THE COURSE OF CHRONIC ACTIVE HEPATITIS

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Summary

THIRTY-one patients with histologically diagnosed chronic active hepatitis were followed clinically, biochemically and histologically for a mean of 32.5 months. Nineteen patients were intravenous drug abusers. Eighteen patients showed histological improvement: of these 14 had hepatitis B virus (HBV) associated disease. Thirteen patients were unchanged or worse on repeat biopsy; 5 of these had HBV associated disease. The results of this study suggest that HBV associated chronic active hepatitis is a less severe disease with a better prognosis than non HBV disease.

Introduction

Chronic active hepatitis was traditionally believed to be a disease with a poor prognosis, and if untreated a life expectancy of about 5 years (MacKay and Wood, 1962; Bearn, Knuckel and Slater, 1956). Subsequent work proved this to be untrue of hepatitis B virus (HBV) associated chronic active hepatitis which was found to have a better prognosis (Sherlock, 1974). In this study, we report the clinical, biochemical and histological prognosis in 31 patients with chronic active hepatitis followed for between 6 and 84 months.

Patients and Methods

Patients were selected for inclusion in this study on the basis of a histological diagnosis of chronic active hepatitis and having had at least one biopsy 6 or more months following the initial biopsy. There were 19 drug abusing patients who were referred from the Drug Advisory and Treatment Centre, and 12 non drug abusing patients who were attending the Department of Medicine and Gastroenterology.

Each patient was examined for stigmata of chronic liver disease and in drug abusing patients stigmata of such abuse was sought.

Each patient had blood taken for estimation of haemoglobin, white cell count, platelet count, prothrombin time, serum aspartate, transaminase (SGPT) alkaline phosphatase, bilirubin, total serum proteins, serum albumin, immunoglobulins, IgG, IgA, IgM, anti-nuclear factor, anti-mitochondrial antibody and smooth muscle antibody. The presence of hepatitis B surface antigen (HB_sAg) and antibody (anti HB_s was sought.

Liver biopsy was performed following informed consent. Histological diagnosis was made according to the criteria suggested in a Review by an International Group (1977) in which the classification of DeGroote and his colleagues (1968) was modified and extended. Chronic active hepatitis was therefore defined as “a chronic inflammatory and fibrosing lesion of the liver, of varied aetiology and varied histological features. The features common to all untreated examples are: piecemeal necrosis together with new fibre formation and lymphocyte infiltration of the portal tracts and lobules. Other infiltrating cells may be found and features of acute hepatitis may be superimposed. Passive septae formed after bridging or multilobular liver cell necrosis may be present. Cirrhosis is not a defining criterion, but may develop”.

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Following diagnosis patients were treated either with prednisolone 10mg daily and azothiaprine 50mg daily (Summerskill *et al,* 1975) or (7 drug abusing patients) sulphasalazine 1g 3 times daily (Fielding, Arthurs and Doyle, 1982).

Patients were reviewed at regular intervals on an out-patient basis and after 6 or more months, one or more repeat liver biopsies were performed. Chronic active hepatitis, chronic persistent hepatitis and cirrhosis were diagnosed according to the criteria of an International Group (1977). Minor changes were said to be present if there was mild swelling of the portal tracts with excess cellular infiltrate with or without foci of hepatocellular necrosis.

Results

Thirty-one patients were studied, 22 male and 9 female whose ages ranged from 12 to 60 (mean 30.5) years. The duration of follow-up was 6 to 84 (mean 32.5) months. Nineteen patients were known intravenous drug abusers. Eight patients had a past history of jaundice between 6 months and 20 years before diagnosis. Twenty-one patients presented initially with jaundice. One had recurrent episodes of jaundice and 2 were never jaundiced.

On examination 16 patients had stigmata of chronic liver disease. Ten patients had hepatomegaly, one also had splenomegaly. Six patients had palmar erythema, 5 had spider naevi, and one had Dupuytren's contractures. Eighteen drug abusing patients had markings compatible with intravenous abuse.

