INTRADIALYTIC TRANSMISSION OF HEPATITIS C VIRUS INFECTION

THESIS
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By
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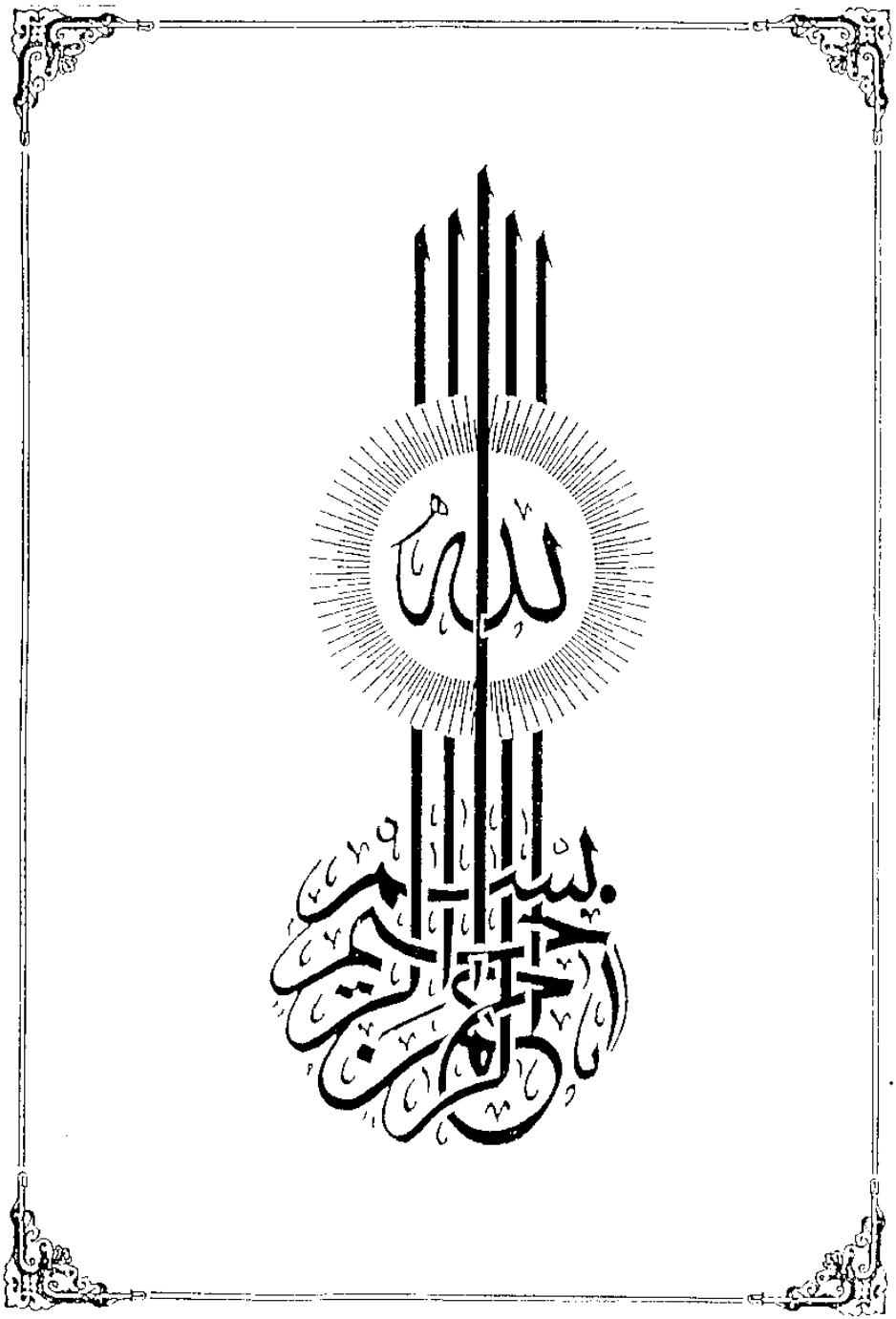

List of abbreviations and symbols:

