HEPATITIS C VIRUS GENOTYPES AND RISK OF HEPATOCELLULAR CARCINOMA IN CIRRHOSIS

Essay

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Presented By

Ahmed Osama Reyad

M.B.,B.CH. (Ain Shams University, 2006)

Supervised By

Prof. Dr. Mahmoud Abd Elmegeid Osman

Professor of Internal Medicine
Ain Shams University

Prof. Dr. Mohamed Abd Elmabood Mohamed

Professor of Internal Medicine
Ain Shams University

Dr. Maha Mohsen Kamal Eldin

Lecturer of Internal Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
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Ahmed Osama

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbrev.	Meaning
AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANC	Absolute neutrophil count.
Anti-LC1	Anti-liver cytosol antibodies type 1
anti-LKM1	Anti-liver and kidney microsomal antibodies type 1
APRI	Aspartate aminotransferase (AST) to platelet ratio index
ASMA	Anti-smooth muscle antibodies
AST	Aspartate aminotransferase
BT	Bacterial translocation
CAH	Chronic active hepatitis
CDC	Centers for disease control
CEA	Carcinoembryonic antigen
CHC	Chronic hepatitis C
CLD	Chronic liver disease
CPH	Chronic persistent hepatitis
CT	Computed tomography
CTA	Computed tomography arteriography
CTAP	Computed tomography arterioportography
CTP	The Child-Turcotte-Pugh
DC	Dendritic cell
DNA	Deoxyribonucleic acid
EIA	Enzyme immunoassays

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Meaning
ELISA	Enzyme linked immunosorbent assays
FHB	Fulminant hepatitis
GFR	Glomerular Filtration Rate
GGT	Gamma glutamyl transferase
GGT	Gamma glutamyl transferase
HAI	Histological activity index
HALT-C	Hepatitis c long treatment against cirrhosis
HBsAg	Hepatitis B surface antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis delta virus
HGV	Hepatitis G virus
HIV	Human immunodeficiency virus
IFN	Interferon
IFN	Interferon
IGFBP-3	Insulin like growth factor binding protein-3
IGF-I	Insulin like growth actor-I
IGF-II	Insulin like growth factor-II
IV	Intravenous
IVC	Inferiro vena cava
LDH	Lactate dehydrogenase
MELD	Model for end stage liver disease.

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Meaning
MRI	Magnetic resonant imaging
NANBH	Non-A, non-B hepatitis
NIH	National Institutes of Health
NS3	The non-structural protein
OLT	Orthotopic liver transplantation
PBC	Primary biliary cirrhosis
PCR	Polymerase-chain-reaction
PCT	Porphyria cutanea tarda
PSC	Primary sclerosing cholangitis.
RAS	Renin Angiotensin system
RFA	Radiofreuqency ablation
RIVKA	Prothrombin induce by vitamin K absence or antagonism
RNA	Ribonuclic acid
SBP	Spontaneous bacterial peritonitis
SEER	Surveillance epidemiology and end results
STD	Sexually transmitted disease
SVR	Sustained virologic response
TMA	Transcription mediated amplification
U/L	Unit/Liter
U/S	Ultrasonography
WHO	World Health Organization

INTRODUCTION

HCV virus identified in 1989 when the genome of the virus was cloned and designated as the hepatitis C virus (HCV), where six major genotypes of HCV have been defined and More than 50 subtypes have also been described; the most common subtypes are 1a, 1b, 2a, and 2b *(Steinmann et al., 2004).*

The evolution of genotypes has been influenced by several factors, including: immune selection, infection patterns, replication efficiency and population migration, which led to a distinct geographic distribution of HCV genotypes *(Kaplan et al., 2003).*

Genotype 1 is most common (60 to 70 percent of isolates) in the United States and Europe, genotypes 2 and 3 are less common in these areas, while genotypes 4, 5, and 6 are rare, genotype 3 is most common in India, the Far East, and Australia, genotype 4 is most common in Africa and the Middle East especially Egypt, genotype 5 is most common in South Africa, genotype 6 is most common in Hong Kong, Vietnam and Australia *(David et al., 2005).*

Acute HCV typically leads to chronic infection in 60 to 80 percent of cases. Approximately 20 to 30 percent of chronically infected individuals develop cirrhosis over a 20 to 30 year period of time *(Chopra, 2007).*

HCV accounts for approximately one-third of HCC cases in the United States. Estimates of the risk of developing HCC once cirrhosis has developed have varied from 0 to 3 percent per year in various reports, there is, however, suggestive experimental evidence that HCV infection itself can promote the development of HCC. Accordingly the HCV genotypes must have an important role in the development of HCC in cirrhosed patients *(Jason et al., 2003).*

In this essay, we will review hepatitis C virus genotypes, hepatocellular carcinoma in details, and the relation between both of them.

