Correlation between Histopathology, Virology and Biochemistry in Chronic Hepatitis C

Thesis

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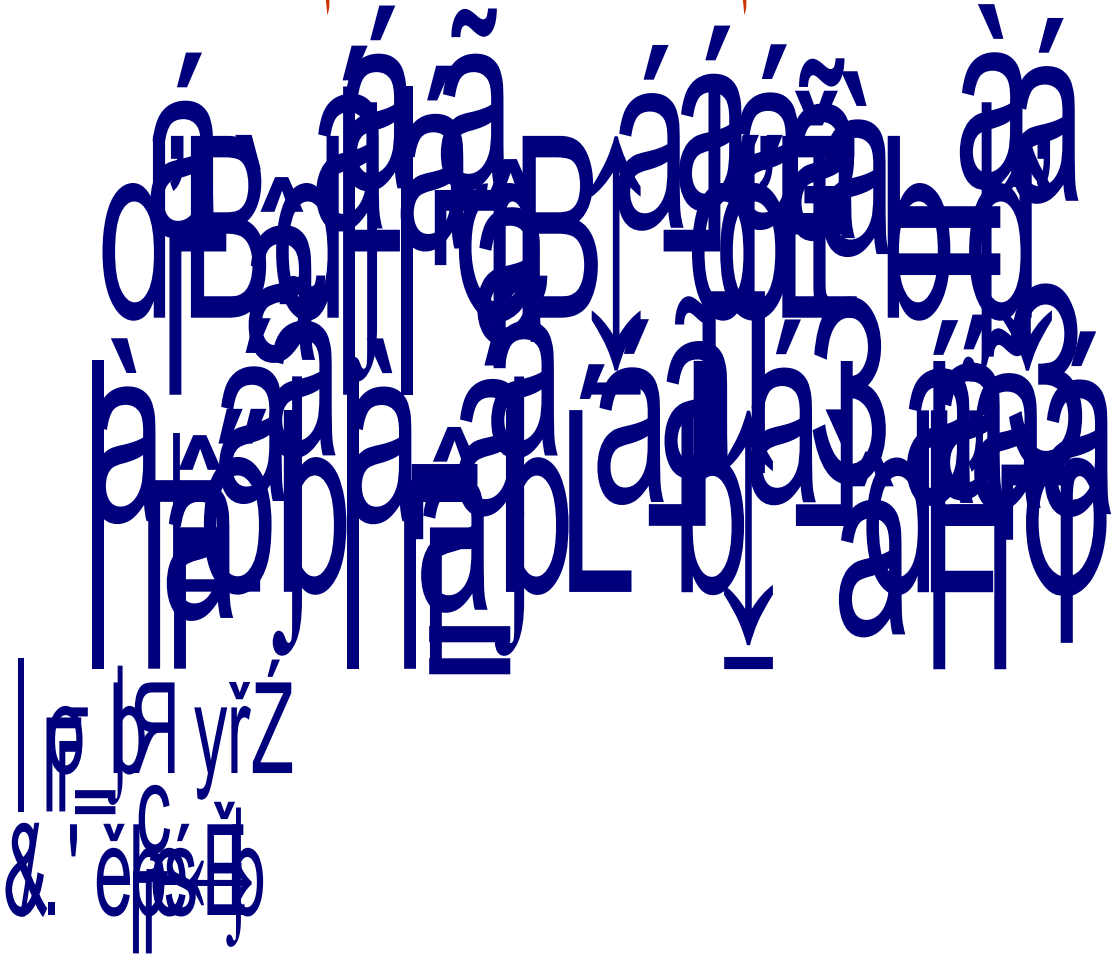

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Contents

Abbreviations

ALT	Alanine transaminase.
AP	Alkaline Phosphatase.
AST	Aspartate transaminase.
CN	Confluent necrosis.
ELISA	Enzyme-linked immunosorbent assay.
IA	Immunosorbent assay
LN	Lytic necrosis.
HCV	Hepatitis C Virus.
HCC	Hepatocellular carcinoma.
HAI	Histological activity index.
IFN	Interferon
PAS-D	Periodic Acid–Schiff stain with Diastase.
PMN	Piece meal necrosis.
PCR	Polymerase Chain Reaction test.
PI	Portal inflammation.
RBV	Ribavirin

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Introduction and aim of the work

Introduction

Hepatitis CVirus (HCV) prevalence rates in the general population are estimated at between 10% and 15% in rural areas, with some age groups suffering from prevalence rates of up to 50%. Incidence rates are estimated at 2-6 per 1,000 per year, a level that will maintain prevalence rates of 5-15% for the foreseeable future. The virus continues to be transmitted in medical and paramedical settings, as well as within communities and families. Approximately 5-7 million Egyptians carry antibodies for HCV **(Egyptian Ministry of Health 2007).**

