Laminin and Chromogranin A levels in viral hepatitis B

Thesis

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Abstract

Background/Aims: Chronic hepatitis B is a serious global health problem. Liver biopsy is currently recommended as the gold standard for the evaluation of the degree of fibrosis in patients with chronic hepatitis B. This procedure, however, is invasive and has potential complications. In this study, we attempted to validate the level of Laminin and chromogranin A as simple laboratory tests in patients with fibrosis in chronic hepatitis B. **Methods:** This study included 30 patients with chronic hepatitis B and 20 control subjects. Plasma samples were taken for Laminin and Chromogranin A assays. **Results:** There was a highly statistical significant difference between control and case groups as regards the mean values ± SD of Chromogranin A ($P < 0.0001$) and Laminin ($P < 0.0001$). Also there was a positive statistically significant correlation when comparing Laminin with AST ($P=.002$) and chromogranin A with AFP ($P =0.012$).

Conclusion: Plasma laminin and chromogranin A levels consider as predictors of liver fibrosis in chronic hepatitis B. Thus, these can be used as noninvasive parameters to monitor these patients.

Keywords: Hepatitis B, Laminin, Chromogranin A, Hepatic fibrosis

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List of Abbreviations

- HBV: Hepatitis B virus
- HBeAg: Hepatitis B e antigen
- DNA: Deoxyribonucleic acid
- HBcAg: Hepatitis B core antigen
- AUG codon: The start codon
- cccDNA: closed circular supercoiled DNA
- mRNA: messenger ribonucleic acid
- HBsAg: Hepatitis B surface antigen
- CHB: Chronic hepatitis B
- TLRs: Toll-like receptors
- IFN: Interferon
- CD4: Cluster of differentiation 4
- CD8+: Cluster of differentiation 8
- CTLs: Cytotoxic T lymphocytes
- ALT: Alanine aminotransferase
- IL: Interleukin
- Th1: T helper 1
- TNF-α: Tumor Necrosis Factor-α
- HSCs: Hepatic stellate cells
- EGF : Epidermal growth factor
- HCC: Hepatocellular carcinoma
- PCR: Polymerase Chain Reaction
- MAPK: The Mitogen-Activated Protein Kinase
- α-DG: α-Dystroglycan
- β-DG : β-Dystroglycan

- APP: Amyloid precursor protein
- SAP: Serum amyloid P
- MECs: Mammary epithelial cells
- CgA: Chromogranin A
- PC : Prohormone convertases
- ALB**:** Albumin
- PLT: Platelet Count
- ALP**:** Alkaline phosphatase
- SD : Standard deviation
- LN : Laminin
- AST: Aspartate transaminase
- ALT: Alanin transaminase
- GGT: Gamma glutamyl transferase
- AFP: Alpha fetoprotein
- ROC**:** Receiver Operating Characteristic
- r **:** pearson correlation

Introduction

Introduction

Hepatitis B virus (HBV) infection affects 350-400 million people all over the world ***(Dienstag, 2008).*** HBV is the most common cause of liver disease worldwide ***(Szomor et al., 2007)***. Patients can develop chronic hepatitis, hepatic cirrhosis or hepatocellular carcinoma in 25-40% of cases ***(Ganem et al., 2004).*** Thus, it is important to prevent the progression of early liver fibrosis to cirrhosis ***(Afdhal et al., 2004).***

Although liver biopsy is the gold standard for the assessment of fibrosis, it has several disadvantages, such as poor patient compliance, sampling error, limited usefulness for dynamic surveillance, and poor intra- and inter-observation concordance ***(Cadranel et al., 2000)*** several noninvasive tests have been developed for this purpose ***(Adams et al., 2005).***

Laminin-111 is one of the best characterized laminins and is composed of the α1, β1, and γ1 chains ***(Aumailley et al., 2005)***. Due to this relationship between laminin tissue deposition and advanced fibrosis, serum levels of laminin have been used by several authors as a non-invasive parameter to assess liver fibrosis in alcoholic patients as well as in those presenting with viral hepatitis and hemochromatosis ***(Lebensztejn et al., 2007)***.

Chromogranin A (CgA) is a well-studied member of the chromogranin/secretogranin family, present in secretory cells of the nervous, endocrine and immune systems (***Helle et al., 2007***) and it is present in serum of patients with neuroendocrine tumors such as carcinoids and endocrine pancreatic tumors***(Maria Chiara Zatelli et al., 2007).***

Aim of Work

The present study aimed at finding the utility of laminin and chromograinin A levels as predictive markers of liver fibrosis in patients with chronic hepatitis B.

