

A DESCRIPTIVE STUDY OF CHRONIC
HEPATITIS AS SEEN AT KENYATTA
NATIONAL HOSPITAL.

A DISSERTATION SUBMITTED IN PART
FULFILLMENT FOR THE DEGREE OF
MASTER OF MEDICINE (MEDICINE) OF
THE UNIVERSITY OF NAIROBI.

BY

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DECLARATION.

I certify that this Dissertation is my own original work and has not been presented for a Degree in any other University.

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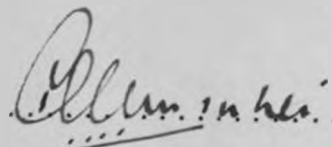

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ABBREVIATIONS:

HBsAg - Hepatitis B surface antigen

CPH - Chronic persistent hepatitis

CAH - Chronic active hepatitis

No - Number

Anti-HBc - Hepatitis B core antibody

Anti-HBs - Hepatitis B surface antibody

ANA - Antinuclear antibody

AMA - Antimitochondrial antibody

SMA - Smooth muscle antibody

% - Percentage

A.S.T - Serum aspartate amino transferase

A.L.T - Serum alanine amino transferase

P.T.I - Prothrombin time index

Anti-HBe - Hepatitis Be antibody

P.A.S - Periodic acid schiff

+ve - Positive

-ve - Negative

n - Number

HBeAg - Hepatitis Be antigen.

HBV - Hepatitis B virus

CLD- Chronic liver disease

SUMMARY.

Over an eight months period, between February 1989 and December 1989, a total of 16 patients (9 males and 7 females) with chronic hepatitis were studied at Kenyatta National Hospital.

The patients studied, had both clinical and a histological diagnosis of chronic hepatitis.

The results showed that, 16(53.3%) of the 30 patients with a clinical diagnosis of chronic hepatitis had a compatible histology. Chronic persistent and chronic active hepatitis occurred in almost equal proportions. There was no case of chronic lobular hepatitis.

Neither clinical features, nor liver function tests could adequately differentiate the two reported histological types.

The aetiological spectrum included hepatitis B virus, alcohol and auto-immune hepatitis.

INTRODUCTION AND LITERATURE REVIEW

Chronic hepatitis is defined as a chronic inflammatory reaction in the liver continuing without improvement for at least six months.¹

Originally it was classified into chronic persistent and chronic active hepatitis², but in 1971, a further type chronic lobular hepatitis was introduced by Popper and schaffner³.

Chronic persistent hepatitis is histologically marked by expansion of the portal zones by mononuclear cells and fibrosis. The limiting plate of the liver cells between portal and liver cell column is intact and piecemeal necrosis of the liver cell is not seen¹. The patient may be asymptomatic or complain of fatigue; poor appetite or fat and alcohol intolerance after an initial illness suggesting acute viral hepatitis. Recurrent jaundice may be a feature⁴. Physical examination may be normal or tender hepatomegaly may be found. Biochemically, serum bilirubin level may be normal or slightly elevated. Serum amino transferase values are usually elevated although the serum total globulin and serum albumin are usually within normal limits.

Chronic lobular hepatitis, termed prolonged or unresolved acute hepatitis has a histological picture of predominantly intralobular inflammation and necrosis, features apparently identical with those of acute viral hepatitis. Piecemeal necrosis and bridging necrosis are not seen.

Patients are usually males and diagnosed after an acute viral like illness in whom the duration of illness exceeds 3 months⁵. The course may be of remissions and relapses which are marked by elevations of serum aminotransferases and bilirubin. Serum auto antibodies (antinuclear, antimitochondrial and smooth muscle antibodies) may be positive and hepatitis B surface antigen (HBsAg) is negative. Hyperglobulinaemia occurs.

Chronic active hepatitis initially termed chronic liver disease of young women⁶, lupoid hepatitis⁷, plasma cell hepatitis⁸ or active "juvenile" cirrhosis⁹, now has an internationally agreed clinico-pathological definition¹⁰. It is a condition of varied aetiology. It is marked by the presence of inflammatory infiltrate of lymphocytes and plasma cells which expand the portal areas, extend into liver lobules causing erosion of the limiting plate and piecemeal necrosis and if severe, central-portal hepatic bridging and rosette formation.

Chronic active hepatitis may exist alone or with evidence of cirrhosis¹², this being termed active post necrotic cirrhosis. In this histological picture, the cirrhosis is usually quite active and regenerating nodules and fibrosis co-exist with areas of more recent parenchymal cell necrosis and collapse which may be piecemeal, bridging or multilobular in pattern.

Symptoms of chronic active hepatitis range from none to incapacitating exhaustion. Fluctuating hepatocellular jaundice is usual. Recurrent symptoms of malaise, anorexia and low grade fever are common throughout the course of illness. Liver function

are abnormal. Serum aminotransferases are elevated, hypergammaglobulinemia is common and there is a variable elevation of serum bilirubin. Circulating autoantibodies may be found.

Previous studies have shown that chronic persistent and chronic lobular hepatitis rarely progress to liver cirrhosis whereas chronic active hepatitis may lead to cirrhosis and hepatic failure. Backer et al⁴ and Chadwick et al¹² followed up patients with chronic persistent hepatitis and none of them developed any features of cirrhosis. Wilkson and colleagues¹³ in 1978, followed up patients with chronic lobular hepatitis with serial biopsies and none of them progressed to cirrhosis. However Degroote et al¹⁴ in a follow up of patients with chronic active hepatitis with moderate severity found that 49% developed liver cirrhosis. This occurred more frequently in the hepatitis B virus positive patients than those who were virus negative.

For many years, hepatitis B virus in the hepatitis B surface antigen (HBsAg) carrier state, hepatitis non A-non B and alcohol have been implicated as aetiological agents in chronic hepatitis.

The hepatitis B virus carrier state is defined as demonstrable persistence of HBsAg for more than three months¹⁵. The hepatitis B viral carrier rate as judged by the presence of surface antigen in serum, ranges from 10-30% in sub-saharan Africa and far east Asia¹⁶. In Kenya, Bowry et al¹⁷ found the carrier rate to be 14%, Parker et al¹⁸ found a prevalence of 6.6% in blood donors in an Urban society whereas Bagshawe¹⁶ in her study of a rural community found the incidence to be 5%. Only Bowry's study used radio-immuno assays

which is the most sensitive screening procedure.

