FREQUENCY OF HEPATITIS C IN PATIENTS WITH BLEEDING ESOPHAGEAL VARICES

Thesis
Submitted for Partial Fulfillment of
Master Degree in
Tropical Medicine
Presented by
Sherine Abd El Salam El Rafei
M.B., Bch.

Supervisors
Prof. Dr. Mohammed Ali Madwar
Professor of Tropical Medicine

Prof. Dr. Mohammed Khairy El Naggar
Professor of Tropical Medicine

Dr. Mohammed Awad Mansour
Assistant Professor of Tropical Medicine

Faculty of Medicine
Ain Shams University
1999

ACKNOWLEDGMENT

I wish to express my deepest gratitude to my supervisors for their guidance, insight and support.

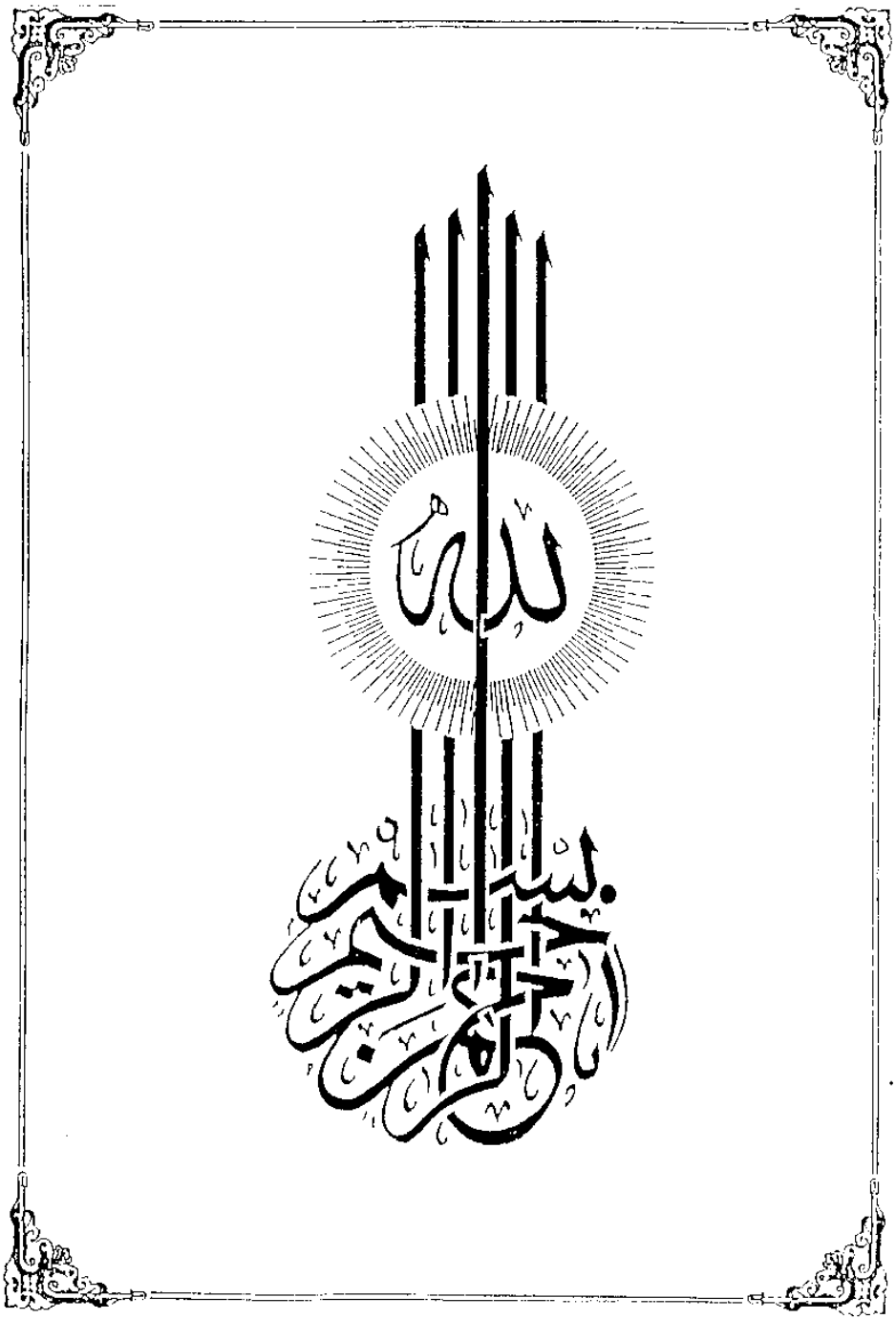
My special thanks go for **Prof. Dr. Mohammed Ali Madwar, Professor of Tropical Medicine**, who suggested the theme of the thesis and whose advice paved my way in the field of Hepatology.