HCV infection becomes a chronic disease in a large proportion of patients, ranging from 55% to 90%; it has a progressive fibrotic nature. Up to 20% of the cases may culminate in cirrhosis; complicated by hepatocellular carcinoma and end-stage liver disease **(Seeff 2002).**

The primary goal of antiviral therapy has always been to achieve viral eradication as a mean of delaying progression to end-stage liver disease and preventing the development of Hepatocellular carcinoma (HCC). As treatment of HCV infection has evolved, some factors have gained importance, such as histological response (improvement of inflammation and fibrosis in liver biopsy) and health-related quality of life. Liver biopsy provides the most accurate information on the stage of fibrosis and grade of necroinflammation. The value of liver biopsy in predicting treatment response is incompletely defined and the relation of liver biopsy findings to standard interferon (IFN) and ribavirin (RBV) treatment outcomes is heterogeneous **(Petrenkienė, et al., 2004).**

The role of liver biopsy in the management of chronic hepatitis C is the "gold standard" for assessing the grade of liver injury and stage of liver fibrosis in anticipation of antiviral therapy as stated by National Institutes of Health Consensus Development Conference in 1997 (**Perrillo 1997)**.

Introduction and aim of the work

Because the rate of progression of chronic hepatitis C is influenced by baseline histological grade/stage, patients can be stratified into those with moderate to severe hepatitis, who merit immediate therapy, and those with mild hepatitis, in whom therapy can be postponed until more effective tolerable treatments become available **(Dienstag 2002).**

Aim of the work

The aim of this work is:

1- To study the pathological changes associated with chronic hepatitis C virus including the degree of necroinflammatory injury and stage of fibrosis.

2- To correlate between the degree of necroinflammatory injury and stage of fibrosis with virology (**PCR**) and biochemistry (**ALT, AST, AP**) in chronic hepatitis C.

Review of literature

Anatomy of the Liver

Macroanatomy: The liver, largest organ in the bodyrepresents 2.5% of the total body weight. It is relatively larger in infancy comprising one eighteenth of birth weight, this is mainly due to a large left lobe. The liver is covered by ribs in the right upper quadrant and projecting below it and coming in contact with abdominal wall only below the right costal margin. There are two anatomical lobes. The right being about six times the size of the left. Lesser segments of the right lobe are the caudate lobe on the posterior surface and the quadrate lobe on the inferior surface, the right and left lobes are separated anteriorly by a fold of peritoneum called the falciform ligament, posteriorly by a fissure for ligamentum venosum and inferiorly by the fissure for ligamentum teres. The liver is kept in position by peritoneal ligaments and by the intra abdominal pressure transmitted by the tone of the muscles of abdominal wall **(Sherlock and Dooley, 2002).**

Functional anatomy: Based on external appearance, the liver has right and left lobesseparated along the line of falciform ligament. This separation, however, does not correlate with blood supply and biliary drainage. A functional anatomy is recognized based on studies of vascular and biliary casts made by injecting vinyl dye into vessels and bile ducts. This classification correlates with that seen by imaging techniques **(Mukai et al., 1987).** The main portal vein divides into right and left branches and each of these supplies two further subunits (called sectors). The sectors of rightlobeare anterior and posterior and of the left lobe are medial and lateral giving a total of four sectors. Using this definition, the right and left side of the liver are divided not along the line of falciform ligament but along a slightlyoblique line to the right of another drawn from the inferior vena cave to the gall bladder below. The right and left lobes are independent as regard to portal and arterial blood supply and bile drainage. Three plains separate the four sectors and contain the three major hepatic vein branches. Closer analysis of these four hepatic sectors produces a further subdivision into segments. There is no vascular anastomosis between the

macroscopic vessels of the segments but communication occurs at sinusoidal level. This functional anatomic classification allows interpretation of radiological data and is of importance to the surgeon planning a liver resection **(Menu, 1991).**

Microanatomy

The hepatic microcirculation:

(1) Portal circulation: Within the liver, the portal vein divides into successive generations of distributing veins, they do not directly feed the sinusoidal circulation. According to their position they may be classified as interlobar, segmental and interlobular. Further branching of these produces the portal vein branches which distribute their blood into the sinusoids. These branches are: preterminal and terminal portal venules from them very short side branches called inlet venules arise guarded by sphincters composed of sinusoidal lining cells **(McCuskey, 2000).**