Previous studies have found that an appreciable proportion of chronic hepatitis are HBsAg carriers. Guardia et al¹⁹ in Spain found the prevalence of HBsAg positivity to be 53% in chronic persistent hepatitis and 42% in chronic active hepatitis, while Vischer²⁰ in Switzerland found the prevalence of 25% and 22% in chronic persistent and chronic active hepatitis respectively. Krassnitisky and colleagues²¹ in Austria found the prevalence to be 14% in chronic persistent and 60% in chronic active hepatitis. However, other studies in Britain²² Denmark²³ and Australia²⁴ showed a lower prevalence of HBsAg.

The carrier state may occur in asymptomatic patients or follow an acute attack of hepatitis with failure of HBsAg to be cleared from the blood. Clinical studies have recorded rates of persistence of HBsAg of 5-10% after symptomatic naturally acquired disease and within this group chronic hepatitis is likely to develop. Redeker et al²⁵ and Nielson et al¹⁵ found 10% and 4-5% progression to chronic hepatitis after acute infection.

Serum antibody to hepatitis B core antigen (Anti-HBc) is another sensitive indicator of viral replication²⁶ and its presence in HBsAg negative chronic hepatitis is another indicator of chronic infection with hepatitis B virus. Gerber et al²⁷ and Bories et al²⁸ reported the presence of serum anti-HBc in 21% and 40% respectively, of patients with HBsAg negative chronic hepatitis.

Hepatitis B virus (HBV) particles are most likely to be present, if Hepatitis Be antigen (HBeAg) is detected in patients

positive for HBsAg. This is the replicative phase of hepatitis B viral infection and associated with high infectivity. The presence of antibody to hepatitis Be antigen (Anti -HBe) indicates integration of viral DNA into host DNA. This occurs after a variable period, often of several years and is associated with low infectivity.

The progression from acute non A, non B hepatitis to chronic liver disease has been reported after blood transfusion related and blood factor related acute disease. The incidence of chronicity seem to be at least 30-40%. Knodell and associates²⁹ found the incidence to be 46% while Berman³⁰ found it to be 23%. Grealdi et al³¹ in Italy, however, found the incidence to be as high as 60%. Liver histology usually shows chronic active or chronic persistent hepatitis, however chronic lobular lesions have also been described³¹.

Alcoholism may be accompanied by liver disease with a histological picture of either chronic active or chronic persistent hepatitis³² and alcohol has been added to the list of aetiological agents responsible for these two patterns of liver damage. It is presumed that subjects consuming at least 80g of alcohol per day for extended periods³³ consume a quantity sufficient to produce chronic liver disease. Characteristics of alcoholic liver disease such as liver cell ballooning, polymorphonuclear inflammation, steatosis and alcoholic hyaline are present minimally or completely absent³².

Previous studies have shown that many patients with alcoholic

liver disease have histological evidence of siderosis³⁵ and occasionally this may occur at a level indistinguishable from idiopathic hemochromatosis.

Chronic persistent hepatitis may complicate long standing chronic colonic diseases for instance ulcerative colitis and regional ileitis or infection with Entamoeba histolytica, salmonella or Schistosoma mansoni but in the later, ova are usually seen in the portal veins.

The aetiological spectrum of chronic active hepatitis extends further to include congenital diseases such as Wilson's disease³⁴ and alpha-1-antitrypsin deficiency³⁵ and drug reactions such as to methyl dopa, isoniazid and oxyphenisatin.

The autoimmune (lupoid) hepatitis is the other entity. Lupoid hepatitis occurs predominantly in young people especially females. There is a strong association with HLA B8 and DR3³⁶ and besides signs of chronic liver disease, other features like amenorrhea, cutaneous striae, acne and hirsutism may be seen. It may be associated with other autoimmune diseases like Hashimoto's thyroiditis, Coombs positive haemolytic anaemia, non deforming migratory polyarthrititis and glomerulitis. Progression to cirrhosis occurs in most instances within two years after onset. Immunological changes seen include the presence of high titre antibodies in serum³⁷. These are anti-nuclear antibody in 80%, smooth muscle antibody in 70% and anti-mitochondrial antibody in 30% of the patients. LE cell phenomenon has been described in 15% of patients¹.

The prevalence of autoantibodies in chronic liver disease varies with the geographical area studied. Autoantibodies were found in 55% of Australians compared to those from Asian countries where the prevalence was 0-14% in chronic liver diseases³⁸.

Autoimmune chronic liver disease is however infrequent in Kenyan Africans occurring in less than 4%^{39,40}. This compares with a study by Sadikali in Uganda⁴¹. Thus auto-immune type of chronic hepatitis vary in the prevalence among races.

In the last few years, chronic hepatitis has become a particularly important clinical entity since clinical trials⁴³⁻⁴⁵ have established that, in some cases, steroids therapy with or without azathioprine can prevent progression to cirrhosis and death from hepatic failure and that many patients have a completely benign form of chronic hepatitis which will not benefit from such treatment.

To date there is no published work done locally about the aetiopathogenesis of chronic hepatitis at Kenyatta National Hospital, hence this study.

AIMS AND OBJECTIVES

- a) To determine the aetiology of chronic hepatitis at Kenyatta National Hospital

- b) To study the clinico-pathological presentation of chronic hepatitis at Kenyatta National Hospital

MATERIALS AND METHODS.

A prospective study was carried out for a period of eight month's. The study was highly selective as only patients with chronic hepatitis as a histological diagnosis were included.

A detailed history was taken, noting in particular, previous history of jaundice, loss of weight, fever, previous history of transfusion, multiple injections, alcohol consumption including quantity and duration and history of ingestion of any of the relevant drugs. Alcohol consumption of more than 80 g per day was considered heavy consumption while consumption of less than 80 g was considered as moderate consumption. A duration of alcohol consumption greater than five years was taken to be associated with hepatotoxicity as is internationally agreed. The grading of weight loss into mild, moderate and severe was subjective and depended on patients observations on history.