I would like to extend my thanks to **Prof. Mohammed Khairy El Naggar, Professor of Tropical Medicine,** whose support was invaluable for the analysis of the results.

My special thanks are extended to **Dr. Mohammed Awad Mansour, Asisstant Professor of Tropical Medicine,** whose advice was the main factor in putting the work in its present form.

In addition, I would like to thank Dr. Amal Mokhtar Lecturer of Community Medicine in the National Research Center, for her kind assistance in the statistical part of this thesis.

Last but not least my special thanks go to my parents, my husband, my brothers, and my parents in law for their support, tolerance, and assistance.



CONTENTS

Introduction

Shistosomiasis remains an important health problem in over 50 countries worldwide (El Toum et al 1994). About 200 million people are estimated to be affected by the disease. Although there are many clinical manifestations associated with shistosoma mansoni infection, the most cause of morbidity is periportal fibrosis and the resultant esophageal varices. (Nash,et al 1982).

Portal hypertension is intially caused by an increase of the intra-hepatic vascular resistance, concomitant vaso-dilatation of the visceral vascular system further elevates pressure within the portal venous system .To relieve this pathological pressure gradient spontaneous porto-systemic collaterals are found. The most relevant collaterals are gastro eosophageal varices. These gastro- esophageal varices are characterized by multiple episodes of hemorrhage extending over many years, (Bosh et al 1992).

Infection with HCV has been identified as the major cause of non –A, non-B hepatitis and cirrhosis (Van Der Poel et al 1994). Recent studies have indicated that in

History of the diseases

Blood borne non-A, non-B hepatitis was first recognized in the mid 1970's by (Prima et al 1974 and Feinstone et al 1975) but identifying the major responsible agent by conventional methods proved to be difficult. In 1989, Choo and colleagues used molecular techniques to clean a clone of viral genome from chimpanzees that were experimentally infected with a contaminated human factor VIII concentrates. The development of an immunoassay based on the detection of circulating antibodies to be a recombinant epitope proved that this virus, designated hepatitis C virus, was the etiological agent in most cases of post transfusion non-A, non-B hepatitis (Alter et al 1989, Aaach et al, 1991). Since then, our knowledge of biology, epidemiology, and patho-physiology of HCV increased exponentially; HCV in the most common cause of post transfusion and community acquired non A, non B hepatitis and cryptogenic cirrhosis world wide, (Hopf et al 1990, & Bruix et al 1989).

Immunobiology of HCV

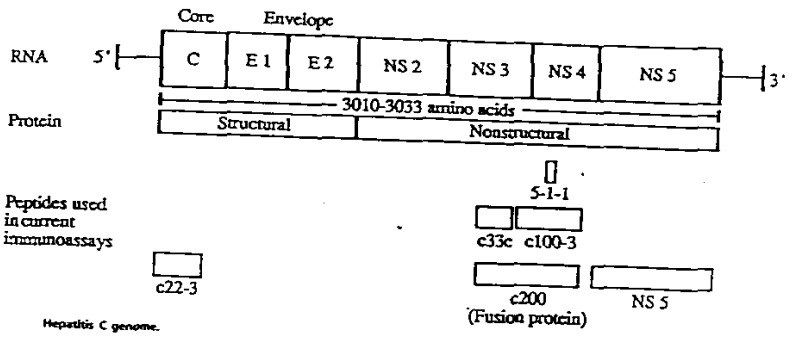


Figure A

Hepatitis C viruses (HCV) is a 50-60-nm diameter single stranded RNA virus that contains a lipid envelope. HCV RNA is a positively – stranded without poly-adenylation, HCV is considered a third genera to the Flairivirus family.

This genome is approximately 9.5 kb with a 5` end that is relatively invariant and not translated into proteins.

The rest of the molecule is translated into a polyprotein almost 3000 aa long. By series of endopeptidase cleavage, at least 10 proteins are created including a 17-20 Kda capsid (core) protein. Two virion envelope proteins (E1 protein is 33 Kda and E2 is 70 Kda)

that form a heterodimer complex, and no less than seven non structural (NS) proteins are though to have membrane binding and protease function. NS3 protein serves both serine protease functions that cleaves the NS4and the NS5 regions and helicase function is essential in unwinding the RNA molecule during replication and translation. The NS4 region is cleaved into two or three proteins, one of which complexes wih the NS3 protein to create endopeptidase activity. The carboxy half of the NS5 protein is a RNA dependant RNA polymerase needed for viral replication. The currently immunoassays measure antibodies to the capsid (C22) and NS3 (C33c) regions and to the C100 –3 region that spans part of both the NS3 and NS4 region (Nishioka et al 1994).

Very little is understood about the replicative cycle and host range of HCV. The virus is thought to replicate by creating RNA complementary to the HCV genome. The negative strand serves as a template for production of HCV genomes and mRNA for protein synthesis (Eckels et al 1996).

