THE VALUE OF HUMAN GLUTATHIONE S-TRANSFERASES IN EARLY DETECTION OF CYSTIC FIBROSIS RELATED LIVER DISEASE

Thesis

Submitted in partial fulfillment for the M.D. in pediatrics

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2012

Acknowledgement

First of all thanks to GOD for all his gifts to me and for his support and great help to finish this work.

It is of great honor for me to work with Professor **Dr. Samiha Samuel,** Professor of Pediatrics, Faculty of Medicine, Cairo University. I feel great gratitude and appreciation for her expert guidance, valuable advice and helpful suggestions to deliver this work.

I would like to express my deep appreciation and gratitude to **Prof. Dr. Mortada El-Shabrawi,** Professor of Pediatrics, Faculty of Medicine, Cairo University, for his close supervision generous support and continuous encouragement.

I am deeply thankful to **Dr. Rania Mohamed Fawzy,** Professor of clinical pathology, Faculty of Medicine, Cairo University, for her kind advice and guidance.

Special thanks to **Dr. Rania Mohamed Samy,** Lecturer of clinical pathology, Faculty of Medicine, Cairo University, for her great help and sincere advice.

Many thanks to **Dr. Doaa Salah El-Gendy** in the unit of ultrasonography in pediatric hospital Cairo University, for her great help in doing ultrasound to all my patients

Dedication

To the soul of my father, to whom, I loved too much

To my mother, god saves her and gives her health and strength.

To my sister for her encouragement.

To my husband for his continuous support, patience and understanding

To my lovely two kids.

For all my professors

For all those who were Teaching and Backing me to reach Such a Stage of Education and Knowledge

Abstract

Objective: Cystic fibrosis (CF) is a genetic disease that typically produces symptoms of malnutrition and chronic respiratory infections and remains the most common life threatening autosomal recessive disorder in white population, with a frequency of about 1 in 2500 live births. For a long time, CF was thought to be a rarity among Arabs. Recently, case reports from several Arab countries have been published, sue**.** CF is caused by mutations in a single gene on the long arm of chromosome 7 encoding a protein called the CF transmembrane regulator (CFTR). The defect in CFTR leads to pathological changes in all organs with mucous secretory glands, e.g. airways, pancrease, gut, biliary tract, vas deferens and sweat glands. With increase life expectancy in patients with CF, liver manifestations complicating the clinical course of the disease have emerged as a significant medical issue and it is now considered the third leading cause of death in patients with CF. Besides improved survival, increased recognition of liver disease (LD) also has been fastened by substantial changes in follow up modalities our time, including more frequently resorting to laboratory determinations and ultrasonography. Children with CF are predisposed to liver disease because of the lack of a functional CFTR protein on the biliary epithelium. The characteristic hepatic histological lesion in CF is focal biliary fibrosis. It is probably due to the focal nature of the damage that the clinical signs arc few and overall hepatic function is preserved until the late stages. The prompt recognition of CF liver disease is now important because of the potential beneficial effects of treatment with ursodeoxycholic acid and the need to design trials of its prophylactic use.

Methods: In our study, we aimed to investigate the early evaluation of clinical, biochemical (mainly serum level of GST) and ultrasonographic features of liver disease in a group of children with CF and comparing them with 2 groups (hepatic group and controls). In a recent study as regard biochemical investigation, it was found that human glutathione- S- transferases (hGST) which are cytosolic detoxification enzyme accounting for about 3% of the cytoplasmic proteins in hepatocytes showed some rise indicating early liver damage. As regard ultrasonography, it was found that abnormal echogenicity was often found in the absence of biochemical and/or clinical disease. It was concluded that periodic ultrasonographic examination could be an early indicator of disease.

Results: As regard the serum level of GST enzyme (normal value about 2000-3000 U/L), the results revealed a highly significant difference between controls and (hepatic + CF) groups. As regard the ultrasongarphic changes among three groups, the results revealed a highly significant difference between controls and Hepatic + CF) groups. From these results we can confirm that GST is a sensitive value in early detection of liver affection in general with no specificity to CF patients.

Conclusion: serum GST with US scan of liver seem to be sensitive markers than transaminases for detection of liver affection in general with no specificity to CF patients, so we can use both of them to detect early liver affection in general included CFLD.

Key words:

(CF- CFTR- CFLD- Biliary fibrosis – GST- U/S)

CONTENTS

List of Abbreviations

∆F508	Delta F 508
ABPA	Allergic bronchopulmonary aspergillosis
ACC	Acetylcysteine
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
C-AMP	Adenosine monophosphate
CF	Cystic fibrosis
CFAA	Cystic fibrosis associated arthritis
CFLD or CFRLD	Cystic fibrosis related liver disease
CFRDM	Cystic fibrosis related diabetes mellitus
CFTR	Transmembrane conductance regulator
CL	Chloride
CO2	Carbon dioxide
CPX	8-cyclopentyl-1,3-Dipropyl xanthin
CT	Computed tomography scan
CVS	Chorionic villus sampling
d	Day
DHLA	Dihydrolipoic Acid
DIOS	Distal intestinal obstruction syndrome
DKA	Diabetic ketoacidosis
DNA	Dinuclutide aminotransferase
DNase	Deoxy libonuclease
EC	Enteric coated

EEG	**Electroencephalogram**
ENac	**Epithelial sodium channel**
ERCP	**Endoscopic retrograde cholangiopathy**
FEV1	**Forced expiratory volume in first second**
FO2	**Oxygen flow**
FVC	**Functional vital capacity**
G6PD	**Glucose -6-phosphate dehyrogenase**
GGT	**4-glutamyltransferase**
GOR	**Gastroesophogeal reflux**
GSSG	**Glutathione disulfide**
GST	**Glutathione –s-stranferase**
hGST	**Hyman glutathione-s-transferase**
HPOA	**Hypertrophic pulmonary osteoarthropathy**
HRCT	**High resolution CT**
IL	**Interleukin**
IRT	**Immunoreactive trypsin**
IU	**International unit**
IV	**Intravenous**
IVIG	**Intravenous immunoglobulins**
K	**Potassium**
LD	**Liver disease**
m	**Month**
MC	**Mucous clearance**
MRCP	**Magnetic resonance cholangiopancreatography**
Na	**Sodium**
NAL	**Nacystelyn**
NSAID	**Non steroidal anti-inflammatory drugs**

PD	**Potential difference**
PEM	**Protein energy malnutrition**
PET	**Pancreatic enzyme therapy**
Ph	**Ph value**
PHT	**Portal hypertension**
PI	**Pancreatic insufficiency**
PKA	**Protein kinase A**
PS	**Pancreatic sufficiency**
Ps.A	**Pseudo monas aeruginosa**
RDA	**Recommended daily allowance**
rhTrx	**Recombinant human thioredoxin**
RNA	**Ribonucleotide aminotransferase**
RV	**Residual volume**
SaO2	**Oxygen saturation**
SLPI	**Secretory leukoprotease Inhibitor**
TIPSS	**Transjugular intrahepatic porto-systemic shunts**
TLC	**Total lung capacity**
TNF	**Tumor necrosis factor**
TRL	**Threonine, arginine, leucine**
TrX	**Thioredoxin**
U.S	**United state**
U/S	**Ultrasonography**
UDCA	**Ursodeoxy cholic acid**
yr	**Years**
α-1AT	**Alpha-1 artitrypsin**

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