Relation Between Occult Hepatitis B and Hepatocellular Carcinoma

Thesis

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By

Akram Abd El-Aziz Yousef

(M.B.B.ch)

Under Supervision Of

Prof. Dr. Amr Abd El-Kader Fatin

Professor of Internal Medicine

Gastroenterology and Hepatology

Faculty of Medicine - Ain Shams University

Dr. Hosam Eldin Abd El-Aziz Mahmoud

Assistant Professor of Gastroenterology and Hepatology

Faculty of Medicine - Ain Shams University

Dr. Amany Talat Kamal

Assistant Professor of Gastroenterology and Hepatology

Faculty of Medicine - Ain Shams University

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List of Abbreviations

ALT:	Alanine transaminase
AST:	Aspartate transaminase
ccDNA:	Covalently closed circular deoxyribonucleic acid
CTL:	Cytotoxic T lymphocytes
DC:	Dendritic cells
HBV:	Hepatitis B virus
HBcAb:	Hepatitis B core antibody
HBcAg:	Hepatitis B core antigen
HBeAb:	Hepatitis Be antibody
HBeAg:	Hepatitis B surface antibody
HBsAg:	Hepatitis B surface antigen
HCV:	Hepatitis C virus
HCC:	Hepatocellular carcinoma
HIV:	Human immune deficiency virus
IFN:	Interferon
IL:	Interleukin
NASH:	Non alcoholic steatohepatitis
NK:	Natural killer
PCR:	Polymerase chain reaction
RNA:	Ribonucleic acid
TNF:	Tumor necrosis factor
U/S:	Ultrasonography
WHO:	World Health Organization

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Introduction

Hepatocellular carcinoma is the fifth commonest malignancy worldwide and one of the most challenging to treat *(Toh Han Chong, ٢٠٠٤)*.

HBV is considered to be the main causative factor of liver cancer, possibly accounting for ٦٠% of cases worldwide and ٧٠ % of cases in endemic areas *(Qin Su et al., ٢٠٠٥)*.

The envelope protein of HBV, hepatitis B surface antigen (HBsAg), is the main marker for ongoing HBV infection *(Damien Jeantet et al., ٢٠٠٢)*.

Occult hepatitis B virus (HBV) infection is generally defined as detection of HBV- DNA in the serum or liver tissue of patient who test negative for hepatitis B surface antigen (HBsAg) *(Jorge A. Marreroa et al., ٢٠٠٤)*.

Lack of HBsAg may be due to rearrangements in HBV genome that interfere with gene expression or lead to Production of an antigenically modified S protein *(Irene Cacciola et al., ١٩٩٩)*.

According to a study published in cancer journal, presence of occult hepatitis B infection increases the risk of liver cancer in patients with chronic hepatitis *(Squadrito G et al., ٢٠٠٦)*.

Aim of the Work

Detection of relation between occult hepatitis B and hepatocellular carcinoma in Egypt.

Hepatitis B Virus

Epidemiology of HBV

HBV worldwide:

Viral hepatitis with various forms of acute and chronic liver disease is with potential and ultimately fatal sequelae, causing a public health problem worldwide *(Poovorawan et al., ٢٠٠٢)*.

Hepatitis B is the most import-ant of several hepatitis viruses of man because of the number of cases of the disease and the frequent occurrence of persistent infection that may lead to cirrhosis and cancer of the liver *(Lee et al., ٢٠٠١)*. HBV infection is the most common cause of chronic liver disease worldwide *(Pramoolsinsup, ٢٠٠٢)*.

Roughly, one third of the world population has been infected with HBV *(Hilleman, ٢٠٠١)*.

Although hepatitis B is an ancient disease, most of the advances in our knowledge of its epidemiology, prevention, pathogenesis, natural history and treatment were made in the last ٣٠ years *(Lok, ٢٠٠٠)*.

HBV is the third most common disease after venereal diseases and chickenpox. It currently infects ٢ billion people in the world, of which ٣٥٠ million are chronic carriers. At least ١ million chronically infected individuals die each year due to HBV- related diseases, especially cirrhosis and liver cancer. The greatest concern about the diffusion of this virus is in endemic regions in central and southern Africa, South-East Asia and South America, where neonatal exposure results in high mortality rates *(Gumina et al., ٢٠٠١)*.

HBV in Egypt:

Hepatitis B is and will for some time be a major health problem in Egypt *(Attia, ١٩٩٨)*.

It is recommended to consolidate the Egyptian programme of infant hepatitis B vaccination, and to extend it to older children and high risk adult groups *(El-Sayed et al., ١٩٩٧)*.

The prevalence of HBsAg carriers in Egypt varies widely with: age, sex, community (urban or rural), schisto-somiasis and/or chronic liver disease, exposure to certain risk factors *(Sherif et al., ١٩٨٥)*.