Nineteen patients were HB_sAg positive and 12 were HB_sAg and anti HB_s negative (Table I). Transaminase levels were normal in only 2 patients at diagnosis and at the end of 12 months in 8 of 25 patients followed for at least one year. In 4 of the 6 patients followed for 6 months levels had returned to normal at the end of this time (Tables II and III). Ten patients had elevated immunoglobulins (Table IV). Total serum proteins were elevated above 80g/l in 5 patients.

TABLE I

Patient group	HB_sAg Positive	HB_sAg and anti HB_s negative
Drug abusers (9)	15	4
Non abusers (12)	4	8
TOTAL	19	12

HB_sAg and anti HB_s status in patients with CAH.

A total of 92 liver biopsies were carried out in these patients. Two patients had 6 biopsies, 2 and 5, 3 hand 4, 10 had 3 and 14 had 2 biopsies. The histological

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TABLE II

SGPT level IU/I (N = <45)	Diagnosis	Twelvemonths
<45	2	8
45- 99	2	14
100- 299	7	2
300- 499	4	1
500- 999	3	
1000-3000	7	

SGPT levels at diagnosis and 12 months in 25 patients followed for over a year.

TABLE III

SGPT level IU/I (N = <45)	Diagnosis	Six months
<45		4
45- 99		2
100- 299		
300- 499	1	
500- 999	1	
1000-3000	4	

SGPT levels in 6 patients followed for 6 months.

TABLE IV

Patient group	No. with abnormal immunoglobulins	IgG N= 90-200 IU/ml	IgM (55-285 IU/ml)	IgA (40-315 IU/ml)
Drug abusers (19)	3	1	3	1
Non abusers (12)	7	4	3	3

Abnormal immunoglobulins in drug abusers and non abusers.

progression is tabulated separately for the HBV positive and HBV negative patients in Tables V and VI.

Two patients developed jaundice during the course of follow-up and 2 patients developed Cushingoid facies; otherwise patients remained clinically well.

Discussion

The evolution of chronic active hepatitis in 31 patients was studied. Nineteen patients had HBV associated disease (Table I). It is possible that the drug abusing patients who were HB_sAg negative may have had chronic liver disease associated with non A and non B viruses as these viruses have been implicated as causal agents in chronic liver disease in parenteral drug abusers (Rakela and Redeker, 1979).

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The non abusing patients without evidence of HBV disease were predominantly female, had a higher frequency of abnormality of serum proteins; immunoglobulins, anti-nuclear factor and smooth muscle antibody were detected more frequently than in the drug abusing group. This would suggest that their disease was of the lupoid variety (Doniach *et at,* 1966).

Of the total group of patients 18 showed an overall histological improvement, 14 of these had HBV associated disease. Of the 13 patients who were unchanged or had deteriorated on repeat biopsy 5 had HBV associated disease.

Traditionally chronic active hepatitis was believed to have a poor prognosis with life expectancy of less than 5 years following diagnosis (Mackay and Wood, 1962; Bearn, Knukel and Slater, 1956), although these early reports would appear to be related to chronic active hepatitis of severe degree only.

Chronic active hepatitis associated with HBV is believed to have a better prognosis than the lupoid variety in which cirrhosis develops rapidly (Sherlock, 1974). The introduction of specific therapy has greatly altered the prognosis. The beneficial effects of steroids in chronic active hepatitis has been shown by numerous clinical trials (Cook *et al,* 1971, Soloway *et al,* 1972; Murray-Lyon *et al,* 1973; Summerskill *et al,* 1975). The majority of studies comparing the natural history of chronic active hepatitis with and without HBV appear to have been related to response to treatment. In 1976 Schalm and his colleagues compared the response of severe chronic active hepatitis with and without HB_sAg to prednisolone and found that HB_sAg related disease responded less well.

In their study of 74 patients followed for a median period of 45 months Dietrickson and Christofferson (1977) concluded that progression is slow and prognosis better in patients with HB_sAg related disease. The findings in this review would support that claim.