Physical examination was done, noting the presence or absence of pallor, jaundice, wasting, hepatomegaly, splenomegaly, ascites and other signs of chronic liver disease such as finger clubbing, loss of pubic and axillary hair, testicular atrophy, gynaecomastia and spider naevi. Liver span of more than 12 cm was taken as hepatomegaly. The grading of jaundice into mild, moderate and severe was on clinical judgement. Mild, being a tinge of yellowness on the sclera. Moderate jaundice was deeper yellow on the sclera and yellowness of the tongue. Severe jaundice was yellowness of the sclera, tongue and skin.

Laboratory investigations included total blood counts, liver

function tests and prothrombin time index (P.T.I). Total blood counts were determined by coulter counter model 5 class V.

Aminotransferases were determined colorimetrically according to the method of Reitman and Frankel⁴⁹. Total serum proteins were determined colorimetrically by Biuret method⁵⁰ and serum albumin by BCG method⁵¹. Alkaline phosphatase levels were determined by King Armstrong method while total bilirubin was determined by Van den Bergh reaction.

Immunological studies for HBsAg, anti-HBs, anti-HBc, HBeAg and anti-HBe, anti-nuclear, smooth muscle and anti-mitochondrial antibodies were also carried out. HBsAg was determined by reverse passive haemoagglutination test (INST OF IMMUNOL- JAPAN) and by Elisa (ABBOT). HBeAg and anti-HBe were determined by enzyme immuno-assay (ABBOT) while autoantibodies were determined by immunofluorescence method as described by Roitt⁵². Stool examination by direct microscopy was done to rule out Entamoeba Histolytica and Schistosoma mansoni infections done.

Liver biopsy was done by Menghini procedure⁴⁶. Liver tissues were fixed in 10% formalin. Sections cut on to slides were stained with haematoxylin and eosin, Manson's trichome, Orcein, Periodic acid Schiff (P.A.S.) and P.A.S. after diastase digestion where it was indicated. Staining for iron and reticulin was also done.

Other features looked for on histology, were evidence of alcoholic liver disease such as Mallory hyaline, fatty changes, ballooning and central vein sclerosis.

Results.

Clinical data.

A total of 16 patients were studied.

The ages of patients studied ranged from 11 years to 59 years with a mean age of 33 years. The frequency distribution of the ages of patients are shown in figure 1. The male to female ratio was 1.2:1.

Fourteen(87.5%) of the patients had non specific symptoms such as fatigue , anorexia and nausea while 11(68.7%) patients reported weight loss; of these only four(36.3%) patients were wasted .

Five(31%) of the patients studied had a previous history of jaundice but were not clinically jaundiced at the time of examination. Nine(56.2%) of the patients had persistent or recurrent jaundice. While in two(12.5%) patients, no previous history of jaundice was elicited.

Only one patient (6.8%) had a history of blood transfusion, this being within a period of less than one year of development symptoms. Eleven(68.7%) of the patients gave no history of alcohol ingestion. Three(18.7) patients had a history of significant alcohol ingestion. There was no history of ingestion of any of the drugs which are implicated in causation of chronic liver disease in any patients.

Prominent clinical findings were hepatomegaly in 13(81.2%)

of the patients and jaundice in ten (62.5%) patients. Splenomegaly alone was not a feature, neither were finger clubbing, loss of pubic and axillary hair, spider naevi and gynaecomastia.

Ascites of mild to moderate degree was found in seven(43.7%) patients. Table 5 shows that recurrent jaundice, weight loss, hepatomegaly and ascites were more frequent in patients with chronic active than with chronic persistent hepatitis. However this was not statistically significant.

Laboratory data.

The mean values for all the liver function tests and the percentages of patients with abnormality, were greater in patients with chronic active hepatitis than in patients with chronic persistent hepatitis. Only serum globulin levels were statistically significant.

Stool examination was negative for Schistosoma mansoni ova and Entamoeba Histolytica trophozoites.

HBsAg was found in serum in only four(25%) patients by both reverse passive haemoagglutination test and Elisa. The proportions of HBsAg was 42.8% in chronic persistent hepatitis and 11.1% in chronic active hepatitis.

Table 9(A) and (B) show the hepatitis B markers in chronic hepatitis: Twelve of the 16 patients had at least one marker. Three of the patients with CPH and one of the two patients CAH with cirrhosis had HBsAg in the sera, while two patients with CPH who were HBsAg negative had anti-HBc in the sera. So anti-HBc in

the HBsAg negative patients was evidence for chronic HBV infection in two(16.7%) patients. Of the six patients who had evidence of chronic HBV infection, five had anti-HBe while one had HBeAg.

Auto-antibodies were found in two of the nine patients with chronic active hepatitis. Both patients were female and HBsAg negative. In one patient all the three autoantibodies (ANA SMA AMA) were found while in the other patients, only SMA was found. The titre of 1:80 was used.

Histological data.

The biopsies of seven patients (four males) were classified as chronic persistent hepatitis while the remaining nine (five males), satisfied the histological criteria of chronic active hepatitis, two of which had co-existent liver cirrhosis. No patient with chronic lobular hepatitis was reported.

In three of the four patients with alcohol related liver disease, there was demonstrable iron staining on the histological sections and in one, there was additional steatosis and ballooning; features of alcoholic liver disease. In one patient chronic active hepatitis was co-existing with liver cirrhosis. There were no characteristic features of alcoholic liver disease such as Mallory hyaline and hepatic venular sclerosis.

Bile retention was present on four histological sections all of which had chronic active hepatitis.

Orcein staining was done on eight of the histological sections including four of the six sections of patients with

evidence of HBV infection and was negative on all the sections.

No positive globules were found on the histological sections on P.A.S staining and P.A.S after diastase digestion. In none of the histological sections was ova of Schistosoma mansoni seen.

Aetiological spectrum.

In chronic persistent hepatitis, hepatitis B viral infection was a prominent aetiological factor, with evidence of infection in five (71.4%) of the seven patients. In one of these patients there was a history of significant alcohol ingestion.

