

3 Biochemical Markers in Blood Can Predict Cirrhotic Evolution of Chronic Hepatitis

Essay

Submitted for partial fulfillment of M.Sc. Degree in
Clinical and Chemical pathology

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2009



Statistical analysis: Data obtained from the study was coded and entered using the software SPSS (Statistical package for social science) version 11. Parametric data was summarized using mean and standard deviation, while non parametric was summarized as median and percentiles for quantitative variables, while frequency and percentages are used for qualitative variables. Comparison between groups was done using chi square and Fischer exact test for qualitative variable, t test and non parametric MannWhitny test were used to compare two groups while ANOVA and nonparametric test (Kruskal Wallis test) were used to compare multiple groups. The correlation analysis was assessed by Pearson coefficient of correlation. ROC curve was done to discriminate between degrees of fibrosis. P-value is considered significant if $P < 0.05$.

ACKNOWLEDGEMENTS

First and foremost thanks to Allah the most beneficial and merciful.

I am greatly honoured to express my supreme gratitude to **Prof. Dr. Mona Salem Kalil**, Professor of Chemical pathology, Faculty of Medicine, Cairo University, for her valuable and constant guidance, fruitful ideas and great encouragement throughout this work.

I wish to express my deep gratitude to **Dr. Nevin Ezz El Din Al Abd** , Assistant Professor of Chemical pathology, Faculty of Medicine, Cairo University, for her valuable, great help and encouragement throughout this work.

I am greatly indebted to **Dr. Abeer Mohamed Mohy El Din** , Lecturer of Chemical pathology, Faculty of Medicine, Cairo University, for her valuable, great help, patience and unlimited generosity in time, effort, supervision and support throughout every step of this work.

My sincere thanks to **Dr. Sherif Hamdy**, Lecturer of Tropical Medicine Departement, Faculty of Medicine, Cairo University, for his help, patience and great support throughout this work.

I am also grateful to to **Dr. Manal Kamal** , Assitant Professor of Chemical pathology, Faculty of Medicine, Cairo University, for her help throughout this work.

Last no words could even express my deepest gratitude to my family, my father, my mother, my brothers and my fiancée.

INTRODUCTION

Chronic liver diseases often begin with the anatomic-clinical state of chronic hepatitis and can evolve to liver cirrhosis and hepatocellular carcinoma, various etiological factors have been associated with chronic hepatitis : B & C hepatitis viruses, alcohol and less frequently such metabolic disorders as α_1 - antitrypsin and ceruloplasmin deficiency and cystic fibrosis (Colombo, 1992).

Infection with hepatitis C virus (HCV) is a major cause of chronic hepatitis, cirrhosis, end-stage liver diseases and hepatocellular carcinoma(HCC) in most western countries where it represent the most frequent reason for liver transplantation (Hoofnagle, 1997).

The cirrhotic evolution of chronic hepatitis is associated with liver fibrogenesis. The timely recognition of liver fibrogenesis can improve the choice and therefore, the outcome of treatment (Schuppan, 1995).

The reference procedure for early identification of cirrhotic evolution of chronic hepatitis is histopathology. This procedure however is invasive and is subject to interobserver variability (The METAVIR cooperative group, 1994) because the alterations in liver morphology are very heterogeneous. Imaging techniques (Pilette et al., 1998) and biochemical markers of liver fibrosis such as fibronectin, pseudocholinestrase and prothrombin concentration have been proposed as indicators of change from chronic hepatitis to cirrhosis (Schuppan et al., 1995).

Fibronectin is a glycoprotein distributed in blood and tissues, present in body in two forms: a soluble form in the plasma and body fluids and insoluble form in connective tissue. Fibronectin is synthesized by a wide variety of cells including fibroblasts, endothelial cells and some epithelial cells, also by mononuclear phagocytes, lymphocytes, glial cell and polymorphnuclear granulocytes. The plasma form is the most prevalent form of fibronectin which is synthesized primarily by the liver (Weller et al., 1990).

Pseudocholinesterase is found in liver, pancreas, heart, white matter of brain and is determined spectrophotometrically at 410 n.m, prothrombin activity or concentration is synthesized in liver and is detected by prothrombin time (Toh CH et al., 2002).

