Study of High Gamma Glutamyl Transferase Cholestasis In Egyptian Children

Thesis

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By

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Hani Khedr

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List of Abbreviations

Abb.	Full term
3βHSD	*3β-hydroxy-C27-steroid oxidoreductase (dehydrogenase / isomerase) deficiency*
5βRD	*5β-reductase*
A1ATD	*Alpha1-antitrypsin deficiency*
ABE	*Acute bilirubin encephalopathy*
ALGS	*Alagille syndrome*
ALP	*Alkaline phosphatase*
ALT	*Alanine aminotransferase*
ARC	*Arthrogryposis- renal dysfunction cholestasis*
ARPKD	*Autosomal recessive polycystic kidney disease*
AS	*Alagille syndrome*
ASD	*Atrial septal defect*
AST	*Aspartate aminotransferase*
BA	*Biliary atresia*
BPA st.	*Branch pulmonary artery stenosis*
BRIC	*Benign Recurrent Intrahepatic Cholestasis*
BSEP	*Bile salt export pump*
CA	*Cholic acid*
CB	*Conjugated bilirubin*
CDCA	*Chenodeoxycholic acid*
CFR	*Case fatality rate*
CLS	*Cholestasis-lymphedema syndrome*
CMV	*Congenital cytomegalovirus*
DB	*Direct bilirubin*
ESLD	*End stage liver disease*
FAB-MS	*Fast atom bombardment-mass spectrometry*
FISH	*Fluorescence in situ hybridization*
GC-MS	*Gas chromatography-mass spectrometry*

List of Abbreviations Cont...

Abb.	Full term
GGT	*Gamma glutamyl transferase*
Hb	*Hemoglobin*
HBS	*Hepatobiliary scintigraphy*
HCC	*Hepatocellular carcinoma*
IB	*Ileal bypass*
IL-6	*Interleukin 6*
KCs	*Kupffer cells*
LT	*Liver transplantation*
MARS	*Molecular Adsorbent Recirculating System*
MDR3	*Multidrug resistance 3 protein*
NAIC	*North American Indian Childhood Cirrhosis*
NBD	*Nasobiliary drainage*
NC	*Neonatal cholestasis*
NICU	*Neonatal ICU*
NNJ	*Neonatal jaundice*
NO	*Nitric oxide*
NP-C	*Niemann-Pick disease*
PEBD	*Partial external biliary drainage*
PFIC	*Progressive Familial Intrahepatic Cholestasis*
pGp	*p-glycoprotein*
PIBD	*Partial internal biliary drainage*
PSC	*Primary sclerosing cholangitis*
PV	*Portal vein*
PVS	*Pulmonary valve stenosis*
RDA	*Recommended daily allowance*
RES	*Reticuloendothelial system*
SI	*Suspicion Index*
SNHL	*Sensorineural hearing loss*

List of Abbreviations Cont...

Abb.	Full term
TB	*Total bilirubin*
TNF-α	*Tumor necrosis factor alpha*
TOF	*Tetralogy of Fallot*
TORCH	*Toxoplamosis, rubella, cytomegalovirus, herpes simplex*
UDCA	*Ursodeoxycholic acid*
VSD	*Ventricular septal defect*
WBCs	*White blood cells*
ZO-2	*Zona occludens 2*

INTRODUCTION

During early life, failure of secretion of both bile and conjugated bilirubin is the commonest manifestation of liver dysfunction. Jaundice is frequently a feature of early rather than late advanced liver disease as is seen in older children ***(Bezerra and Balistreri, 2001).***

Cholestasis is defined as a decrease in bile flow due to impaired secretion by hepatocytes or due to obstruction of bile flow through intra or extrahepatic bile ducts ***(Nazer, 2014).*** It is also defined biochemically as a direct bilirubin greater than 2 mg/dl or more than 20% of the total bilirubin ***(Venigalla and Gourley, 2004)***. Hyperbilirubinemia characterized by jaundice, acholic stool, dark urine and hepatomegaly must always be considered as a pathological state ***(Suchy, 2004).***

Gamma glutamyl transferase (GGT) is an enzyme found in cell membranes of many tissues mainly in the liver, in both the hepatocytes and bile ducts. It is also found in the intestine, spleen, heart, brain, and seminal vesicles, but the liver is considered the source of normal enzyme activity. GGT levels are increased in patients with liver diseases in general, including cholestasis ***(Davit-Spraul et al., 2010).***

The differential diagnosis of high GGT in the category of infantile cholestasis is extensive and can be classified based on the anatomic location of pathology into extrahepatic and

intrahepatic aetiologies. Biliary atresia, choledochal cyst, bile duct stenosis, primary sclerosing cholangitis, choledochal pancreatico- ductal anomaly and neoplasm are examples of extrahepatic causes while, idiopathic neonatal hepatitis, progressive familial intrahepatic cholestasis type 3, Alagille syndrome are common intrahepatic etiologies ***(Fischler et al., 2007; Nguyen et al., 2014).***

In a recent study the predictive parameters of unfavorable outcome of intrahepatic cholestasis at presentation included etiology, age of onset, positive consanguinity and itching, where at 3rd month of follow-up they included enlarged firm liver, persistently pale stool, high ALT and AST. At one year, outcome could be predicted by the presence or absence of splenomegaly and low serum albumin ***(Abdel-Ghaffar et al., 2014).***

AIM OF THE WORK

The aim of this study was to evaluate patients with high GGT non surgical cholestasis as regard their different aetiologies, demograhic characteristics, clinical picture and outcome.

Chapter One

GAMMA-GLUTAMYL TRANSFERASES

Gamma glutamyl transferases (GGT) are highly conserved enzymes that occur in bacteria, yeast, plants and in animals from nematodes to humans ***(Rawlings et al., 2006).*** It is a two substrate enzyme that removes the terminal γ- glutamyl residue from a molecule of the general form Glu-γCO-NH-R by breaking the amide bond and transfers it to receptive molecule. Some of the common physiological γ-glutamyl substrates are glutathione ***(Elce and Broxmeyer, 1976),*** γ-poly glutamic acid ***(Kimura et al., 2004)*** and glutamine ***(Minami et al., 2003).***

Sites of production

GGT is found mainly in the membranes of cells that show high secretory or absorptive capacity: the epithelial cells lining the biiary tract, hepatic canaliculi, proximal renal tubules, pancreatic acinar tissue, pancreatic ductules, and intestinal brush border cells ***(Rawlings et al., 2006)***

GGT bioclinical conditions

GGT levels in blood are routinely measured in clinical laboratories. Indeed, GGT in serum is mainly derived from the liver, thus the enzyme is used as marker of liver or biliary tract-associated diseases. The higher the GGT level the greater the ‘‘insult’’ to the liver. Serum levels of GGT are affected by