Significant heterogeneity exists among different HCV isolates, (Weiner et al 1991). The most highly

conserved sequence is the HCV C region followed by relatively well conserved NS3, NS 4, and NS 5 which are relatively well conserved.

E1, E2, NS1, and NS 2 show substantial variation among different groups. There is also variation among isolates within each group as well as in serial isolates from the same infected host. (Weiner et al 1991,& Murukawa et al 1992).

Pathological process of chronic hepatitis C

The basic morphologic changes in HCV infection are the same as in chronic hepatitis B and D, including chronic inflammation, fibrosis of portal tracts, and varying degrees of hepatocyte necrosis. (Kobayashi et al 1993).

There have been reports that HCV has characteristic, although not pathogenomic, histological features which are not commonly observed in chronic hepatitis B and D, or auto immune hepatitis (Gerber 1994).

In the hepatic lobules, micro or macro vesicular steatosis, infiltration of sinusoids by lymphocytes, activation of macrophages and other sinusoidal lining cells eosinophilic degeneration of hepatocytes with progression to granular acidophilic bodies (apoptosis), or extensive hydropic swelling of hepatocytes are often seen, (Gerber 1995).

The portal tracts contain an accumulation of lymphocytes, sometimes in follicular form with formation of germinal centers and alterations of bile ducts. Small or medium sized bile ducts, often located at the periphery of lymphoid aggregates, are infiltrated by lymphocytes. The bile duct epithelium exhibits focal degeneration and necrosis, vaculation or eosnophilia of cytoplasm, and piling up of bile duct epithelial cells with over lapping nuclei or loss of polarity. Proliferation of bile basement membrane of the damaged bile ducts is evident on diastase digested periodic acid schiff staining, (Gerber 1995).

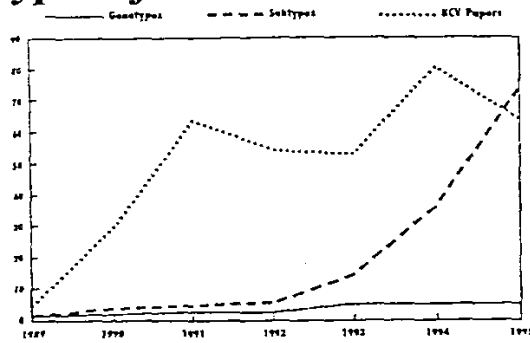
In three histologic studies of a total of 124 patients, bile duct damage was seen in 60% lymphoid aggregates, follicles, or both appeared in 75% and steatosis was

observed in 52% of patients, (Bach et al 1992, Scheuer et al 1992,& Gerber 1994).

A combination of two of these three characteristic alterations is seen over half of the patients with chronic hepatitis C and is very helpful in the histologic diagnosis of the disease, but must be confirmed by specific serologic tests for the presence of HCV (Gerber 1995).

Schmid et al (1982) reported that acute NANB hepatitis was more likely to progress to sever chronic disease when the first biopsy specimen showed marked portal lymphocytic infiltration. This study suggested that the intensity of the initial pathological lesions predict long term outcome of this disease.

Genotypes of HCV



Discovery of HCV genotypes. The number of known HCV types (solid line), subtypes (dashed line), and HCV papers (papers published with "hepatitis C" in the title or abstract, figures divided by 10, dotted line) are plotted against year.

Fig B

1-Classification (genotypes, types, groups).

The extent of virus variation has been summarized by classifying HCV into six genotypes, 1,2,3,4,5,6. (Okamoto et al 1992). Chan et al 1992 grouped HCV isolates into three major types based on phylogenetic bases and Simmonds et al 1993 divided each type into two subtypes a, b.(i.e. 1a , 1b 2a , 2b , 3a, and 3b).

In another classification by Houghton et al 1991, group I corresponds to genotype 1 (1a), group II to genotype 2 (1b), group III includes genotype 3 (2a) and genotype 4 (2b); their group IV encompasses genotype 4

(3a) , and group 5 includes a group variants reported exclusively from south Africa.

Four of the six genotypes contain subtypes (a,b,c) (Dusheiko et al 1994). The six genotypes of HCV differ in nucleotide sequence by 30% over the complete virus genome. These are further divided into numerous more closely related virus subtypes that differ by more than 20% in sequence. Within each subtype sequence vary by no more than 10%. Over the last few years, the number of known HCV genotypes has increased almost exponentially (fig B). So that the six distinct HCV types now comprise at least 74 reported subtypes (Smith et al 1995).

Geographical Distribution

Geographical differences in the distribution of virus genotypes are now well documented and presumably reflect the epidemiological history of the virus. Virus genotypes 1,2,and 3 account for the majority of HCV infections in Western Europe and North America, genotype 4 has been found with great frequency only in Central and North Africa and the Middle East, and