The Reflection of Hepatitis B Virus Genotyping on Histopathological Pattern and Clinical Presentation Among Egyptian Patients with Chronic Hepatitis B Infection

Thesis

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List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
BP	Barber Protein
ºC	Degree Centigrade
CCP	Critical control point
CAST	Council for Agriculture Science and Technology
CDC	Centers for Disease Control & Prevention
CFU	Colony Forming Unit
CMIR	Cell Mediated Immune Response
CT	Cholera Toxin
E coli	Escheretia coli
EIA	Enzyme Immuno-Assay
ELISA	Enzyme Linked Immune Sorbent Assay
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
GIT	Gastro-Intestinal Tract
HACCP	Hazard analysis critical control point
Ig A	Immunoglobulin A
Ig G	Immunoglobulin G
Ig M	Immunoglobulin M
LIS	Lysine Iron Sugar
LMI	Lymphocyte Migration Inhibition
LPS	Lipopolysaccharide
LT	Heat Labile enterotoxin
2-ME	2-mercaptoethanol
MIO	Motility Indole Ornithine
NTS	Non Typhoidal Salmonella
OMPS	Outer membrane proteins
OR	Odds Ratio
S Ig A	Salmonella Immunoglobulin A
TAB	typhi, paratyphi A & paratyphi B
TSI	Triple Sugar Iron agar
UK	United Kingdom
Vi	Virulence
VICPS	Vi Capsular Polysaccharide Vaccine
WHO	World Health Organization
WTA	World Trade Organization

List of Abbreviations

ADCC	Antibody Mediated Cellular Cytotoxicity
ADV	Adefovir Dipivoxil
AHF	Acute hepatic Failure
ALT	Alanine Aminotransferase
AST	Aspartate Amino transferase
AVH	Acute Viral Hepatitis
BCP	Basal Core promoter Mutations
cccDNA	Covalantly Closed Circular DNA
CHB	Chronic Hepatitis B
CTL	Cytotoxic T Lymphocytes
DNA	Deoxy Ribonucliec Acid
DNA Pol	DNA Polymerase
EASL	European Association for the Study of the Liver
ELISA	Enzym Linked Immunosorbent Assays
HBcAb	Hepatitis B core Antibody
HBcAb Igm	Hepatitis B antibody Immunoglobulin M
HBeAg,Ab	Hepatitis B e antigen and antibody
HBIG	Hepatitis B Immunoglobulines
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCW	Health Care workers
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigen
IFN Alpha	Interferon Alpha
IVUD	Intravenous drug users
Line probe Assay	Line Probe Assay
NHTMRI	National Hepatol. Trop. Med. Research Institute
NIH	National Instiute of Health
NK	Natural Killer Cells
OLT	Orthotopic Liver Transplantation
PCR	Polymerase Chain Reaction
Peg IFN Alpha	Pegylated Interferon Alpha
RFLP	Restriction Fragment Length Polymorphism
TNF	Tumour Necrosis Factor
WHO	World Health Organization

Introduction

Since its first description more than 30 years ago, infection with hepatitis B virus (HBV) has been recognized as a major cause of chronic liver disease, liver cirrhosis and hepatocellular carcinoma world wide, with peak prevalence in the Far East and African regions***.(Zoulim. 2004)***

Despite the development and use of highly protective HBV vaccines in the last two decades, still the WHO estimates that over 2 billions of the world population have been infected with HBV and between 350- 400 million individuals are currently chronic carriers of the virus, with at least 1 million deaths occurring annually as a direct consequence of the infection***.(Maddery et al ., 2001***)

HBV belongs to the hepadnaviridae family, a tiny extraordinary DNA virus that posses the smallest genome of all human viruses (***Wang et al., 2002)***

Mode of transmission of the disease is mainly parenteral through contaminated unscreened blood transfusion and often by intimate sexual contact ***(Mc Mahon et al., 2001***). Passage of the virus from an infected mother ,the so called vertical transmission, also plays a role in wide-spreading HBV. The chance increases in acute rather than chronic carrier-mothers. (***Chang, 2000***). Dialysis machines, dental procedures, and un-sterile surgical instruments are important routes of HBV transmission.(***Wang et al., 2002***).

Clinically the disease could present as either acute or chronic hepatitis. Acute hepatitis B usually presents by an increase in ALT and AST levels and is defined by detectable HBsAg, HBcAb (Igm)or both.(***Decker.1998***). Duration of the disease is variable, and improvement

could be monitored by seroconversion of HBeAg to HBeAb and complete cure by seroconversion of HBsAg to HBsAb (***Furusyo et al., 1999).*** Complete clinical recovery occurs in 90 – 95 % of the horizontally transmitted cases, unlike vertically transmitted ones that retain the infection and become chronic in 70 -80 % of cases (***Furusyo et al., 1999).***

Chronic infection is characterized by the persistence of serum HBsAg and HBcAb. HBV DNA may remain detectable in serum or liver using polymerase chain reaction (PCR) based tests following the disappearance of HBsAg in serum , the clinical significance of the persistence of very low levels of HBV DNA is still controversial ***(Brechot et al., 2001)***.

Approximately 10% of adults and about 90% of neonates contracting HBV will not clear the HBsAg from serum within 6 months and become chronic carriers ***(McMahon et al., 2001)*** they mostly have normal liver profile and on the level of liver biopsy may present by non specific minimal abnormalities through to chronic hepatitis and cirrhosis ***(Thursz, 2001)***.

However the clinical course that HBV leads is quite variable, from completely asymptomatic disease through to mild constitutional manifestations and, finally complications as liver cell failure, ascites, esophageal varices, encephalopathy and / or hepatocellular carcinoma ***(Thakur et al., 2002)***, which suggests the presence of certain viral factors behind those variations.

The recent application of molecular technology for gene amplification and sequencing to the study of these viruses, especially those that cause persistent infections, has unraveled their significant heterogenicity and their potential for rapid evolution ***(Esteban, 1999)***.

Based on an 8% nucleotide divergence of HBV genome, HBV is classified into seven genotypes:A to G which tend to be distributed geographically. ***(Norder et al., 1992) and(Stuyver et al., 2000).*** An eighth genotype, designated H ,was reported from Central America ***(Arauz-Ruiz et al., 2002).*** Four fundamental antigenic subtypes and five other subtypes are antigenically defined, based on amino acid substitutions in the 5 protein ***(Kato et al., 2001)***

The clinicopathological outcome of the disease was found to be closely related to the subtype backbone ***(Chan et al., 2002)a***.

Genotype A was found to be associated with less severe liver disease than genotype D. Moreover, genotype D was also more prevalent than genotype A among patients with Child-Pugh B or C cirrhosis. ***(Thakur et al., 2002)***.

. In addition, genotype B was found to be associated with severe icteric flares ***(Chan et al., 2002)b***.

Nevertheless, HBV genotypes may be related to the development of HCC ***(Kao et al., 2000)b*** and may also affect the response of patients to lamuvidine therapy either in chronic HBV cases or after liver transplantation ***(Ben Ari et al., 2003)***.