In chronic active hepatitis, hepatitis B viral infection contributed in one(11.1%) patient, alcohol in three (33.3%) while lupoid (auto-immune) hepatitis in two (22.2%) patients. Drugs implicated in causing chronic hepatitis and alpha-1-anti trypsin deficiency were not causative factors.

Wilson's disease was not adequately investigated for, however in the three patients with chronic active hepatitis whose cause was not found, slit lamp microscopic examination for Kayser Fleischer rings in the cornea was negative.

TABLE 1: Chronic hepatitis as a histological diagnosis in patients with the clinical diagnosis according to sex.

| Sex | No. of patients with +ve histology | No. of patients with -ve histology | Total |
|--------|------------------------------------|------------------------------------|-------|
| Male | 9 | 10 | 19 |
| Female | 7 | 4 | 11 |
| Total | 16 | 14 | 30 |

The table shows that only 16 (53.3%) of the 30 patients with a clinical diagnosis of chronic hepatitis had a compatible histological diagnosis. Nine (56.3%) of the 16 patients were males.

FIG 1: AGE DISTRIBUTION OF PATIENTS WITH CHRONIC HEPATITIS

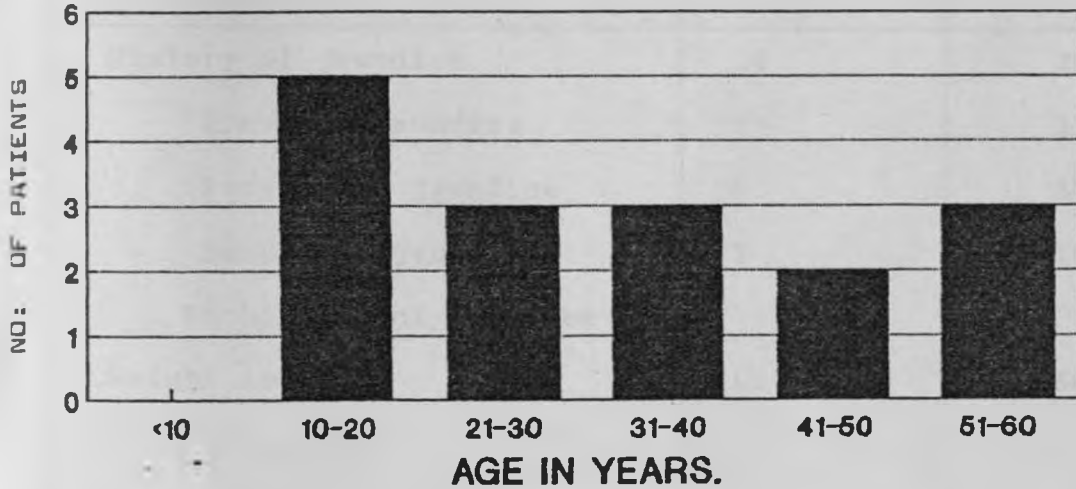


FIG. 1 shows the age distribution of 16 patients with chronic hepatitis. Most patients were young. 68.7% being less than 40 years.

TABLE 2: Symptomatic presentation and important features in history in 16 patients.

| Features | Number of patients | % of total |
|------------------------------|--------------------|------------|
| History of jaundice | 14 | 87.5 |
| Previous jaundice | 5 | 31.2 |
| Persistent jaundice | 6 | 37.5 |
| Recurrent jaundice | 3 | 18.7 |
| No history of jaundice (2) | | |
| Weight loss | 11 | 68.8 |
| None (5) | | |
| Mild | 8 | 50.0 |
| Moderate | 3 | 18.8 |
| Severe | Nil | Nil |
| Anorexia | 7 | 43.7 |
| Fatigue | 7 | 43.7 |
| History of alcohol ingestion | 5 | 31.3 |
| None (11) | | |
| <80g/day | 2 | 12.5 |
| >80g/day | 3 | 18.7 |
| Fever | 2 | 12.5 |
| History of transfusion | 1 | 6.0 |
| Multiple injections | Nil | Nil |
| Relevant drug ingestion | Nil | Nil |

Table 2 shows that jaundice and non specific symptoms such as weight loss, fatigue and anorexia were prominent features.

TABLE 3: Findings on physical examination.

| Feature | Number of patients | % of total |
|-----------------------------|--------------------|------------|
| Jaudice | 10 | 62.5 |
| None (6) | | |
| Mild | 8 | 50.0 |
| Moderate | 2 | 12.5 |
| Severe | Nil | Nil |
| Hepatomegaly alone | 10 | 62.5 |
| Ascites | 7 | 43.7 |
| Wasting | 4 | 25 |
| Hepatosplenomegaly | 3 | 18.5 |
| Pallor | 3 | 18.5 |
| Finger clubbing | Nil | Nil |
| Spider naevi | Nil | Nil |
| Loss of pubic/axillary hair | Nil | Nil |
| Gynaecomastia | Nil | Nil |

Table 3 shows hepatomegaly and jaundice to be the commonest presenting signs in chronic hepatitis.

TABLE 4: Frequency distribution of the histological types.

| Type | Number(%) |
|---|-----------|
| Chronic persistent hepatitis | 7(43.7) |
| Chronic lobular hepatitis | Nil |
| Chronic active hepatitis | 7(43.7) |
| Chronic active hepatitis with cirrhosis | 2(12.5) |
| Total | 16(100) |

Nine (56.2%) of the patients had chronic active hepatitis with or without cirrhosis while seven (43.7%) had chronic persistent hepatitis.

TABLE 5: The frequency of clinical features in the different histological types.

| Features | CPH n=7 (% of patients) | CAH n=9 (% of patients) |
|-----------------------------|----------------------------|----------------------------|
| <u>Symptoms</u> | | |
| Persistent jaundice | 42.8 | 33.3 |
| Recurrent jaundice | 14.2 | 22.2 |
| Fever, anorexia and fatigue | 57.1 | 33.3 |
| Weight loss | 28.5 | 55.6 |
| History of transfusion | 14.2 | Nil |
| <u>Signs</u> | | |
| Presence of jaundice | 57.1 | 55.6 |
| Hepatomegaly | 42.8 | 55.6 |
| Hepatosplenomegaly | 28.5 | 11.1 |
| Ascites | 28.5 | 55.6 |

Table 5 shows that recurrent jaundice, weight loss, hepatomegaly and ascites were more frequent in patients with CAH than CPH. However, this was not statistically significant.