In Japan, the mean interval between infection and development of HCC is 30 years. A study from the US shows a long time lag (mean 28 years, range 8-42) between transfusion-associated hepatitis and development of HCC. There is conflicting information on the relationship between HCV genotype and progression to HCC in longitudinal studies. It is suggested by some authors that genotype 1b (most prevalent in Europe and Japan) is associated with a higher incidence of HCC than infection with other genotypes *(Kiyosawa et al., 1998).*

Finally, this essay will provide the latest guidelines in the management of HCV and HCC.

AIM OF THE WORK

In this essay, we aim to highlight the relation between hepatitis C virus (HCV) virus genotypes and incidence of hepatocellular carcinoma (HCC) in patients with liver cirrhosis.

HEPATITIS C VIRUS (HCV)

Introduction

Background: The World Health Organization (WHO) estimates 170 million individuals world-wide are infected with hepatitis C virus (HCV). However, the prevalence of HCV infection varies throughout the world. For example, ***Frank et al. (2000)*** reported that Egypt has the highest number of reported infections, largely attributed to the use of contaminated parenteral antischistosomal therapy. This has led to a mean prevalence of HCV antibodies in persons in Egypt of 22%. According to the US Center for Disease Control and Prevention, 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 and, according to a report

by *Davis et al. (2003)*. The most common indication for orthotopic liver transplantation (OLT) in the United States *(Sandeep and Vinod, 2006)*.

HEPATITIS C VIRUS

HCV Viral Components showing the envelope 1 and 2 protein complex with its nucleocapsid protein and the RNA genome (Fig.1).

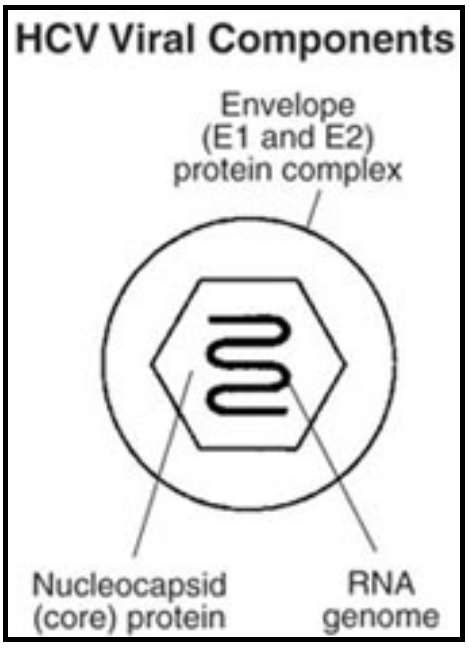

Figure (1): HCV viral components *(Nieves et al., 2006).*

HCV is a small (40 to 60 nanometers in diameter), enveloped, single-stranded RNA virus of the family Flaviviridae and genus hepacivirus. Because the virus mutates rapidly, changes in the envelope proteins may help it evade the immune system. There are at least six major genotypes and more than 50 subtypes of HCV. The

different genotypes have different geographic distributions. Genotypes 1a and 1b are the most common in the United States (about 75 percent of cases). Genotypes 2 and 3 are present in only 10 to 20 percent of patients. There is little difference in the severity of disease or outcome of patients infected with different genotypes. However, patients with genotypes 2 and 3 are more likely to respond to interferon treatment.

A high prevalence of HCV-4 (10.2%) was found. This genotype is found more commonly in Egypt, Central Africa and the Middle East *(Nieves et al., 2006)*.

HEPATITIS C VIRUS VIROLOGY

Hepatitis C virus and its genotypes

HCV is a member of the Flaviviridae family, genus Hepacivirus. Six HCV genotypes and a large number of subtypes (1a, 1b, 1c, *etc.*) have been identified. So far the only natural host for HCV is man. All HCV genotypes have a common ancestor virus. However, HCV genotypes 1, 2, and 4 emerged and diversified in Central and Western Africa, genotype 5 in South Africa, and genotypes 3 and 6 in China, South-East Asia and the Indian subcontinent. The rest of the world, in particular industrialized areas, harbor a small number of HCV subtypes that could widely spread because they met an efficient route of

transmission, such as blood transfusion or the intravenous use of drugs. They include genotypes 1a, 1b, 2a, 2b, 2c, 3a, 4a and 5a *(Simmonds et al., 2005)*.

HCV virion and lifecycle

The HCV virion is made of a single-stranded positive RNA genome, contained into an icosahedral capsid, itself enveloped by a lipid bilayer within which two different glycoproteins are anchored *(Penin et al., 2004).* The genome contains three distinct regions: (1) a short 5′ non-coding region that contains two domains, a stem-loop structure involved in positive-strand priming during HCV replication and the internal ribosome entry site (IRES), the RNA structure responsible for attachment of the ribosome and polyprotein translation; (2) a long, unique open reading frame (ORF) of more than 9000 nucleotides which is translated into a precursor polyprotein, secondarily cleaved to give birth to the structural proteins (the capsid protein C and the two envelope glycoproteins E1 and E2) and to the non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B). The functions of the non-structural proteins have been elucidated by a large number of studies and by analogy to related viruses; only NS4B and NS5A have no well-defined functions to date; (3) a short 3′ non-coding region principally involved in minus-strand priming during