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
°C    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
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ADCC</td>
<td>Antibody Mediated Cellular Cytotoxicity</td>
</tr>
<tr>
<td>ADV</td>
<td>Adefovir Dipivoxil</td>
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<tr>
<td>AHF</td>
<td>Acute hepatic Failure</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Amino transferase</td>
</tr>
<tr>
<td>AVH</td>
<td>Acute Viral Hepatitis</td>
</tr>
<tr>
<td>BCP</td>
<td>Basal Core promoter Mutations</td>
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<tr>
<td>cccDNA</td>
<td>Covalently Closed Circular DNA</td>
</tr>
<tr>
<td>CHB</td>
<td>Chronic Hepatitis B</td>
</tr>
<tr>
<td>CTL</td>
<td>Cytotoxic T Lymphocytes</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxy Ribonucleic Acid</td>
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<tr>
<td>DNA Pol</td>
<td>DNA Polymerase</td>
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<tr>
<td>EASL</td>
<td>European Association for the Study of the Liver</td>
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<tr>
<td>ELISA</td>
<td>Enzym Linked Immunosorbent Assays</td>
</tr>
<tr>
<td>HBeAg,Ab</td>
<td>Hepatitis B e antigen and antibody</td>
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<tr>
<td>HBeAg</td>
<td>Hepatitis B surface Antigen</td>
</tr>
<tr>
<td>HBCAb</td>
<td>Hepatitis B core Antibody</td>
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<tr>
<td>HBCAb Igm</td>
<td>Hepatitis B antibody Immunoglobulin M</td>
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<tr>
<td>HBIG</td>
<td>Hepatitis B Immunoglobulines</td>
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<tr>
<td>HBsAb</td>
<td>Hepatitis B surface Antibody</td>
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<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
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<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
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<td>Hepatitis C virus</td>
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<td>HCW</td>
<td>Health Care workers</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HLA</td>
<td>Human Leucocyte Antigen</td>
</tr>
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<td>IFN Alpha</td>
<td>Interferon Alpha</td>
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<tr>
<td>IVUD</td>
<td>Intravenous drug users</td>
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<tr>
<td>Line probe Assay</td>
<td>Line Probe Assay</td>
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<tr>
<td>NIH</td>
<td>National Institute of Health</td>
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<tr>
<td>NK</td>
<td>Natural Killer Cells</td>
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<tr>
<td>OLT</td>
<td>Orthotopic Liver Transplantation</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>Peg IFN Alpha</td>
<td>Pegylated Interferon Alpha</td>
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<tr>
<td>RFLP</td>
<td>Restriction Fragment Length Polymorphism</td>
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<tr>
<td>TNF</td>
<td>Tumour Necrosis Factor</td>
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<td>WHO</td>
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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 widespread 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
Introduction & Aim of the Work

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 HBeAb. 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 heterogeneity 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).