
قَالُوا سُبْحَانَكَ لاَ
عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ
أَنتَ الْعَلِيمُ الْحَكِيمُ
صدق الله العظيم

Assessment of CD4 and CD8 in Chronic Hepatitis (C) with and without Cirrhosis

THESIS

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Marwa Mahmoud Shawki

Contents

LIST OF TABLES

List of Figures

LIST OF ABBREVIATIONS

Ab	Antibody
Ag	Antigen
ALT	Alanine aminotronsferase
AST	Aspartate amino transferase
CD	Cluster of differentiation
CMI	Cell mediated immunity
CTL	Cytotoxic T Lymphocyte.
CMV	Cytomegalo virus
DC	Dendritic cell
EDTA	Ethylene diamine tetracetic acid
ELISA	Enzyme linked immunosorbent assay
ELISPOT assay	Enzyme Linked Immunosorbent Spot assay
ER	Endoplasmic Reticulum
FBS	Fetal Bovine Serum
FS	Forward Scatter
GBD	Global Burden of Disease
GAG	Glycosamine Glycans
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HENCORE	Hepatits C European Network for C-operative Research
HIV	Human immune deficiency virus
HLA	Human leukocytic antigen
HS	Highly significant
HVR	Hypervariable region
ICS	Intra Cellular Cytokine Staining
IFN	Interferon
IFN- ß	Interferon beta
IFN- α	Interferon alpha
IFN- γ	Interferon gamma
Ig	Immunoglobulin
IL	InterLeukin
IRES	Internal ribosome entry site
IVDUs	intraverous drug users
LDL	Low density Lipoproteins
LDLR	Low Denisty Lipoprotein Receptor
LT	Liver Transplantation
mDC	Myeloid dendritic cell
MHC	Major histocomptibility complex
MICA	MHC class 1 related chain A/B

MNL	Mono Nuclear Layer
NCR	Non Coding Region
NF.B	Nuclear Factor B
NK cell	Natural killer cell
NS	Non significant
NS	Non structural
P	Significance level
PBMC	Peripheral blood mononudear cells
PCR	Polymerase chain reaction
pDC	Plasmacytoid dendritic cell
PHS	Pooled Human Serum

PKR	Inducible protein kinase
PT	Prothrombin Time
RIBA	Recombinant Immuno Plot Assay
RNA	Ribonucleic acid
S	Significant
SD	Standard devidation
SGOT	Serum Glutamic Oxaloacetic Transferase
SGPT	Serum Glutamic Pyruvate Transferase
SPSS	Statistical package for special sciences
SR-B1	Scavenger Receptor class B type 1
STD	Sexual Transmitted Disease
SVR	Sustained Virological Response
TCR	T Cell receptor
TGF-ß	Transforming growth factor-beta
Th1	T helper 1 cell
Th2	T helper 2 cell
TLR	Toll- like receptor
TM	Transmembrane
TNF	Tumour necrosis factor
Tregs	Regulatory T- cells
UTR	Untranslated Region
VLDL	Very Low Denisty Lipoproteins
WHO	World health organization

Introduction

T- lymphocytes, with their diffuse effector functions and their regulatory effect on other immune cells, play a central role in inflammatory diseases such as infectious diseases, autoimmune diseases, graft versus host diseases and allograft rejection, of particular interest. T cells are believed to be involved in the pathogenesis of important liver diseases including both autoimmune liver diseases and viral hepatitis. ***(Lai et al., 2003)***

Chronic viral hepatitis caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) is the most common chronic liver disease. In addition to playing a crucial role in the control of HBV and HCV, T cells responses are also responsible for the liver injury during acute and chronic phases of viral hepatitis. ***(Ward et al., 2002)***

Knowledge on hepatitis virus immunology has provided important insight to the understanding of T cell role in immunity of autoimmune liver diseases ***(Leshner F, 2000)***

Hepatitis C virus is the major cause of chronic liver disease. HCV is a positive stranded RNA virus belonging to the family of Flavivirus. Replication of the virus takes place primarily in the liver, making HCV infection the leading cause of chronic hepatitis in the worldwide ***(Thimme et al., 2002)***