TABLE 6: Liver function tests in chronic persistent hepatitis.

| Test | Mean | Standard deviation | Normal for laboratory | Percentage of patients with abnormality |
|--------------------------------|------|--------------------|-----------------------|---|
| Bilirubin (µmol/L) | 37.1 | 35.9 | 3-21 | 57.0 |
| AST (Units/L) | 47.3 | 22.6 | <40 | 57.0 |
| ALT (Units/L) | 30.6 | 19.9 | <45 | 28.5 |
| Albumin (g/L) | 33.1 | 6.1 | 32-52 | 57.0 |
| Globulin (g/l) | 33.7 | -- | -- | -- |
| Alkaline Phosphate (K.A.Units) | 17.0 | 11.00 | 2-14 | 28.5 |
| P.T.I. (%) | 97.1 | 10.5 | | -- |

Table 7: Liver functions tests in chronic active hepatitis:

| Test | Mean | Standard deviation | Normal for laboratory | Percentage of patients with abnormality |
|-----------------------------------|-------|--------------------|-----------------------|---|
| Bilirubin (µMol/L) | 22.0 | 217.6 | 3-21 | 66.6 |
| AST (Units/L) | 83.4 | 56.2 | <40 | 77.7 |
| ALT (Units/L) | 59.0 | 40.4 | <45 | 66.6 |
| Albumin (g/L) | 32.00 | 9.7 | 32-52 | 66.6 |
| Globulin (g/L) | 48.00 | -- | -- | -- |
| Alkaline Phosphatase (K.A. Units) | 18.2 | 11.2 | 2-14 | 44.4 |
| P.T.I. (%) | 86.4 | 11.8 | -- | -- |

Tables 6 and 7 show that both the mean values for the liver function tests which were evaluated and the percentages of patients with abnormality were higher in CAH than CPH. However, only serum globulin levels were statistically significant ($P < 0.02$).

Table 8: Frequency of HBsAg in Sera in the different histological types.

| Type | No. of Sera | No positive of for HBsAg (%) |
|--|-------------|------------------------------|
| Chronic persistent hepatitis | 7 | 3(42.8) |
| Chronic active hepatitis with or without cirrhosis | 9 | 1(11.1) |
| TOTAL | 16 | 4(25.0) |

Table 8 shows that four (25%) of the 16 patients were HBsAg positive.

Table 9 (A): Hepatitis B markers in chronic hepatitis.

| Type of CLD / hepatitis markers | HBsAg | Anti-HBs | Anti-HBc | HBeAg | Anti-HBe |
|---------------------------------|-------|----------|----------|-------|----------|
| CPH n=7 | 3 | 1 | 6 | 1 | 4 |
| CAH n=7 | Nil | 4 | 4 | - | - |
| CAH with cirrhosis n=2 | 1 | 1 | 2 | Nil | 1 |

Table 9(B):

| Type of CLD Hepatitis markers | HBsAg + Anti-HBc | Anti-HBs + Anti-HBc | Anti-HBc (without HBsAg or Anti-HBs) | HBeAg | anti-Hbe |
|----------------------------------|------------------------|---------------------------|---|-------|----------|
| CPH n=7 | 3 | 1 | 2 | 1 | 4 |
| CAH N=7 | Nil | 4 | Nil | - | - |
| CAH c Cirrhosis N=2 | 1 | 1 | Nil | Nil | 1 |

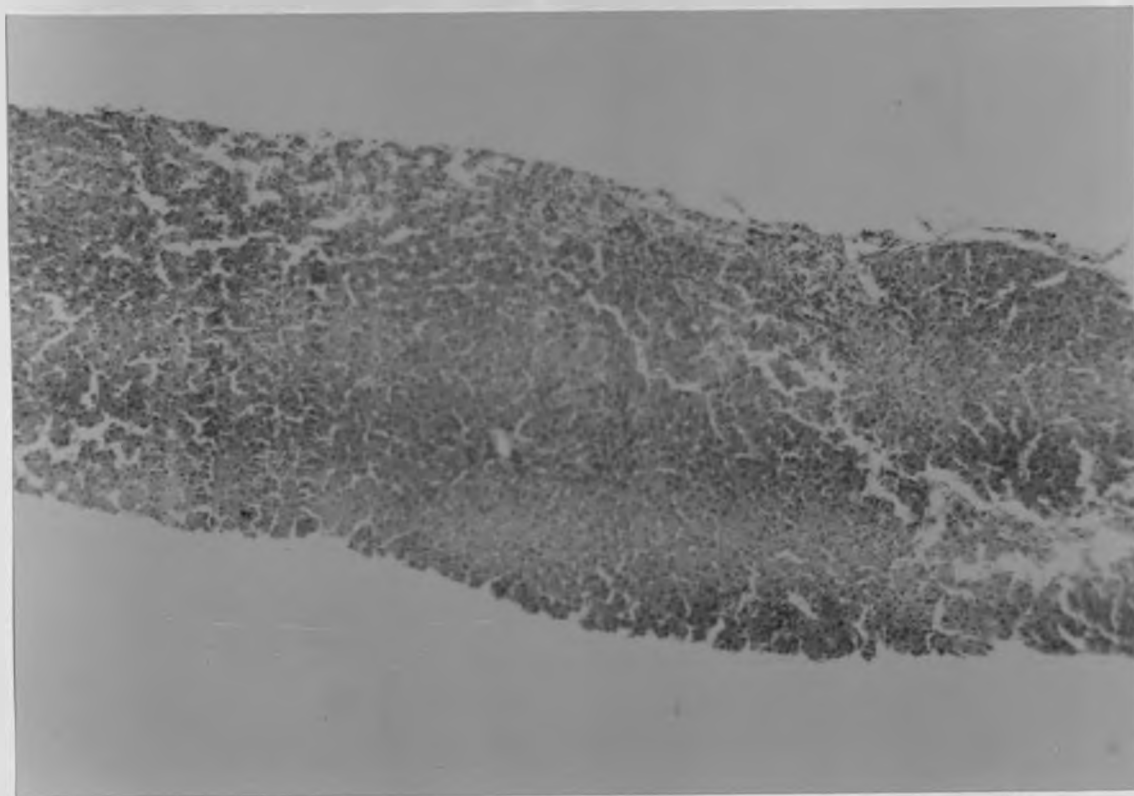
Tables 9A and B show that if HBsAg and anti-HBc (in the HBsAg -ve) are used as markers of chronic HBV infection, six (37.5%) of the 16 patients are chronic HBV carriers.

