ASSESSMENT OF LIVER DISEASE PROGRESSION AMONG SURVIVORS OF CHILDHOOD MALIGNANCY WITH CHRONIC HEPATITIS C

Thesis

Submitted for Partial Fulfilment of M.Sc degree in Paediatrics

By

Fatma Ahmed Taha Marzouk
M.B., B. Ch.
Faculty of Medicine -Tanta University

Under Supervision of

Prof. Dr. Manal Hamdy El-Sayed
Professor of Pediatrics
Faculty of Medicine –Ain shams university

Prof. Dr. Gamal Eldin Mohamed Gamil
Professor of Tropical and Hepatology
Faculty of Medicine-Cairo University

Dr. Dalia Nabil Toaima
Lecturer of Pediatrics
Faculty of Medicine –Ain shams university

Faculty of Medicine - Ain Shams University
2014

Acknowledgment

First and foremost, I feel always deeply indebted to ALLAH, the Most Gracious and the Most Merciful.

I would like to express my deepest gratitude and cardinal appreciation to Prof. Dr. Manal Hamdy Elsayed, Professor of Pediatrics, Faculty of Medicine, Ain Shams University who kindly supervised and motivated the performance of this work, for her kind guidance and constant encouragement throughout this work.

I am greatly honored to express my sincere appreciation to Prof. Dr. Gamal Eldin Mohamed Gamil, Professor of Tropical and Hepatology, Faculty of Medicine, Cairo University for his continuous support, help and generous advice throughout this work.

I am sincerely indebted to Dr. Dalia Nabil Toaima, Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University, for her guidance and sincere help from beginning of the current work.

I would like to express my deepest thanks to Prof. Alaa El Haddad, Dean of the National Cancer Institute and Prof of Pediatric Oncology, for his patience and valuable instructions. I am deeply indebted to his guidance, sincere directions

I am sincerely indebted to Dr. Amira Mohsen Abd Elhameed, Researcher, Community Medicine Department, National Research Center, for her sincere help in statistical part.

I am deeply grateful for Dr. Aisha El Sharkawy, Lecturer of Tropical and Hepatology , Cairo University, for her valuable help in liver assessment by fibroscan.

Finally, I want to dedicate this work to all the members of my family because of their patience and support.

Fatma Ahmed Taha Marzouk

List of Contents

Title | Page No.

List of Tables

List of Tables (Cont...)

List of Figures

List of Figures (Cont...)

List of Abbreviations

Abb.	Meaning
AIH ..... :	Autoimmune hepatitis
Alb ..... :	Albumin
ALL ..... :	Acute lymphoblastic leukemia
ALP ..... :	Alkaline phosphatase
ALT ..... :	Alanine aminotransferase
AML ..... :	Acute Myeloid Leukemia
Anti-HBc ..... :	Hepatitis B core antibody
Anti-HBs ..... :	Hepatitis B surface antibody
anti-HCV ..... :	Hepatitis C Virus antibody
APRI ..... :	AST-to-Platelet ratio Index
ARFI ..... :	Acoustic radiation force impulse imaging
AST ..... :	Aspartate aminotransferase
CBC ..... :	Complete blood count
CHC ..... :	Chronic hepatitis C
CLD ..... :	Chronic liver disease
CMV ..... :	cytomegalovirus
CRP ..... :	C Reactive Protein
CT ..... :	Computed tomography
D.bil ..... :	Direct bilirubin
EBV ..... :	Epstein-Barr Virus
ECM ..... :	extracellular matrix
EIA ..... :	Enzyme immunoassays
ELISA ..... :	Enzyme Linked Immuno sorbent Assay
ERCP ..... :	Endoscopic retrograde cholangiopancreatography
FAB ..... :	French-American-British
FDA ..... :	Food and Drug Administration
Fig ..... :	Figure
FS ..... :	Fibrosis score
GGT ..... :	Gamma-Glutamyltransferase
HAV ..... :	Hepatitis A Virus
HBV ..... :	Hepatitis B Virus
HBsAg ..... :	Hepatits B surface antigen
HBV ..... :	Hepatitis B virus

List of Abbreviations (Cont...)

Abb.	Meaning
HCC ..... :	Hepatocellular carcinoma
HCV ..... :	Hepatitis C virus
HCV Ab..... :	Hepatitis C Virus antibody
HCV-PCR ..... :	Hepatitis C Virus- Polymerase Chain Reaction
HD..... :	Hodgkin's Disease
HDV..... :	Hepatitis D Virus
HEV..... :	Hepatitis E Virus
HIV ..... :	Human Immunodeficiency Virus
HLA ..... :	Human leucocyte antigen
HSC..... :	Hepatic stellate cells
HVPG..... :	Hepatic-vein portal gradient
IASL..... :	International Association for the Study of the Liver
ICC ..... :	Intra-class correlation coefficients
IL-1b ..... :	Interleukin-1b
INF..... :	Interferon
IFN-α ..... :	Interferon α
IFN –γ..... :	Interferon- γ
INR ..... :	International normalization ratio
IQR ..... :	Inter-quartile range
kPa ..... :	Kilopascals
LSM ..... :	Liver stiffness measurement
MRI ..... :	Magnetic resonance imaging
NAFLD ..... :	Non alcoholic fatty liver disease
NHL..... :	Non-Hodgkin's lymphoma
NK..... :	Natural killer
NPV ..... :	Negative predictive value
P-C ..... :	Portal-central
PCR..... :	Polymerase Chain Reaction
PEG-IFN ..... :	Pegylated interferon
PEG-IFNα-2b..... :	Peginterferon -α-2b
P-P ..... :	portal-portal

PPV ..... : Positive predictive value

List of Abbreviations (Cont...)