Review of Literature

Viral hepatitis B

Hepatitis B virus (HBV) poses a great threat to humans, with serious consequences including liver cirrhosis, hepatocellular carcinoma and polyarteritis nodosa ***(Ganczak et al., 2009).*** This infection is prevalent in Asia, Africa, Southern Europe and Latin America ***(Hong et al., 2009).***

About one third of the world's population, more than 2 billion people, have been infected with the hepatitis B virus. This includes 350 million chronic carriers of the virus. Approximately 5-10% of infected adults and 80-90% of children become chronic carriers of HBV ***(Mendy et al., 2008).***

Hepatitis B virus infection may either be acute (self-limiting) or chronic (long-standing). Persons with self-limiting infection clear the infection spontaneously within weeks to months. Children are less likely than adults to clear the infection. More than 95% of people who become infected as adults or older children will stage a full recovery and develop protective immunity to the virus ***(Dienstag, 2008).***

The acute illness causes liver inflammation, vomiting, jaundice and rarely death. Chronic hepatitis B may eventually cause liver cirrhosis and liver cancer; a fatal disease with very poor response to current chemotherapy ***(Chang, 2007)***. The infection could be preventable by vaccination ***(Pungpapong et al., 2007)***.

Transmission

The HBV is present in high concentration in blood, serum, serous exudates, saliva, semen, vaginal fluid and most body fluids ***(Ray, 2003).***

In high endemic regions, such as Asia, Africa, Pacific Islands and the Arctic, early perinatal and horizontal infection in childhood is the main

route of HBV transmission. While in low endemic areas, such as Western countries, HBV is a predominant disease in adolescents and adults due to high risk sexual behaviors or drug injections ***(Mahtab et al., 2008).***

The vast majority of early perinatal or horizontal infections in childhood are the main route of HBV transmission in infants whose mothers are hepatitis B e antigen (HBeAg) positive, and over 90% of them will become chronic HBV carriers ***(Ying-Hui Shi and Chang-He Shi, 2009).***

The use of unsafe injections poses a particular public health problem in developing countries ***(Simonsen et al., 1999)***. Contaminated needles cause 8-16 million HBV infections each year, compared with 2.3-4.7 million hepatitis C virus infections, and 80,000-160,000 human immunodeficiency virus infections ***(Kane et al., 1999).***

HBV can be transmitted between family members within households, possibly by contact of non-intact skin or mucous membrane with secretions or saliva containing HBV ***(Victorian Government Health Information, 2009)***. However, at least 30% of reported hepatitis B among adults cannot be associated with an identifiable risk factor ***(Shapiro, 1993).***

Structure

Hepatitis B virus (HBV) is a member of the Hepadnavirus family ***(Lai et al., 1991)***. The virus particle, virion, consists of an outer lipid envelope and an icosahedral nucleocapsid core composed of protein. The nucleocapsid encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity ***(Locarnini, 2004).***

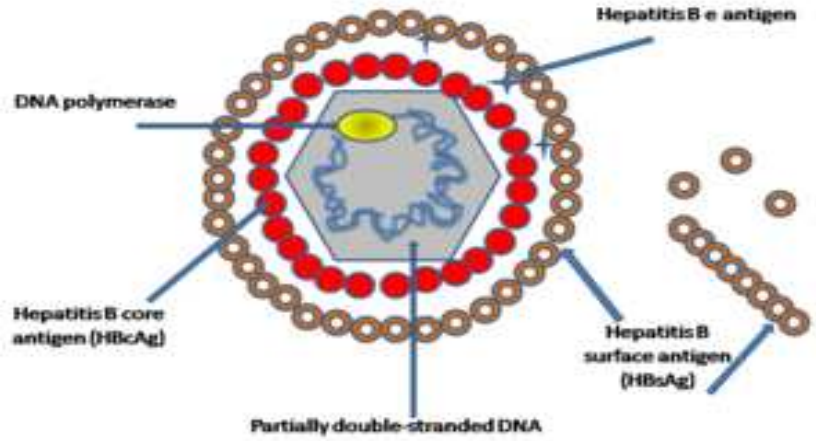

Figure (1): A simplified drawing of the HBV particle and surface antigens (TimVickers, 2007).

The outer envelope contains embedded proteins which are involved in viral binding of, and entry into, susceptible cells. The virus is one of the smallest enveloped animal viruses with a virion diameter of 42nm, but pleomorphic forms exist, including filamentous and spherical bodies lacking a core. These particles are not infectious and are composed of the lipid and protein that forms part of the surface of the virion, which is called the surface antigen (HBsAg), and is produced in excess during the life cycle of the virus ***(Howard, 1986)*.**

The genome

The genome of HBV is made of circular DNA, but it is not fully double-stranded. One end of the full length strand is linked to the viral DNA polymerase. The genome is 3020–3320 nucleotides long (for the full-length strand) and 1700–2800 nucleotides long (for the short length-strand) ***(Kay and Zoulim, 2007)***.

There are four known genes encoded by the genome, called C, X, P, and S. The core protein is coded for by gene C (HBcAg), and its start codon is preceded by an upstream in-frame AUG start codon, from which the pre-core protein is produced. HBeAg is produced by proteolytic