TABLE 10: Distribution of chronic persistent and chronic active hepatitis according to aetiology

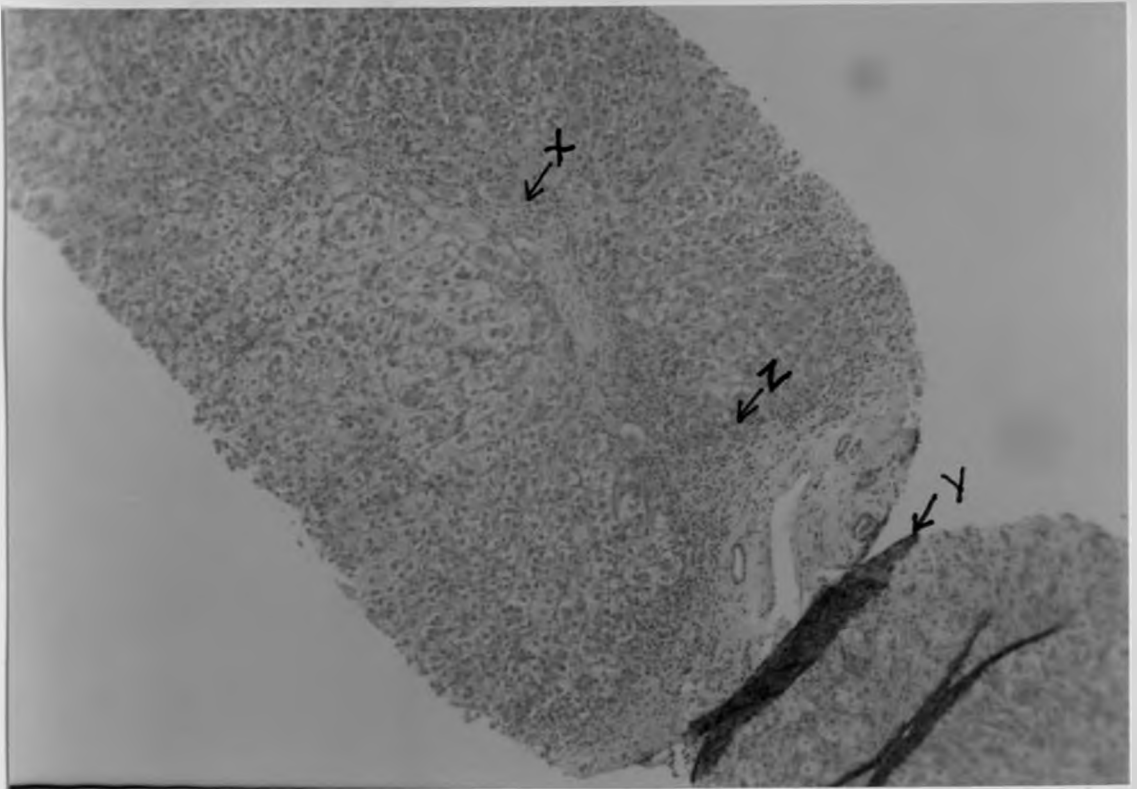
| Aetiology | CPH NO (%) | CAH NO (%) |
|--|---------------|---------------|
| Hepatitis B virus | 5 (71.4) | 1 (11.1) |
| Alcohol | Nil | 3 (33.3) |
| Auto immune | - | 2 (22.2) |
| Drug related (Drugs implicated in chronic hepatitis) | - | Nil |
| Alpha-1-anti trypsin deficiency | - | Nil |
| Idiopathic | 2 (28.5) | 3 (33.3) |
| Total | 7 (100) | 9 (100) |

Table 10 shows that hepatitis B virus was the commonest cause in chronic persistent hepatitis while alcohol was the commonest in chronic active hepatitis.

PHOTOGRAPH 1 Showing features of chronic persistent hepatitis.
(H/E, X40)



PHOTOGRAPH 2 Showing features of chronic active hepatitis.
(H/E, x40)



