.

Biliary atresia is an important cause of neonatal cholestasis. Early diagnosis and surgery for biliary atresia is important to ensure higher success rates for surgery and better long- term outcomes ***(Hartley, 2009)***.

Bile duct paucity syndromes include Alagille syndrome in which the main clinical features are: Cholestasis, characteristics facies (e.g. Broad forehead, deep set eyes), skeletal abnormalities, cardiac disease (e.g., peripheral pulmonary stenosis) ***(Alagille, 1985)***.

The outcome of Alagille syndrome depends on the hepatic and extra hepatic disease. The majority of children have a benign course. Most estimates put overall mortality at 20-25% ***(Roberts, 2008)***.

Progressive familiar intrahepatic cholestasis (PFIC) is a heterogeneous group of autosomal recessive liver disorder of childhood in which cholestasis of hepatocellular origin often present in the neonatal period or the first days of life and leads to death from liver failure at age ranging from infancy to adolescent ***(Jacqemin and Hadchouel, 1999)***.

In most patients, disease progresses inevitable to hepatic failure although there may be attacks followed by transient improvement. Thus affected patients are good candidates for liver transplantation particularly when they have been appropriately managed avoiding problems such as the neuropathy associated with vitamin E deficiency ***(De Vree et al., 1998)***.

# AIM OF WORK

The objective of this study is to describe the clinical profile of patients presenting with cholestatic disorder of infancy through reviewing of medical data of the Pediatric Hepatology Unit at Cairo University Children Hospital with following objectives:

**1-** To identify the prevalence of cholestatic disorders of infancy among infant and children with liver disease in the Pediatric Hepatology Unit at Cairo University Children Hospital.

**2-** To identify the etiologies of Cholestasis and familiar conditions namely PFIC.

**3-** To identify the clinical profile of the patients with special consideration to the age of presentation, course of disease, medical and surgical management and its effect on outcome.

**4-** To identify candidates for liver transplantation among patients.

**5-** To construct a detailed clinical data sheet that can be a basis for data collections for similar causes in the future.

# Chapter I

# CHOLESTATIC DISORDERS OF INFANCY

## Mechanism of cholestasis

Bile is a vital secretion essential for intestinal digestion and absorption of lipids. Bile is an important route of elimination for environmental toxins, carcinogens, xenobiotics include drugs, and their metabolites. Bile secretion is also a major route for endogenous compounds and metabolic products such as cholesterol, bilirubin and steroid hormones ***(Nathanson and Boyer, 1991)***.

Bile secretion is an osmotic process driven predominantly by the active excretion of organic solutes into bile canaliculi, followed by the passive inflow of water, electrolytes, and non-electrolytes (e.g. glucose) from hepatocyes and across semipermeable tight junctions. The main organic bile solutes of bile are bile salts, phospholipids and cholesterol, which form mixed micelles in bile. Extrusion of bile salts from hepatocytes is also critical for liver cell viability, as the intracellular accumulation of bile salts may lead to cell death by apoptosis and/or necrosis ***(Higuchi and Gores, 2003)***.

## Molecular Determinants of Cholestasis:

Bile secretion is mediated by several ATP binding cassette (ABC) transporters located in the canalicular membrane of hepatocytes ***(Meier and Stieger, 2002)***.

Among these ABC transporters, the bile salt export pump (BSEP, or ABCB11) represents the primary if not the sole transport system for the canalicular excretion of bile salts ***(Wang et al., 2001)***.

Cholestasis results when bile production in the liver is impaired, either from defect in canalicular secretion from the hepatocyte or from primary diseases of cholangiocytes, cholestatic disorder in hepatocytes arise from genetic mutation, or following drug, toxic, or viral injury ***(Trauner et al., 1998)***.

Cholangiocytic genetic disorders producing cholestasis include cystic fibrosis, Alagille's syndrome and progressive familial intrahepatic cholestasis (PFIC) of infancy, which represents a group of inherited cholestatic diseases that are classified into three subtypes. One of these subtypes, PFIC II, is associated with mutation in the BSEP gene ***(Jansen et al., 1999)***.

PFIC I and PFIC III are caused by mutation in the genes encoding FICI (ATP8B1) MDR3 (ATCB4), respectively ***(De Vree et al., 1998)***.

Irrespective of whether cholestasis results from genetic or acquired disorders of hepatocytes or cholangiocytes, the end result is altered expression and function of several molecular determinants of bile formation and enterohepatic circulation of bile salts ***(Boyer, 2002)***.

**Manifestations of Cholestatic Liver Disease in Infants:**

Jaundice is the most overt physical sign of liver disease and occurs more commonly in the neonatal period than at any other time of life.