SOME HISTOPATHOLOGICAL, IMMUNOLOGICAL AND IMMUNOFLUORESCENT ASPECTS OF NON-A, non-B HEPATITIS

THESIS

Submitted in Partial Fulfilment

of Master Degree

in

(INTERNAL MEDICINE)

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1990

ACKNOWLEDGEMENT

I would like to express my sincere gratitude and heartfelt thanks to Prof. Dr. NABIL AZIZ SCHOUKRY, Professor of General Medicine, Ain Shams University, to whom I am greatly indebted for his valuable guidance, expert assistance and fruitful criticism. This study could not have been done without his constant help.

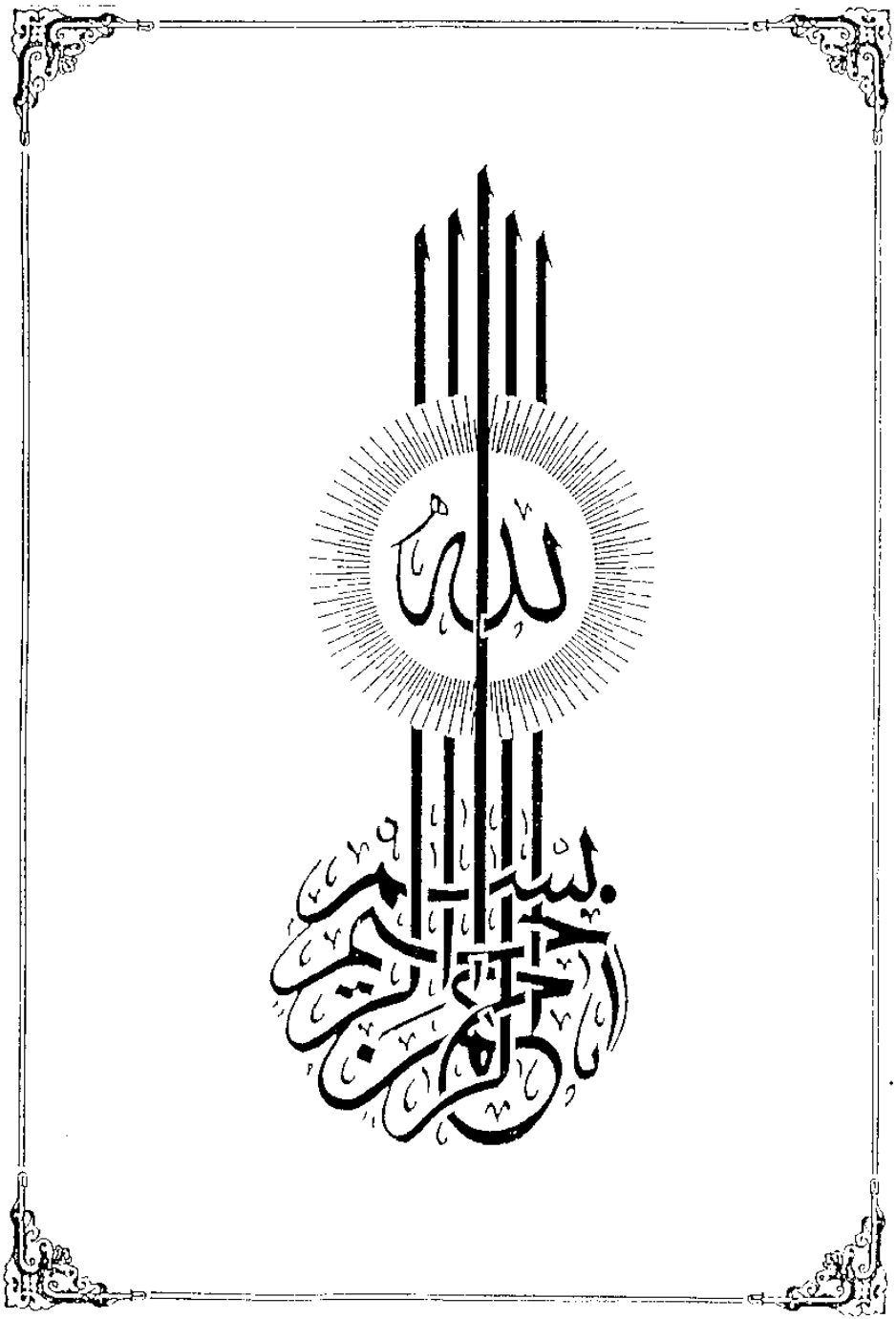
I wish thank Prof. Dr. IBRAHIM KHALIL ALI, Professor of Clinical Pathology, Ain Shams University, for his valuable advice.

I wish thank Dr. YEHIA EL CHAZLI, Assistant Professor of General Medicine for his valuable guidance and advice.

I wish thank Prof. Dr. SHERIF ABD EL FATTAH for referring some cases included in this study.

