Cholestatic Disorders Of Infancy : A Detailed Study Of Cases Presenting During 2006 In The Pediatric Hepatology Unit At Cairo University Children's Hospital

M.S. Thesis in Pediatric

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2008

ACKNOWLEDGEMENT

This work could not have been accomplished without the aid and co-operation of many contributors and no acknowledgement can pay sufficient tribute to their contribution to its achievement.

I would like to express my profound gratitude to ***Prof. Dr. Hanaa Mostafa El-Karaksy,*** Professor of Pediatrics, Cairo University for her extraordinary organization, supervision, guidance and valuable advice throughout the course of this work.

Since gratitude also expressed to ***Prof. Dr. Rokia Mohamed El-Sayed,*** Professor of Pediatrics, Cairo University for her encouragement, support and generous help.

I Owe a special depth of thanks and appreciation offered to ***Prof. Dr. Gamal El-Den Mohamed Taha,*** Professor of Pediatrics, Beni-Suief University for his helpful discussion and continous care.

No acknowledgment could be sufficient for them.

ABSTRACT

Cholestatic liver disease in infancy is caused by a wide range of condition including genetic, metabolic, obstructive and less commonly infective causes.

This is a retrospective study of the clinical profile of patients presenting with cholestatic disorders of infancy through reviewing the medical records of the Pediatric Hepatology Unit at Cairo University Children's Hospital during the period from 1st January to 31st of December 2006 .

In our study, Infants suffering from cholestasis presented at a mean age of 3.53±5.39 (range 0-10) months to our medical attention. The mean age at onset of symptoms was 1.85±4.27 months (range 0-12).

Jaundice was the most frequent symptom, representing 98.9% of all symptoms. EHBA was the most common diagnosis (17%) of cases.

Key words : cholestasis, infant, jaundice, neonate.

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List of Abbreviation

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ABC: ATP binding cassette.
ALT : Alanine amino transferase.
AS : Alagille syndrome.
BR1C : benign recurrent intrahepatic cholestasis.
BSEP: Bile salt export pump.
CC: Choledochal cysts
CSF: Cerebro spinal fluid.
DNA : Deoxy riboneuclic acid.
EBV: Ebstein Bar Virus.
EHBA: Extrahepatic biliary atresia.
ERCP: Endoscopic retrograde cholangiopancriatography.
GOT: Gamma glutamile transferase
HbsAG: hepatitis B surface antigen.
HCV: Hepatitis C virus
HIV: Haman immune deficiency virus.
HLA: Histocompitability antigen.
1 gM: Immunoglobulin M
MCH: Major histocompetability complex.
MDR: Multi drug resistance.
MRC: Magnetic resonance cholangiography.
MRP2: Multi-drug resistance associated protein.
NH: Neonatal hepatitis.
NPC: Niemann-Pick Disease
PC: Prothrombin concentration.
PCR: polymerase chain reaction.
PFTC: Progressive familial intrahepatic cholestasis.
PT: Prothombin time.
RNA: Ribo-neuclic acid.
TC sign: Triangular cord sign.
TORCH: Toxoplama. Rubella. Cytomegalovirus and Herpes.
TPGS: Alpha Tocopheryl Polyethylene Glycol Succinate.
UDCA: Urso deoxy cholic 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 a measurable decrease in bile flow, pathologically as the histologic presence of bile in liver cells and biliary system, and clinically as the accumulation in blood and extrahepatic tissues of substances normally excreted in bile [e.g, bilirubin, bile acids, and cholesterol] ***(Suchy, 2007)***.

Cholestatic liver disease in infancy is caused by a wide range of conditions including genetic, metabolic, obstructive and less commonly infective causes. Parenteral nutrition can lead to cholestasis and biliary hypoplasia is responsible for less than 5% of cases ***(Abdullah et al., 1997; Stormon et al., 2001)***.

Biliary atresia, a progressive sclerosis of the extrahepatic biliary tree that occurs only within the first 3 months of life, is one of the most common causes of neonatal cholestasis and

accounts for over half of children who undergo liver transplantation ***(Sokol, 2001)***.

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

The outcome of syndromic bile duct paucity is most directly related to the severity of the hepatic and the cardiac lesions, with mortality predominantly attributable to these two organs ***(Kamath and Piccoli, 2003)***.

Progressive intrahepatic cholestasis is a heterogeneous assortment of familial disorders of unknown cause which progress to cirrhosis and death, usually in the first or second decades. Most reported cases are without distinguishing pathological or biochemical criteria. The presenting feature may be jaundice in the neonatal period or jaundice, pruritus or malabsorption appearing later in infancy ***(Mowat, 1998)***.

Aim of Work

The aim of the present study is to describe the clinical profile of patients presenting with cholestatic disorders of infancy through reviewing the medical records of the Pediatric Hepatology Unit at Cairo University Children's Hospital during the period from 1st January to 31st of December 2006 with the following specific objectives :

(1) Identify the incidence of cholestatic disorders of infancy among infants and children with liver disease in the Pediatric Hepatology Unit, Cairo University Children's Hospital.

(2) Define the various causes of cholestasis considering the frequency of familial conditions namely PFIC.

(3) Identify the clinical profile of patients with special consideration to age of presentation, course of disease, medical and surgical management and its effect on outcome.

(4) To identify the need for liver transplantation among cholestatic infants and children.

(5) To construct a detailed clinical data sheet that can be the basis for data collection for similar cases in the future.

Chapter (1)

Cholestatic Disorders Of Infancy

Mechnisms Of Cholestasis

Bile formation is a vital process. Bile acids are molecules formed from enzymatic catabolism of cholesterol in the hepatocyte. The synthesis of bile acids is a regulated process dependent on cholesterol intake and the availability of bile acids. Bile acid seccretion is critical for intestinal digestion of lipids and assimilation of lipid soluble nutrients ***(Trauner et al., 1998)***. In addition toxic material is excreted in bile, including cholesterol and bilirubin. Bile formation is an osmotic process; active secretion of solute is the driving force for the osmotic attraction/ excretion of water ***(Muler and Jansen, 1998)***.

In parallel with the transport of water-soluble bile constituents, lipid vesicles are detached from the apical membrane of hepatocytes to form biliary micelles composed of phospholipids, cholesterol, and bile salts. High molecular weight bile constituents, such as plasma proteins are secreted by vesicular transport and by apical exocytosis. A host of nuclear receptors have been identified, which are involved in the coordinated regulation of bile acid formation **(Repa et al., 2000) .**