Note

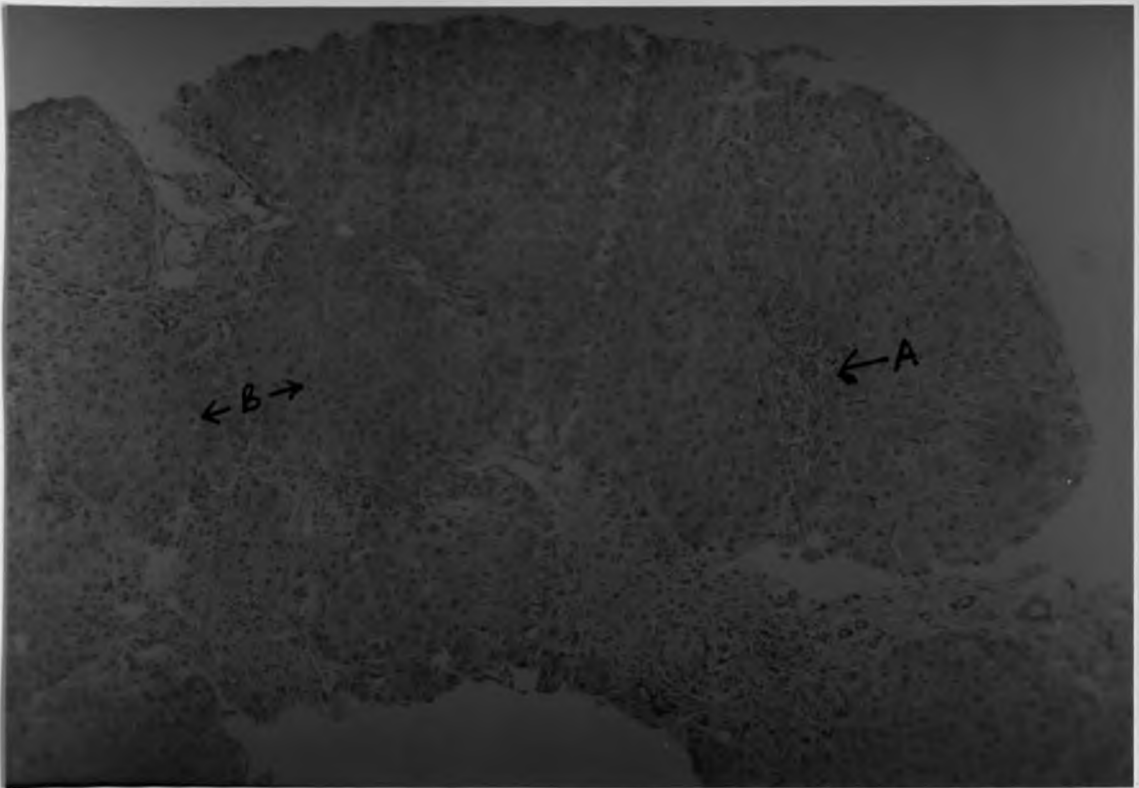
Arrow X - Shows bridging necrosis.

Arrow Z - Shows piecemeal necrosis.

Arrow Y - Shows an artefact.

PHOTOGRAPH 3 Showing features of chronic active hepatitis with cirrhosis.

(H/E, x40)



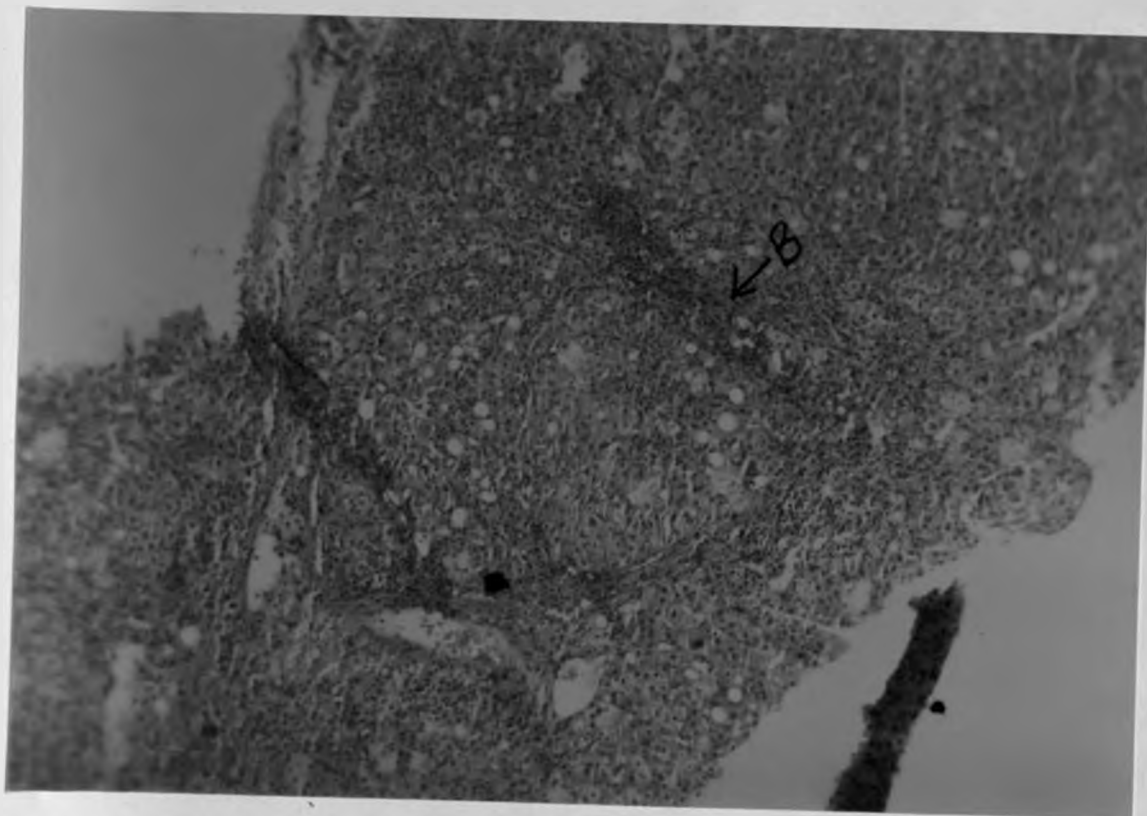
Note

Piecemeal necrosis (Arrow A) co-existing with liver cirrhosis.

Arrows B show liver nodules.

PHOTOGRAPH 4 Showing features of alcoholic chronic active hepatitis.

(H/E, x40)



Note

Marked steatosis with bridging necrosis (Arrow B)

Discussion

Chronic hepatitis has become an important entity in the last few years, since some patients have the benign forms (chronic persistent hepatitis and chronic lobular hepatitis) while others have a more aggressive form (chronic active hepatitis), which in some, clinical trials⁴³⁻⁴⁵ have established the benefits of steroid therapy.

Clinical presentation is varied and ranges from asymptomatic patients with biochemical abnormalities to hepatocellular jaundice, hepatosplenomegaly and features of chronic liver disease such that a definite diagnosis can only be made on histology.

Aetiology varies in different geographical areas. HBV and auto-immune hepatitis are considered the major aetiological factors. However, alcohol, drugs and congenital diseases play a role.