Abb.	Meaning
PT ..... :	Prothrombin time
RIBAs ..... :	Recombinant immunoblot assays
SD ..... :	Standard deviation
Sec ..... :	Second
SVR..... :	Sustained Virological Response
T.bil ..... :	Total bilirubin
TCR ..... :	T-cell receptor
TE ..... :	Transient elastography
TLC ..... :	Total leukocytic count
TM..... :	Time movement
TMA..... :	Transcription mediated amplification
TNF-a ..... :	Tumor necrosis factor a
US ..... :	Ultrasonography
WBCs ..... :	White blood cells
WHO ..... :	World Health Organization

INTRODUCTION

Hepatitis C virus (HCV) is the most common etiology of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in the Egypt. Although the transmission of this disease has declined since the development of blood donor screening tests for the virus, there are many patients surviving with chronic transfusion-acquired infection. The natural history of hepatitis C infection in children. The tempo from childhood infection to development of chronic hepatitis, cirrhosis, and hepatocellular carcinoma has not been established. Young age at infection has been proposed to be a determinant for the lack of progression of HCV infection and hepatocellular damage ***(Vogt et al., 1999 and Minola et al., 2002).***

Preliminary reports have suggested that survivors of childhood cancer are a growing and vulnerable population. Patients who were treated for childhood cancer before HCV donor screening was implemented constitute a large population at risk for transfusion-acquired HCV infection. This cohort is unique in comparison with other groups with HCV infection in that these patients acquired the infection when they were young and were likely receiving immunosuppressive or hepatotoxic therapy. Reports with relatively brief follow-up suggest that the risk for progression to clinically significant liver disease is low for survivors of childhood cancer ***(Arico et al., 1994 and Locasciuli et al., 1997).***

Pediatric cancer patients frequently require blood and blood products during therapy; thus, those who were treated before the current HCV blood donor screening methods were initiated in 1992 have an elevated risk of transfusion-acquired HCV. As in the general population, chronic HCV infection in pediatric cancer survivors is associated with liver fibrosis, cirrhosis, hepatocellular carcinoma, extra-hepatic manifestations, and impaired quality of life. In cancer survivors, these effects may be compounded by exposure to immunosuppressive and hepatotoxic chemotherapy ***(Castellino et al., 2004).***

Progressive hepatic fibrosis with the development of cirrhosis is a feature of almost all chronic liver diseases. Approximately 10–20% of patients with chronic hepatitis C virus infection have cirrhosis at first clinical presentation, and as many as 20–30% of those who donot have cirrhosis will eventually develop this condition and its complications within one or more decades ***(Benvegnù et al., 2004).***

Liver fibrosis assessment plays an important role in hepatology. Besides its importance for prognosis, determining the level of fibrosis reveals the natural history of the disease and the risk factors associated with its progression ***(Abenavoli et al., 2007).***

Liver biopsy is the gold standard for the assessment of fibrosis stage in chronic hepatitis. However, liver biopsy is an invasive and expensive procedure ***(Bedossa et al., 2003).*** Non-

invasive assessment of liver fibrosis is a major objective that has been encouraging many approaches, such as Transient elastography (TE) with the use of a new apparatus, FibroScan (EchoSens, Paris, France) for measurement of liver stiffness and (the aminotransferase-to-platelet ratio index (APRI) ***(Wai et al., 2003 and Ziol et al., 2005).***

TE provides a quantitative operator-independent measurement of liver stiffness. The best known contributor to liver stiffness is the amount of fibrosis; however, recent findings suggest that inflammation, interstitial fluid and even vascular conditions can have an impact on the stiffness measurement obtained by TE ***(Kazemi et al., 2006)***. Thus, TE has the potential to provide much more information than just an assessment of fibrosis, and specialists must put the elastographic results in perspective with the rest of their clinical findings ***(Foucher et al., 2006).***

Aim of the Work

Assessment of liver disease progression among survivors of childhood malignancy with chronic hepatitis C virus infection using multimodality approach including transient elastography and comparing its findings with FIB4 and APRI and their correlation with other parameters as liver functions,ferritin, platelet and duration of chemotherapy.

Chapter I

Hepatitis C Virus Infection in Children

Hepatitis or inflammation of the liver can be due to a variety of causes of which viral infection is the most important, and leads to significant morbidity and mortality. Viral hepatitis is caused by infection with one of the five known viruses, which predominantly affect the liver the hepatitis A, B, C, D and E viruses (HAV, HBV, HCV, HDV and HEV) ***(Kumar et al., 2010).*** Many viruses in addition to the primary hepatotropic viruses (hepatitis A-E) should be considered in the etiology of hepatitis that occurs in children. The nonhepatotropic viruses account for up to 10% of viral hepatitis and may cause severe liver disease especially in neonates and immunocompromised patients. Some of these relatively common non-hepatotropic viruses are Epstein-BarrVirus (EBV), cytomegalovirus (CMV), herpes simplex virus, enterovirus, adenovirus, rubella and parvovirus ***(Tezer et al., 2008).***

Hepatitis C virus (HCV) was identified in 1989 and since then significant advances have been made in understanding the molecular biology, pathology, and treatment of HCV liver disease ***(Mohan et al., 2010).*** HCV is a small, enveloped virus (Figure 1), a member of the Flaviviridiae family and the lone