Aim of work

To study the ability of three serum biochemical markers: fibronectin, pseudocholinesterase and prothrombin activity when combined in specific equation can differentiate between chronic active hepatitis and cirrhotic patients compared to histopathological method.

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LIST OF ABBREVIATIONS

HCV:	Hepatitis C virus
RNA:	Ribonucleic acid
HCC:	Hepatocellular carcinoma
WHO:	World health organization
ESLD:	End stage liver disease
PAT:	Parenteral antischistosomal therapy
MELD:	Model for end stage liver disease
ECM :	Extracellular matrix
DDR:	Discoidin domain receptors
MMP:	Matrix metalloproteases
TIMP:	Tissue inhibitor of metalloproteinase (TIMP)
MT1_MMP :	Membrane-type 1-matrix metalloproteinase
ALT:	Alanine transaminase
EIA :	Enzyme immunoassay
FDA:	Food Drug Administration
PCR:	Polymerase chain reaction
HAI :	Histological Activity Index
AST:	Aspartate transaminase
GGT:	Gamma glutamyl transferase
ALP:	Alkaline phosphatase
PGA:	Prothrombin, Gamma glutamyl transferase, Aplyprotein
APRI:	AST-to-Platelet Ratio Index
FN:	Fibronectin
LETs :	Large external transformation sensitive protein

SF ANTIGEN:	Soluble fibroblast antigen
CAF:	Cell adhesion factor
CIG:	Cell in soluble globulin
RGD:	Arg-Gly-Asp
GAG:	Glycosaminoglycan
EGF:	Epidermal growth factor
GLN:	Glycine
LYS:	Lysine
FNBPA :	S. aureus surface protein
IL-1 :	Interlukin 1
ELISA:	Enzyme-Linked Immunosorbent Assay
MBNA:	Mercapto-nitro-benzoic acid
PT:	Prothrombin time
BCG:	Bromocresol green
DPC:	Diagnostic Products Corporation
RP:	Reference curve
FNP:	Fresh Frozen plasma
INR:	International Normalised Ratio
CAH:	Chronic active hepatitis
ROC:	Reciever Operator Characteristic

CHAPTER 1

Hepatitis C Virus

Infection with hepatitis C virus (HCV) is currently a major cause of chronic hepatitis, cirrhosis, end-stage liver disease and hepatocellular carcinoma in most Western Countries where it represent the most frequent reason for liver transplantation (Zong et al.,2006). HCV is a spherical, enveloped, RNA virus of the Flaviviridae family. It was cloned in 1989 and was found to be the cause of 80% to 90% of cases of non-A, non-B hepatitis (Lauer and Walker, 2001).

Its genome is a positive, single-stranded RNA molecule that replicates at a rate of 10 trillion new virions per day. A highly heterogeneous virus, HCV has approximately 70% homology between all isolates. As HCV replicates, RNA-dependent polymerases often introduce random nucleotide errors, which over time, result in slow genetic evolution of the virus (Genovese et al.,2005).

At least 6 genotypes of HCV have been described. Genotype 1 is the most common in North America. It accounts for more than 60% of infections and is followed in frequency by types 2 and 3. Type 4 is most prevalent in Egypt (accounts for >90% of infection in Egypt), type 5 in South Africa, and type 6 in Southeast Asia. The extensive genetic heterogeneity of HCV has important diagnostic and clinical implications, perhaps explaining difficulties in vaccine development and the lack of response to therapy (Lauer and Walker, 2001).

The lack of a vigorous T-lymphocyte response and the high propensity of the virus to mutate appear to promote a high rate of chronic infection.

HCV replicates preferentially in hepatocytes but is not directly cytopathic, leading to persistent infection. During chronic infection, HCV RNA reaches high levels, generally ranging from 10^5 to 10^7 international units (IU)/mL, but the levels can fluctuate widely. However, within the same

individual, RNA levels are usually relatively stable (NIH Consensus Statement, 2002).