In Kenya, HBV plays a major role since the HBsAg carrier rate is high, ranging from 5-14% depending on the method used. While auto-immune hepatitis is rare.^{39,40}

In the present study, only chronic persistent and chronic active hepatitis were seen. Clinical presentation varied in the two forms. Fourteen (87.5%) patients had an initial attack clinically like acute viral hepatitis, either in the past or with persistence of symptoms beyond six months. However, this was not a distinguishing feature between the two forms, since it occurred

in equal frequencies. Recurrent jaundice was a feature of both forms as has been noted previously.^{4,1} Chronic hepatitis may not necessarily be preceded by a clinically recognizable acute episode. This was noted in two (12.5%) of the 16 patients studied.

The degree of jaundice, symptoms of fatigue and anorexia and hepatomegaly were however milder in chronic persistent than in chronic active hepatitis. This is comparable to findings by Backer et al.⁴ The observation that splenomegaly was more associated with chronic persistent hepatitis than chronic active hepatitis can not be explained. It is possible that splenomegaly might have been due to other causes.

Two patients with histological features consistent with chronic persistent hepatitis had ascites, these results are inconsistent with previous reports.^{1,4} One patient was a young man, with HBsAg in serum and a history of heavy alcohol ingestion with malnutrition. The latter may have been a contributing factor to the presence of ascites and oedema. In the second patient, the presence of ascites can not be explained and patient will need longer follow up with repeated needle biopsies to determine progress.

In this study, males predominated in both forms of chronic hepatitis. The predominance of males in chronic active hepatitis may be due to the observation that auto-immune hepatitis is infrequent in Kenyan Africans,^{39,40} while the predominance of male in chronic persistent hepatitis is in keeping with previous observations.^{1,4}

Chronic active hepatitis may co-exist with cirrhosis on autopsy at time of presentation.^{47,11} This was seen in 12.5% of patients.

The mean values of serum bilirubin, aminotransferases and globulin and the percentages of patients with abnormality were higher in chronic active than in chronic persistent hepatitis. Only serum globulin levels were statistically significant ($P < 0.02$).

Although the P.T.I in chronic active hepatitis was lower than in chronic persistent hepatitis, it was not altered to a degree where aspiration biopsy proved hazardous.

Distosoma mansoni ova were not seen on stool examination. Rectal snips were not done routinely since the ova were looked for in liver histology, the latter being more specific since the presence of ova in stool and on rectal snips may just be an association rather than a causal relationship.

The prevalence of 25% of HBsAg in patients with chronic hepatitis is comparable with studies done in Switzerland²⁰ and²¹ but in England, Denmark and Australia the incidence was lower. The studies did not show a persistent pattern of the presence of HBsAg positivity in chronic persistent and chronic active hepatitis. In the present study, HBsAg was found in three of the patients with chronic persistent and in one of the nine patients with chronic active hepatitis.

Hoofnagle et al²⁶ suggested that anti-HBc in the HBsAg negative was another sensitive indicator of HBV replication. Studies by Gerber et al²⁷ in the U.S.A. and Bories et al²⁸ found anti-HBc in 21% and 40% in HBsAg negative patients. In the present study, anti-HBc was found in two (16.6%) of the 12 HBsAg negative patients.

Of the six patients who had evidence of chronic HBV infection, only one patient was highly infective. The rest had low infectivity as evidenced by presence of anti-HBe. The results can be explained by the observations that in four of these patients the initial acute attack had occurred 4-12 years before this study, hence the sero-conversion from HBeAg to anti-HBe. In one of the patients with chronic active hepatitis with coexisting cirrhosis the presence of anti-HBe, makes the follow up of the patient mandatory since malignancy may originate in the clones of cells where viral DNA integrates into host DNA.

In the past, alcohol has been recognized as a causative factor in chronic hepatitis.^{1,32,33} The quantity and duration of ingestion are important for development of alcoholic hepatitis. Mechanisms have been suggested to explain the association between chronic alcoholism and chronic hepatitis.³² In this study, a quarter of the patients had a history of alcoholism. Evidence of alcoholic liver disease like liver cell ballooning and steatosis were seen on histology in only one patient. However, demonstrable iron staining was seen in three of the four patients. These observations are comparable to previous observations,^{40,33} that

characteristic histological features of alcoholic liver disease may not be seen and that haemosiderosis could be used as a histological feature. In one patient in whom balloon degeneration, steatosis and sclerosis were not seen on histology, the demonstration of HBsAg in serum is likely to influence the development of the liver disease.

Studies of caucasian population^{38,49} have shown that a large, though variable, proportion of HBsAg negative cases possess autoantibody markers associated with lupoid hepatitis. However studies done in Kenya³⁹ and Uganda⁴¹ did not confirm this, neither has this study. In fact there was no difference between this study group and the controls which have been studied in the past.³⁹

In this study the role of non A non B is not determined. In the patient with a previous history of transfusion, there was ant-HBc demonstrated in the serum. In this study, there is absence of drug induced chronic hepatitis. Most drugs implicated as a cause of chronic hepatitis are widely used at Kenyatta hospital, and it can only be assumed that the mechanisms leading to the development of hepatitis may be absent in the hospital.

In the three patients with chronic active hepatitis where there was no causal relationship, the absence of Kayser Fleischer rings in the cornea does not rule out Wilson's disease and rubeinic acid staining for liver copper is essential.

Conclusion

Non specific symptoms such as anorexia, fatigue and weight loss, jaundice and hepatomegaly were the main presenting features in chronic hepatitis. However, neither these features, nor the laboratory features could differentiate between the two forms of chronic hepatitis.

Hepatitis B virus was the commonest cause of chronic hepatitis. Alcohol and lupoid hepatitis contributed in a few cases. However in a proportion of cases no apparent cause could be found and in these Wilson's disease and Non A,non B hepatitis could not be ruled out.

Recommendations

1. Histological confirmatory diagnosis of chronic hepatitis is still essential since there are neither clinical nor laboratory features which are confirmatory.
2. In patients management and in determining prognosis, it is important to have histological categorisation, clinical features and aetiological agents of chronic hepatitis considered together.
3. Since six of the 11 patients with identifiable causes were due to HBV, Immunization against the virus is recommended.
4. A larger study would be necessary to make more definite conclusions as to the possible aetiological factors.

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