Serum Interleukin-8 and Interleukin-6 in Children with Biliary Atresia: Relationship with Disease Stage

Thesis

Submitted for partial fulfillment of master degree in Pediatrics

By

Hend Adel Bassiony Ismail

M.B.B.CH

"Ain Shams University"

Under supervision of

Assist. Prof. Lerine Bahy El-Din El-Shazly

Assistant Professor of pediatrics

Ain Shams University

Assist. Prof. Amel Abdel Magied El-Faramawy

Assistant Professor of pediatrics

Ain Shams University

Dr. Amal Ahmed Abbass

Lecturer of clinical pathology

Ain Shams University

Faculty of Medicine

Ain Shams University

2010

Acknowledgement

First and above all my deepest gratitude and thanks to ***ALLAH*** the source of all knowledge for achieving any work in my life.

It has been a great honor to proceed this work under supervision of ***DR. Lerine Bahy EL–Din EL-Shazly,*** Assistant professor of pediatrics. Ain Shams University. I am greatly indebted to her for suggesting, planning the subject, supervising the whole work and for her continous encouragement .

I would like to express my sincere gratitude and appreciation to ***DR. Amel Abdel Magied EL- Faramawy,*** Assistant Professor of pediatrics, Ain Shams University .For her guidance ,valuable advice ,great effort and generous help in this work.

I would like to express my deep obligation to ***DR. Amal Ahmed Abbass,*** Lecturer of Clinical Pathology, Ain Shams University, for her generous help and support throughout the practical part of this work.

No words could adequately express my deep appreciation to my great parents, my husband and my daughter for their love ,care and continous support .I will indebted to them all my life.

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List of Abbreviations

AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AP	Alkaline phosphatase
BA	Biliary atresia
CBC	Complete blood picture
CBD	Common bile duct
CHD	Common hepatic duct
CMV	Cytomegalovirus
CRP	C- reactive protein
DISIDA	Diisopropyl iminodiacetric acid
ds RNA	Double stranded ribo nuclear acid
ELISA	Enzyme Linked Immuno Sorbent Assay
GGT	Gamma glutamyl transferase
Hb	Hemoglobin
IG	Immunoglobulin
IL	Interleukin
IL-Ra	Interleukin -1 receptor antagonist
INF	Interferon
INR	International normalization ratio
IRF	Interferon – regulatory factor
LHD	Left hepatic duct

LP	Lipopeptide
LPS	Lipopoly saccharides
MCT	Median chain triglycerides
MHC	Major histocompatibilty complex
PAMPs	Pathogen associated molecular patterns
PAS	Periodic acid -Schiff
PFIC	Progressive familial interahepatic cholestasis
PG	Peptidoglycan
PMNs	Polymorphonuclear lymphocytes
RBCs	Red blood cells
RHD	Right hepatic duct
SD	Standard deviation
ss RNA	Single stranded ribo nuclear acid
T4	Thyroid hormone, thyroxine
TH	T helper cells
TLRs	Toll like receptors
TMB	Tetramethyl benzidine
TPGS	Tocopherol polyethylene glycol succinate
TSH	Thyroid stimulating hormone
VDRL	Veneral Disease Research Laboratory
WBCs	White blood cells

Introduction

Biliary atresia is a condition of uncertain cause where part, or all, of the extra-hepatic bile ducts are obliterated by inflammation and subsequent fibrosis, leading to biliary obstruction and jaundice. It is fatal if untreated. A viral aetiology has been proposed although the association with other congenital anomalies in some cases suggests a possible developmental abnormality **(Kelly and Davenport, 2007).**

In children, despite early diagnosis and prompt surgical intervention to improve biliary drainage, most patients will either require liver transplantation or die as a result of progressive liver fibrosis. The cause and pathogenesis of fibrosis are unknown. Genetic, viral and host immune factors are putative etiopathogenetic mechanisms of this disease **(Nobili et al., 2004).**

Bezzerra et al. (2002) have recently shown by large scale gene expression analysis that liver tissues from children with biliary atresia are characterized by the coordinated over expression of genes related to proinflammatory immunity. These findings led the authors to the conclusion that an inflammatory response could play a role in disease pathogenesis and ultimately in liver damage.

Inflammatory cytokines, such as (IL)-1b, IL-6 and tumor necrosis factor TNF, play a pivotal role in the induction and maintenance of the systemic and local inflammatory response. They induce endothelial cells to express adhesion molecules and to produce chemokines and are therefore responsible for the recruitment of inflammatory cells **(Kaplanski et al., 2003).**

They are also responsible for the stimulation of both leukocytes and stromal cells (i.e. fibroblasts), leading to the production of tissue-damaging substances, such as metalloproteinases and oxygen radicals. In this respect, IL-8, whose production is induced by TNF and IL-6, is not only a potent recruiter of neutrophils and T cells but also a potent stimulator of the degranulation. Several studies have addressed the role of these cytokines in a variety of liver disease **(Baggiolini et al., 1994).**

Aim of the Work

The objective of this study is to investigate the role of IL-8 and IL-6 in the pathogenesis of biliary atresia and to evaluate the relation between it and the clinical outcome.

Anatomy of the biliary tract

Biliary tract pathology is commonly encountered and it can also present significant diagnostic and therapeutic challenges to the practitioner. One of the main challenges is attributable to the variability in the anatomy of the biliary system. The development of the liver and biliary system is a complex process that can lead to numerous anatomic variations. A thorough knowledge of this anatomy is essential in radiologic, endoscopic, and surgical approaches to the biliary system **(Bannister, 1995)**.

Embryology of the biliary system

The biliary system and liver originate from the embryonic foregut. Initially, at week four, a diverticulum arises from the ventral surface of the foregut (later duodenum) cephalad to the yolk sac wall and caudad to the dilation that will later form the stomach. The development of the liver involves an interplay between an endodermal evagination of the foregut and the mesenchymal cells from the septum transversum. The liver diverticulum initially separates into a caudal and cranial portion. The caudal portion gives rise to the cystic duct and gallbladder and the cranial portion gives rise to the intrahepatic and hilar bile ducts. As the cranial diverticulum extends into the septum transversum mesenchyme, it promotes formation of endothelium and blood cells from the mesenchymal cells.