Epidemiology

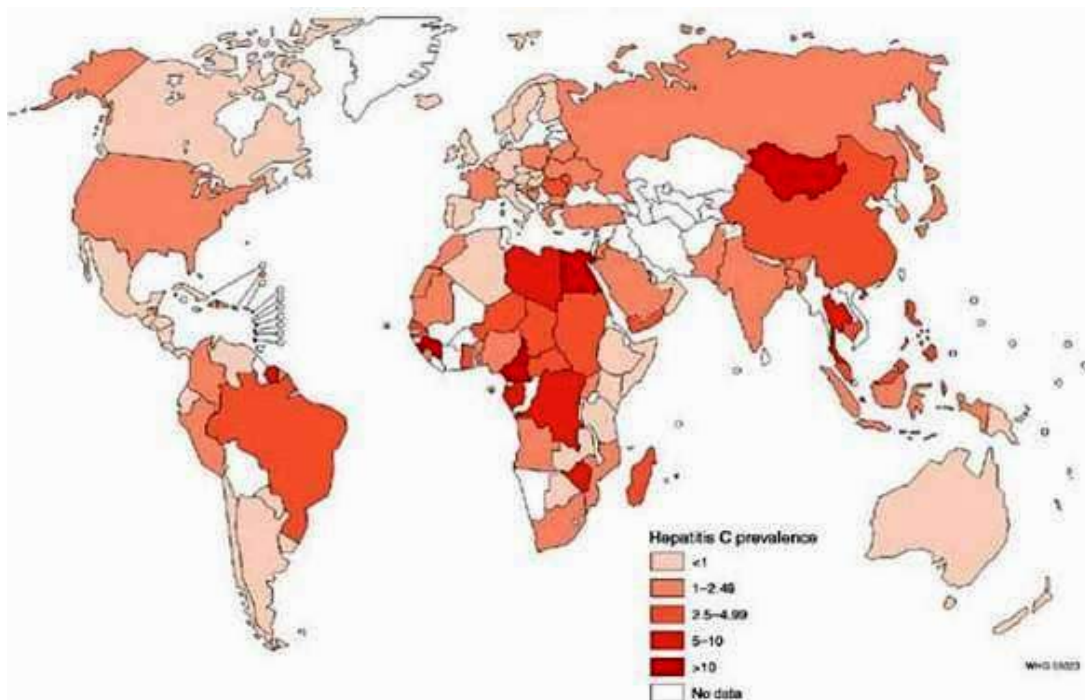


Fig. (1): Prevalence of hepatitis C virus.

According to World Health Organization (WHO) estimates, 3% of the world's population, or approximately 170 million people, are infected with (HCV) (WHO epidemiology report, 2002).

In the United States alone, roughly 4 million individuals are infected with HCV, with an average acquisition rate of 28,000 people per year (NIH Consensus Statement, 2002).

In endemic areas such as Egypt, more than 10% of the population is infected (WHO epidemiology report, 2002).

The incidence of acute HCV infection has decreased by more than 80% since the early 90s, with the screening of blood donors likely contributing to the greatest proportion of this decrease (CDC, 1998).

Individuals who contract hepatitis C have an 85% chance of developing persistent or chronic HCV infection, which is associated with an increased risk of progressive liver disease leading to cirrhosis and, in some cases, hepatocellular carcinoma (HCC), end-stage liver disease (ESLD), or death. Currently, HCV-related liver disease is the leading indication for liver transplantation in the United States (NIH Consensus Statement, 2002).

The population of Egypt has a heavy burden of liver disease, mostly due to chronic infection with HCV. Overall prevalence of antibody to HCV in the general population is around 15-20%. The risk factor for HCV transmission that specifically sets Egypt apart from other countries is a personal history of parenteral antischistosomal therapy (PAT). (Frank et al., 2000).

Desert areas of Egypt have the lowest rates of infection and cities have lower rates than rural areas. Rates in the Nile Delta (Lower Egypt) are higher than the Nile Valley (Middle and Upper Egypt). (El Gohary et al., 1995; Darwish et al., 1996 and Mohamed et al., 1996).

Transmission of HCV

HepatitisC virus has been isolated from blood, saliva, urine, semen, and ascitic fluid Parenteral transmission remains the primary mode of spread of HCV (Deuffic-Burban et al., 2009).

The most common mode of HCV transmission is percutaneous, through intravenous-drug use and previously from blood transfusions. Blood transfusion was the most common mechanism of transmission before blood