α-IFN:	Alpha interferon
ALT:	Alanine aminotransferase
AST:	Aspartate aminotransferase
CAH:	Chronic persistent hepatitis
DNA:	Deoxyribonucleic acid
ELISA:	Enzyme linked immunosorbent assay.
GGT:	Gamma glutamyl transferase
gp:	Glycosylated protein
HAV:	Hepatitis A virus
HBcAg:	Hepatitis B core antigen
HBsAg:	Hepatitis B surface antigen
HBV:	Hepatitis B virus
HCV:	Hepatitis C virus
HEV:	Hepatitis E virus
HIV:	Human immunodeficiency virus
HS:	Highly significant
MHC:	Major histocompatibility complex.
MUTIW:	Million unit twicely per week
NANBH:	Non-A, non-B hepatitis
NK:	Natural killer
NS:	Non-significant
NS:	Non structural (proteins)
PBC:	Primary biliary cirrhosis
PCR:	Polymerase chain reaction
RIBA:	Recombinant immunoblotting assay.
RNA:	Ribonucleic acid
S:	Significant
SOD:	Superoxide dismutase
ULN:	Above normal limit

Content:

INTRODUCTION
AND
AIM OF THE WORK

Introduction:

Patients undergoing chronic hemodialysis have an increased risk of exposure to viral hepatitis. The risk of hepatitis B infection for such patients was recognized many years ago. Problems due to hepatitis B have been reduced by use of immunization, periodic testing, isolation of infected patients, and by improved disinfectant procedures ***(Alter et al., 1986)***. Viral hepatitis continues to be a serious problem in dialysis units where hepatitis C is thought to be the current major cause of hepatitis in these units ***(Zeldis et al., 1990)***.

The high positivity rate in those patients who give no history of blood transfusion implies that there must be other undetermined modes of transmission of this infection in hemodialysis units ***(Soblipkoter et al., 1990)***.

Aim of the work:

The aim of this study is:

1. To review some procedures in dialysis units to investigate their possible role in HCV transmission.
2. To see if patients with HCV have to be isolated and whether use isolated machines or not.

REVIEW OF LITERATURE

VIRAL HEPATITIS

Definition:

The term hepatitis is applied to a broad category of clinicopathologic conditions that result from the damage produced by viral, toxic, pharmacologic, or immune-mediated attack up on the liver. Clinically, the liver may be enlarged and tender with or without jaundice, and laboratory evidence of hepatocellular damage is invariably found in the form of elevated transaminase levels. Independent of the cause, the clinical course of hepatitis may range from mild or inapparent to a dramatic illness with severe hepatocellular dysfunction, marked jaundice, impairment of coagulation, and disturbance of neurologic function ***(Ockner, 1992)***.

Classification of viral hepatitis *(Sherlock and Dooly, 1993):*

I. Hepatotropic viral hepatitis:

A. Hepatitis A virus (HAV):

It is 27 nm RNA virus that is classified as an enterovirus within the picornaviridae family ***(Feinstone et al., 1973)***. Replication of HAV appears to be limited to the liver and only one serotype of HAV has been recognized in humans ***(Deinstag, 1991)***. The main route of transmission is fecal-oral, transmission

between index cases and house-hold contacts and via intimate exposure are the predominant modes of spread. It does not become chronic and no chronic virus carriers exist *(Deinstag, 1991)*.

B. Hepatitis B virus (HBV):

The human hepatitis B virus was the first recognized hepadinivirus and has been classified as hepadinivirus type 1. It is a 42 nm DNA virus, the virion is composed of viral surface, core and "e" nucleocapsid antigen, the entire genome of HBV has been cloned. Replication of HBV is largely confined to the liver, but extrahepatic replication at several sites has been shown *(Deinstag, 1991)*.

Variations of HBV have been recognized, the most important variation is an HBV mutant that has been found primarily in Mediterranean and Asian populations, it has a single-base substitution in the precore gene that prevents translation of HBeAg. Patients who have this mutant strain may have active viral replication without HBeAg. This strain is associated with fulminant hepatitis and severe exacerbations of chronic hepatitis B *(Keeffe and Benver, 1993)*.

Hepatitis B infection is endemic with high prevalence in Africa, Eastern Europe, the Mediterranean area, Asia and area of south America. In these regions, greater than 50% of the populations have evidence of prior hepatitis B infection *(Kuo et al., 1989)*.

Hepatitis B infection is transmitted mainly parenterally or through close personal contact. It became chronic in a certain number of cases and can lead to cirrhosis and/or primary hepatocellular carcinoma ***(Shafritz and Kew, 1981)***.

C. Hepatitis C virus HCV (parenterally transmitted NANBH):

It is a lipid enveloped 50-60nm single stranded RNA virus of approximately 10,000 nucleotides that may account for as many as 90% of post transfusion hepatitis where all blood donations are screened for hepatitis B surface antigen ***(Zuckerman, 1989)***. There are at least 8 genotypes of HCV ***(Atsuhiko et al., 1992)***.