(2) Arterial circulation: The hepatic artery branches accompany the portal veins and two or more branches may be present within each portal area. The terminal distribution of the arteries is by three routes: into periportal plexuses,peribiliary plexuses and terminal hepatic arterioles **(Takasaki and Hano, 2001).**

(3) Venus drainage: The blood enters the terminal hepatic venules (the central veins of the classic lobules) after perfusing the parenchyma via the sinusoids. Several collecting venules may drain the blood from individual lobules into the terminal venules. Scanning electron microscopy has clearly demonstrated in the walls of the veins fenestrations through which the sinusoids open. The terminal vein branches unit to form intercalated veins which form the larger hepatic vein branches **(Mac Sween et al., 2002).**

Classic hepatic lobule: Microscopically and functionally the liver has been subdivided classically into roughly hexagonal lobules, 1-2 mm in diameter, oriented about a central vein. The blood supply to the liver parenchyma flows from the portal

tract positioned at the angles of the hexagon. Each portal area contains a comparatively wide, thin walled branch of the portal vein and a narrower, thicker walled branch of the hepatic artery that represents the vessel supplying hepatic sinusoids with portal and the arterial blood , small branch of the bile duct recognizable by its simple cuboidal epithelial lining and thin walled lymphatic vessel. These four tubes and their surrounding connective tissue are known as a portal tract. The layer of hepatocytes immediately bordering the portal tract is known as the limiting plate. It has been realized that the blood flow and function of the liver are more accurately represented by the unit structure known as the hepatic acinus **(Young and Heath, 2000).**

Hepatic acinus: The hepatic parenchyma is divided into structural units of first order, second order and third order based on the terminal portal circulation.***Simple acinus:***It was defined as a small parenchymal tissue irregular in size and shape, arranged around portal tract. The acinus lies between two (or more) terminal hepatic venules. The parenchyma of the acinus is divided into three zones: zone I being closest to the arterial and portal supply, zone 3 being closest to the central vein and zone 2 being intermediate. Zones 1, 2, 3 represent areas which receive blood progressively poorer in nutrients and oxygen. There is apparent continuity between zone 3 of adjacent simple acinus **(Carmack, 2001).**

The complex acinus iscomposed of at least three simple acini and a sleeve of parenchyma around the preterminal vessels which comprises small clumps - acinuli - which are supplied by venular and arteriolar branches from the preterminal vessels. The complex acini subdivide the liver into circulatory zones **(MacSween et al., 2002).**

Hepatocytes: The hepatocytes within the liver usually are arranged as anastomosing plates one cell thick.Hepatocytes are large polyhedral cells with round nuclei with peripherally dispersed chromatin and prominant nucleoli. The nuclei vary greatly in size, reflecting an unusual cellular feature in more than half of the

hepatocytes, doubled in 25% of the cells. Cytoplasm is strongly eosinophilic due to numerous mitochondria. Liver cells are rich inglycogen; it accumulates in cytoplasm producing vacuolated appearance **(Young and Heath, 2000).**

Hepatic sinusoids: The sinusoids have an average diameter of about 10 µm but they distend to about 30 µm. The periportal sinusoids are more tortuous than the perivenular ones. Hepatocyte surfaces bordering on liver sinusoids are covered with microvilli; they occupy a perisinusoidal space (space of Disse) that lies between hepatocytes and the endothelial lining of their associated sinusoids. In addition, the perisinusoidal space contains reticuler fibres and small amounts of discontinuous non obstructing basement membrane (fenestrated). Four distinct types of sinusoidal cellscan be identified: endothelial cells, the hepatic stellate cells found in the space of Disse, the kupffer cells and liver-associated lymphocytes lie on the luminal aspect of the endothelium **(Burt et al., 1993).**

Sinusoidal lining cells: They are readily distingushable from hepatocytes by their flattened condensed nuclei and attenuated poorly stained cytoplasm. These form an attenuated cytoplasmic sheet perforated by numerous holes (fenestrae). There is continuity between the sinusoidal lumen and perisinusoidal space of Disse; this allows endothelial cells to filter the sinusoidal blood. Another unusual feature of sinusoidal endothelial cells is their high endocytotic activity **(Wisse et al., 1985).**

Hepatic stellate cells: Within the space of Disse are stellate cells whose long cytoplasmic processes surround the sinusoids. They were named by many terms as Ito cells, hepatic lipocytes, fat storing cells, hepatic stellate cells and also the parasinusoidal cells **(Ramadori, 1991).** They are not readily visualized on light microscopy but they may be prominent in some pathological conditions **(Cameron et al., 1997).**

The hepatic stellate cells have four main functions:

- They act in a pericyte-like manner around the sinusoids and may have a role in the control of micro vascular tone **(Ramadori, 1991).**