A long-term follow-up study of chronic active hepatitis was published in 1978 by DeGroote *et al.* Thirty-five patients,

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TABLE V
Histological evolution in 19 HBV positive patients.

First biopsy	Second biopsy	Third biopsy	Fourth biopsy	Fifth biopsy	Sixth biopsy
CAH	Minor changes	Minor changes			
CAH	Increased cellular activity and necrosis	CAH with early cirrhosis			
CAH with early cirrhosis	Less activity Less fibrosis	Minor changes	Minor changes		
CAH	CAH with less infiltrate Less necrosis				
CAH	Less activity	CPH			
CAH	CAH with virrhosis Less activity				
CAH	Less activity				
CAH	CAH more fibrosis	CAH less activity			
CAH	CAH less activity				
CAH	CAH less activity				
CAH	CAH less activity				
CAH with early cirrhosis	Improved				
CAH	CAH less activity				
CAH with cirrhosis	CAH with cirrhosis but less hepatocellular necrosis	Unchanged			
CAH with Cirrhosis	Increased Cellular infiltrate and increased necrosis	Unchanged	Further Progression in severity	Unchanged	No improvement
CAH with early cirrhosis	Increased fibrosis	CAH with Established cirrhosis	Unchanged		
CAH with cirrhosis	Persistance of Hepatocellular necrosis	CAH with cirrhosis and fatty infiltration			
CAH	CAH less activity				
CAH	CAH less activity				

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TABLE VI
Histological evolution in 12 HBV negative patients.

First biopsy	Second biopsy	Third biopsy	Fourth biopsy	Fifth biopsy	Sixth biopsy
CAH with early cirrhosis	Increased cellular infiltrate and fibrosis	CAH with cirrhosis and fatty infiltrate	Unchanged		
CAH	CAH less fibrosis Reduced Cellularity				
CAH with cirrhosis	CAH with cirrhosis	Decreased fibrosis but persistent hepatocellular necrosis	Improved minor changes	Minor changes	
CAH	CAH with cirrhosis	Unchanged			
CAH with early cirrhosis	CAH with established cirrhosis	Unchanged	Unchanged	Reduced cellularity and fibrosis	Improvement maintained
CAH with early cirrhosis	Less necrosis Less cellular infiltrate	Unchanged	Further reduction in activity	Less cellular infiltrate Less fibrosis	
CAH with cirrhosis	Unchanged				
CAH with early cirrhosis and fatty infiltration	Unchanged				
CAH with early cirrhosis	Unchanged				
CAH	CAH				
CAH with early cirrhosis	Unchanged	Increased cellular infiltrate More hepatocellular necrosis			
CAH	CAH with early cirrhosis				

17 of whom were HB_sAg positive, were followed for up to 15 years (mean 87 months). All patients except one were treated with prednisolone and/or azothiaprine. After stopping therapy 13 patients relapsed; the majority of relapses were seen in HB_sAg positive patients. Two-thirds of HB_sAg positive patients developed cirrhosis between the second and fifth year of evolution compared with less than one-third of the HB_sAg negative group. Although the patients involved in that study of DeGroote and his colleagues (1978) compare closely with those in this review, the results do not. Our HB_sAg positive patients had a histologically less severe disease with less cirrhosis than the HB_sAg negative group.

The majority of drug abusing patients in our study who were treated with prednisolone and azothiaprine did not comply with therapy. Paradoxically this may have had a beneficial effect on the course of their disease, as a recent report suggests that prednisolone used to treat HB_sAg associated chronic active hepatitis may have a deleterious effect on the course of the disease (Lam *et at,* 1981).

Koretz *et at* (1980) pointed out that the most severe chronic active hepatitis is not associated with HBV and that the majority of patients seen by them had a less severe illness

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which was HBV related. Nevertheless the incidence of cirrhosis among those patients was 43%, comparable to the 45% initially reported in severely ill patients (Cook *et al,* 1971).

The results of this study would support the concept of HBV associated chronic active hepatitis being a less severe disease than non HBV associated chronic active hepatitis; with slower progression and a better prognosis.

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