Before All Thanks God.

Samya Ahmed



C O N T E N T S

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INTRODUCTION AND AIM OF THE WORK

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Hepatitis B viruses, drugs, autoimmunity and Non A Non B viruses were on top of the aetiologic factors of chronic hepatitis. An overlap between the biochemical findings was present inbetween different types of chronic hepatitis, the histopathologic and immunologic features between different common groups were not heavily investigated (Boyer 1982; Shorey 1985 and Shoukry 1987).

It become the aim of this work to review the clinical, biochemical, histopathological and immunological aspects of Non A Non B viruses, at the same time 50 patients with chronic hepatitis will be investigated biochemically for (GOT, GPT, γ GT, serum alkaline phosphatase, Serum bilirubin, proteins), serologically for HBsAg, C.M.V., Eb virus, serum IgG, IgM, IgA, and IgD and immunofluorescent study for anti-smooth muscle with antimitochondrial with antinuclear, besides histopathological examination of liver biopsies.

REVIEW OF LITERATURE

CHRONIC HEPATITIS

Definition:

Chronic hepatitis is defined as a chronic inflammatory reaction in the liver continuing without improvement for at least six months (Schever, 1986).

When there is evidence of persistent elevation of serum enzymes for more than 6 months following an attack of acute viral hepatitis the condition is arbitrarily considered to have become chronic hepatitis (Schiff, 1982).

In practice two main different definitions of chronic hepatitis have been proposed. One is based on a combination of the activity and the duration of the illness, and the other on its duration alone (Summerskill, 1974). The former definition depends on unremmiting active liver disease, defined by a serum transaminase activity increased at least ten times or an activity increased at least five times with the serum gammaglobulin increased at least twice presenting without improvement for at least ten weeks. This occurs in less than two percent of patients with acute viral hepatitis and one third of such patients die within six months if no treatment is given (Summerskill, 1974).

For hepatitis to be chronic, biochemical signs must be present for at least ten to twelve weeks. These criteria

identify patients with chronic active hepatitis (Summerskill, 1974 and Geal et al., 1968).

The other definition takes as its criterion clinical or biochemical evidence of hepatitis continuing for more than six months (Sherlock, 1974; Boyer, 1976).

The fulfilment of six months is an arbitary minimum time accepted by some authers (DeGroote et al., 1968; Hegarty and Williams, 1985). The fulfilment of these criteria indicates the need for a liver biopsy to define the type of chronic hepatitis present. A diagnosis of chronic liver disease usually cirrhosis, may be made at the onset when features such as spider telangiectasia, hepatosplenomegaly, ascitis or hypoalbuminaemia and hyperglobinaemia are found at presentation (Hegarty and Williams, 1985).

Cirrhosis is defined as a widespread fibrosis with nodule formation. The normal zonal architecture of the liver is disturbed and cannot be recognized (Sherlock, 1989).

Classification:

Little more than a decade ago, the term "chronic hepatitis" was designated as a single, poorly understood

disease, characterised by its clinical longevity and by liver biopsy findings of an active hepatic necro-inflammatory process. Although it was recognised that chronic hepatitis could progress to severe hepatic necrosis and or cirrhosis, it also can resolve spontaneously, there were no good guideliness for predicting clinical outcome (Kaplan, 1983).

Chronic hepatitis was originally classified into two types chronic persistent and chronic active "agressive" (De Groote et al., 1968). This has proved to be an over simplification of the problem, a further type, chronic lobular hepatitis, has been introduced and the chronic active form has been subdivided into a mild and severe type (International Group, 1977; Schalm et al., 1976).

Chronic persistent hepatitis is marked by expansion of the portal zone by mononuclear cells and some fibrosis The limiting plate of liver cells between portal zones and liver cell columns is intact. Piecemeal necrosis of liver cells is not seen (Sherlock, 1989).

Chronic persistent hepatitis represents an inactive phase of chronic active syndrome, accompanied by mild hepatic enzyme abnormalities which may persist for many months even years. It may simply represent a delayed recovery phenomenon of acute hepatitis. It is relatively benign disorder that is ultimately self limited (Krugman et al., 1978).

Chronic lobular hepatitis is sometimes termed prolonged or unresolved acute hepatitis. Many of the histological features resemble acute viral hepatitis, but the duration is greater than three months. The picture is predominantly that of intralobular inflammation and necrosis. Piecemeal necrosis and bridging necrosis are not seen (Sherlock,1989).

Chronic active hepatitis implies continuing distruction of the liver. It is characterised by progressive degeneration of hepatocytes over the pane of years, and continuous erosion of the hepatic functional reserve, and the gradual development of cirrhosis in most cases. It is usually by hepatitis B virus (HBV) or non-A, non-B (NANB) viruses (Schiff, 1982).