Egypt was reported by *Andre,* ٢٠٠٠ to be an area of high prevalence for HBV however *Poynard,* ٢٠٠٢ reported it to be an In the early ٨٠s, carriage rate of ٣.٢٥% and ٣.٦%

were reported in Alexandria and Cairo by ***Mailoum and colleagues*** and ***Shoeb*** respectively and ***El-Razky et al.*** found that, among school children ٥-١٥ years from a rural village in Dakahlia, the exposure rate for HBV infection was ٢٢% with frequency of HBsAg of ٤% by counterimmune electrophoresis, ١٦% by reversed passive haemag-glutination and ١٨% by other tests .the frequency of HBsAb was ٤.٥%. A carriage rate of ٦.٧% was reported in two rural villages in the Nile Delta by HBsAg alone ***(Emain, ١٩٩٤)***.

In the mid ٨٠s; higher prevalence was reported as follows; ٨.٨% in Lower Egypt and ١١.٧% in Upper Egypt with more prevalence in young adults and in males man females in both communities by ***Sherif et al***.

The overall seroprevalence of HBV when HBsAg and/or HBcAb were assessed was found to increase progressively with age peaking in the ٤٠-٦٧ years old group at a rate of ٦٦% which is an extraordinarily high seroprevalence rate ***(Darmsh et al., ١٩٩٦)***. ***El-Sayed*** found it to be ٢٠.٧% collectively in all age groups in ١٩٩٦ and ١٩.٦% in ١٩٩٧ ***(El-Sayed)*** ١٩٩٦ and ***El-Sayed, ١٩٩٧)***. There is the impression that HB carriage rate is decreased from ١٠% ***(Sherif et al., ١٩٨٥)*** to ٣.٢% ***(Zakaria et al., ٢٠٠٠)***. In another study, HBV markers (presence of either anti-HBc and/or TIBsAg) were found to be prevalent in ٢٤% of the

villagers in the northern Egyptian Nile Data *(Kamel et al., ١٩٩٤).*

As for acute HBV infection, the prevalence of HBV in Egypt is not yet adequately estimated after the use of hepatitis B vaccine *(Zakaria et al., ٢٠٠٠).* However *Orfi,* ٢٠٠٢ stated that the prevelance of acute HBV infection was ١٢% in children ٤-١٤ years old and ٥٠.٩% in adults > ١٤ years old. The most common age group infected by HBV ranged from ٢١-٣٠ years (٤٢.٤%). whereas the least infected age group was from ٤-٨ years (٣%). The most common risk factor for infection with acute HBV was accidental puncture in (٥٦.١%), followed by dental procedures in (٤٨.٥%) and surgical intervention in (٢٤.٢%).

Geographical distribution:

Asia and Africa have previously been classified as areas of high endemecity for HBV but in some countries highly effective vaccination programmes have shifted this pattern towards intermediate or low endemicity. Thus, China is now the only country in Asia where HBV end-emeicity is high. Countries with intermediate endemicity include India, Korea, Philippines, Taiwan and Thailand and those with low endemicity include Japan, Pakistan, Bangladesh, Singapore, Sri Lanka and Malaysia. Most countries in Africa have high HBV endemicity, with the exceptions of Tunisia and Moracco which have intermediate

endemicity. In the middle east, Bahrain, Iran Israel and Kuwait are areas of low endemicity. Cyprus, Iraq and Emirates have intermediate endemicity. Egypt, Jordan, Oman, Palestine, Yemen and Saudi Arabia have high endemicity *(Andre, ٢٠٠٠)*.

Mode of transmission:

Hepatitis B is most commonly acquired during adult life either by sexual transmission or through intravenous drug use. Healthcare workers also have a risk of acquiring hepatitis B through needle sticks and cuts sustained during the care of patients. Because healthcare instructions require that healthworkers receive vaccination for hepatitis B, this mode of transmission is becoming loss common. infection through blood product transfusion is now rare because blood banks screen blood donors for hepatitis B, hepatitis C and HIV *(Lee, ١٩٩٧)*.

Familial clustering of hepatitis B virus infection in related to perinatal transmission, and is the main cause of familial type hepatocellular carcinoma *(Chen et al., ٢٠٠٤)*.

The latent period from the onset of infection to the diagnosis of hepatocellular carcinoma may range from ٢٠-٥٠ years *(Tsukuma et al., ١٩٩٣)*.

Structure:

HBV is the prototype member of hepadnaviridae family, which also infects ducks, ground squirrels and woodchucks *(Jack, ٢٠٠٤)*.

HBV virions are double-shelled particles, ٤٠ to ٤٢ nm in diameter with an outer lipoprotein envelope that contains three related envelope glycoproteins (or surface antigens). Within the envelope is the viral nucleocapsid are core. The core contains the viral genome *(Don Ganem et al., ٢٠٠٤)*.

The hepatitis B virus genome is a relaxed circular, partially double stranded DNA of about ٣٢٠٠ base pairs. There are four partially overlapping open reading frames encoding the envelope (pre-S/S), core (pre core/core), polymerase (P) and X proteins (X) the pre S/S open reading frame encodes the large (L) middle (M) and small (S) surface glycorpoteins. The pre core/core open reading frame is translated into a precore polypeptide, which is modified into a soluble protein, HBeAg and the nucleocapsid protein, hepatitis B core antigen. The polymerase protein functions as a reverse transcriptase as well as a DNA polymerase. The X protein is a potent trans activator and may play a crucial part in hepatocarcinogenesis *(Seeger et al., ٢٠٠٠)*.