D. Hepatitis Delta virus (HDV):

It is a defective RNA-containing virus that requires the helper function of the hepadiniviruses to replicate. HDV hepatitis may occur as either a coinfection with HBV (the two agents inoculated simultaneously) or as a superinfection in the setting of established chronic HBV infection ***(Bomino et al., 1987)***.

E. Hepatitis E virus (HEV) (Enteric transmitted NANBH):

It is a small RNA virus that causes epidemic or enterically transmitted acute NANB hepatitis.

Hepatitis E occurs predominantly in the Indian subcontinent, South central Asia, and the Middle East, but is spreading to the North and West Africa. Transmission is associated with contaminated food or water (poor sanitation). It does not lead to chronic hepatitis or carrier state ***(Purcell, 1990)***.

II. Viscero-tropic viral hepatitis:

The liver is involved as a part of infection of many viruses, The Epstein-Bar virus, cytomegalovirus, yellow fever virus, the hemorrhagic fever viruses such as Lassa, Marburg, and Rift vally fever viruses, but the term viral hepatitis is generally restricted to the hepatotropic viruses only ***(Zuckerman, 1989)***.

HEPATITIS C VIRUS (HCV)

The availability of specific serological markers to diagnose hepatitis virus A and B infections did not resolve the diagnostic problem of acute and chronic hepatitis, particularly that developing after blood transfusions. A third major category has always been suspected but, in the absence of a diagnostic test, has been designated non-A, non-B virus hepatitis. The third type has now been identified and called hepatitis C virus (HCV) ***(Sherlock et al., 1993)***.

Introduction and discovery:

The existence of hepatitis agents besides HAV and HBV was suggested by the following observations ***(Dienstag, 1983)***:

1. Occurrence of more than two distinct attacks of acute hepatitis in drug addicts and hemophiliacs.

2. The unimodal pattern of incubation period of transfusion associated hepatitis intermediate in time between the expected modes for the incubation periods of HAV and HBV infection.

3. Failure to detect HBsAg in almost all cases of post transfusion hepatitis and the limited impact of screening donor blood for HbsAg of the frequency of such

hepatitis in blood recipients.

4. Failure of anti-HBs in blood recipients to protect the recipients from hepatitis after transfusion.

5. Reduction of frequency of not only HBV but also non-B hepatitis after transfusion as a result of elimination of commercially obtained donor blood.

It was called non-A, non-B hepatitis. Non-A, non-B hepatitis was diagnosed by exclusion in patients with acute hepatitis but without serologic evidence of hepatitis A or B infection ***(Weisiger, 1990)***.

In ***1989, Houghten and co-workers*** in chronic corporation in California announced the identification and cloning of a viral genome that appeared to be related to the agent of classic parentrally transmitted NANBH. By using the molecular biologic techniques, they developed a radioimmunoassay for antibody to this agent, which they have called hepatitis C virus.

Morphology and ultrastructure of HCV:

The virus is an approximately 10,000 nucleotide, linear, and single-stranded RNA virus of the flavivirus family ***(Alter and Hoofnagle, 1989)***. It has a diameter of 30-60 nm, a lipid envelope and an RNA genome with a single open reading frame ***(Dolan et al., 1991)***.

Recently, pestiviruses are classified within the flaviviridae family as a separate genus. Accordingly, HCV may be classified as a third genus within this family based on the greater sequence similarity observed with pestiviriuses in the 5'-RNA and helical regions ***(Miller and Purcell, 1990)***. Morever, in abundance of N-glycosylation sites within the putative N-terminal glycoprotein region, HCV appears to be a closer relative to pestiviruses than the flaviviruses ***(Choo et al., 1989)***.

Now, it is settled that the viral genomic RNA is a single stranded RNA with a single long reading frame. The gene product is a viral polyprotein precursor of 3011 amino acids, which undergoes proteolytic post-transitional cleavage to yield structural (core and envelope) and non-structural (protease, helicases, RNA dependant RNA polymerase) proteins. To some extent knowledge of the nature of HCV proteins is based on predictions made from nucleotide sequences, but an increasing number of proteins are being recombinantly expressed ***(Pounder, 1992)***.

The structural proteins are derived from the 5'-third of the genome ***(Okamoto et al., 1990)*** and the non-structural proteins from the 3' (NS 1 to NS 5) regions. The 5' end begins with a non-coding region of at least 341 bases. This sequence of HCV appears to be highly conserved, with a high degree of sequence homology among most isolates so far sequenced ***(Choo et al., 1991)***. Two glycosylated proteins gp-35 and gp-70 may be coded by the E_1 and E_2 regions of the genome,