Chronic active hepatitis is marked by the presence of an inflammatory infiltrate primarily of lymphocytes and plasma cells which greatly expands the portal areas. This inflammatory infiltrate extends into the liver lobules, causing erosion of the limiting plate and piecemeal necrosis (Sherlock, 1989).

The severe form is marked by fibrous septa extending into the liver cell columns with isolation of groups of liver cells in the form of rosettes. Intra-hepatic bridging either portal-central or portal - portal is seen (Sherlock, 1989). The milder form shows only slight erosion of the

limiting plate with some piecemeal necrosis but without bridging or rosette formation (Sherlock,1989).

This classification of chronic hepatitis is important in terms of prognosis. The chronic persistent and chronic lobular types do not progress to cirrhosis. Mild chronic active hepatitis may occasionally progress to cirrhosis but this is unusual. The severe chronic active hepatitis does so progress and indeed cirrhosis may already be present, co-existing with the chronic active hepatitis (Sherlock, 1989).

Aetiology:

Chronic hepatitis affects both sexes and all age groups and clinical symptoms and physical findings do not necessarily need to be present. Other known chronically active liver disease such as alcoholic liver disease, primary biliary cirrhosis, hemochromatosis or cirrhosis from alpha-1-antitrypsin deficiency are usually readily excluded if appropriate diagnostic procedures are performed. For example, liver biopsy is usually diagnostic in the patient with alcoholic liver disease or hemochromatosis, whereas periodic acid Schiff positive granules can be found in the hepatocytes of Wilson's disease which often presents as chronic hepatitis or cirrhosis in the second decade of

life (Sternlieb et al., 1972), and will be recognised insignificent percent if all young patients with chronic hepatitis have serum ceruloplasmin, 24 hours urine determination of copper excretion, besides the screening of the asymptomatic chronic carriers of hepatitis B antigen (Singleton et al., 1971; Simon et al., 1974).

Serological markers of autoimmunity such as antinuclear factors, smooth muscle antibodies, and elevated serum levels of immunoglobulins which have been considered clinical hallmarks of chronic active hepatitis by some authorities (Read et al., 1963; Mistlis et al., 1970) do not always correlate with the clinical course of the chronic hepatitis and are not always observed in patients with all chronic active forms of the disease.

Epidemiological studies have not detected an increase in the incidence of patients with chronic active hepatitis after epidemic hepatitis A infection (Bothwell et al.,1963; Nefzer et al., 1963; Zieve et al., 1953; Neefe et al.,1955).

Serological tests for hepatitis B surface antigen (HBsAg) have been observed in a variable percentage of patients with chronic active hepatitis, ranging from 10 to 67% of cases in some reported studies (Nielson et al.,1971; Wright et al., 1969; Prince et al., 1970; Blumberg et al., 1970).

Chronic hepatitis B is found predominantly in males. The very young and the very old are at particular risk (Sherlock, 1989).

Neither epidemiologic nor serologic evidence implicating HAV infection in the development of chronic liver disease (Rakela et al., 1978). In one study approximately 10% of patients with acute hepatitis A had elevated serum aminotransferase levels three months after the onset of illness but complete resolution was documented by six months in all (Dienstag et al., 1978).

Hepatitis A is characterised by absence of chronic hepatitis, no long term carrier states and no recognized association with either cirrhosis or hepatocellular carcinoma (Stollerman et al., 1978).

In 19 patients followed up by biopsy-verified acute viral hepatitis to chronic active liver disease and 74 patients followed to complete resolution verified by a normal liver biopsy, sera from the acute phase were studied for serologic evidence of hepatitis type A and B. Eleven of the 19 patients who developed chronic active liver disease progressed from acute hepatitis B and 7 from acute hepatitis type non-A,non-B. One patient could not be classified because the sera were exhausted. None had

serological markers of actual hepatitis type A infection. Of the 74 patients with a histologically complete resolution, the acute episode could be classified as type B hepatitis in 47 and type A hepatitis in 13 patients. The remainder 14 patients were classified as having acute viral hepatitis type non-A,non-B. The findings confirm that type B and non-A,non-B hepatitis may give rise to chronic liver disease, whereas type A hepatitis so far has not been demonstrated to initiate a chronic liver disease (Mathiesen et al., 1980).

In the majority, chronic liver disease is not preceded by a recognizable acute attack of hepatitis B. In others the acute episode progresses directly to chronicity. In others, again, although the clinical picture at the apparent onset is of an acute illness, chronic hepatitis already exists. About 10% of adult patients suffering acute type B hepatitis fail to clear HBsAg from the blood in twelve weeks and become chronic carriers. Neonates acquiring hepatitis B have a 90% chance of becoming chronic carriers (Sherlock, 1989).

Acute non-A, non-B hepatitis is frequently followed by a carrier state. In the United States, this may be about 3% after a single unit blood transfusion and in other countries it can be considerably higher. It is not