HCV persists in the majority of infected individuals (~ 70%) but the incidence of asymptomatic infection or transient disease followed by spontaneous recovery may be under estimated ***(Ulsenheimer et al., 2003)***

There is growing research to determine the long term outcomes of the disease but there is limited information on what underlies the difference in immune responses ***(Chang et al., 2001)***

Liver damage is not directly caused by the virus, rather is interplay between the virus and the immune system which results in the replacement of healthy liver tissue with fibrous scar tissue. Individuals with chronic hepatitis C infection frequently exhibit no symptoms. Some may report non-specific symptoms such as fatigue, muscle aches, nausea and anorexia. Antibodies directed against several HCV proteins can be detected in chronic patients. A variety of autoimmune or immune complex-mediated diseases have also been associated with chronic HCV infection ***(Tedeschi, 2009).***

Aim of the work

Aim of the study is to find a correlation between the laboratory results, abdominal ultrasound and level of CD4 and CD8 in order to try to determine the role of T cells in the long term outcome of the disease.

Historical Background of Hepatitis C virus

The World Health Organization (WHO) estimates 170 million individuals worldwide are infected with hepatitis C virus (HCV). However, the prevalence of HCV infection varies throughout the world. For example, 1 decade ago, Frank et al reported that Egypt had the highest number of reported infections, largely attributed to the use of contaminated parenteral antischistosomal therapy ***(Frank C et al., 2000)***

This led to a mean prevalence of HCV antibodies in Egypt of 22%.

According to the US Centers for Disease Control and Prevention (CDC), an estimated 1.8% of the US population is positive for HCV antibodies. Because 3 of 4 seropositive persons are also viremic, this corresponds to an estimated 2.7 million people with active HCV infection nationwide. Infection due to HCV accounts for 20% of all cases of acute hepatitis, an estimated 30,000 new acute infections, and 8000-10,000 deaths each year in the United States.

Medical care costs associated with the treatment of HCV infection in the United States are estimated to be more than $600 million a year. Most patients infected with HCV have chronic liver disease, which can progress to cirrhosis and hepatocellular carcinoma (HCC). Chronic infection with HCV is one of the most important causes of chronic liver disease (see the following image) and, according to a report by Davis et al, the most common indication for orthotopic liver transplantation (LT) in the United States ***(Davis GL et al., 1989)***

Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are anti-HCV positive. Egypt has higher rates of HCV than neighboring countries as well as other countries in the world with comparable socioeconomic conditions and hygienic standards for invasive medical, dental, or paramedical procedures. The strong homogeneity of HCV subtypes found in Egypt (mostly 4a) suggests an epidemic spread of HCV. Since a history of injection treatment has been implicated as a risk factor for HCV, a prime candidate to explain the high prevalence of HCV in Egypt is the past practice of parenteral therapy for schistosomiasis. The large reservoir of chronic HCV infection established in the course of these campaigns remains likely to be responsible for the high prevalence of HCV morbidity and may be largely responsible for the continued endemic transmission of HCV in Egypt today ***(Lavanchy D & McMahon B , 2000)***

Epidemiology of Hepatitis C virus

The estimated global prevalence of HCV infection is 2.2%, corresponding to about 130 000 000 HCV-positive persons worldwide (fig.1). Because many countries lack data, this estimate is based on weighted averages for regions rather than individual countries. Region-specific estimates range from < 1.0% in Northern Europe to > 2.9% in Northern Africa. The lowest prevalence (0.01%-0.1%) has been reported from countries in the United Kingdom and Scandinavia; the highest prevalence (15%-20%) has been reported from Egypt. An estimated 27% of cirrhosis and 25% of HCC worldwide occur in HCV-infected people ***(Perz et al., 2006)***

Figure (1) Estimated HCV prevalence by region (***Global burden of disease (GBD) for hepatitis C***)

There are both geographic and temporal differences in the patterns of HCV infection. For example, vastly different countries, including the United States, Australia, Turkey, Spain, Italy, and Japan, belong to regions of the world with similar overall average prevalences of HCV infection (1.0%-