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A Study of chronic Hepatitis in northern India

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ABSTRACT

Clinical, biochemical, immunological and morphological features of 16 patients of chronic hepatitis are reported. All the patients presented with persistent/progressive or recurrent hyperbilirubinaemia of more than 12 weeks. Hepatocellular failure with or without signs of portal hypertension, bleeding tendency and hepatic encephalopathy were other important clinical presentations. Serum alkaline phosphatase over 30 KAU was present in about one third of the patients. Study for hepatitis B antigen (HBAg) was positive in three fourth of the cases. Differences between HBAg positive chronic hepatitis observed in the present study and chronic active hepatitis described from the West have been highlighted. On the basis of morphological findings patients were categorised into portal and lobular hepatitis (4 cases), periportal and lobular (3 cases), chronic hepatitis undetermined type (2 cases) and cirrhosis of the liver with activity (7 cases). Progression from chronic hepatitis to cirrhosis of liver was documented by serial liver biopsies in 3 cases within 4 months to one and a half year after initial illness. The disease had an overall mortality of 37.5 per cent with poor response to steroid therapy.

INTRODUCTION

Chronic hepatitis is defined as persistent or progressive liver disease characterised by clinical, biochemical and morphological evidences of hepatic dysfunction of more than three months duration (Mistilis and Blackburn, 1967; Sherlock, 1972; Murray Lyon *et al.,* 1973). Chronic hepatitis is of two types: chronic persistent hepatitis and chronic aggressive (active) hepatitis. Chronic persistent hepatitis is a benign condition characterised by malaise, fluctuating transaminase levels and portal hepatitis on histology. Chronic aggressive hepatitis, on the other hand, is a more serious disease with progression to cirrhosis liver in more than 50 per cent cases within 5 years. There is marked derangement of liver functions and periportal hepatitis with or without lobular hepatitis on histology. When systemic manifestations like acne, skin rashes, ulcerative colitis and Sjogren syndrome are present the term 'chronic active hepatitis' is used. In the absence of such manifestations the condition is called chronic persistent hepatitis. The object of the present study was to characterise the clinical, biochemical, immunological, morphologic features and natural history of chronic hepatitis as seen in northern India and to study its association with hepatitis B antigen.

MATERIAL AND METHODS

Sixteen patients presenting with persistent/progressive hepatocellular (non-surgical) jaundice of more than 12 weeks were taken up for the present study. All the cases were admitted to All-India Institute of Medical Sciences (A.I.I.M.S.) Hospital during July 1971 to December, 1973. Detailed clinical, biochemical and immunological study was done and recorded on a pre-planned proforma. Follow-up record was maintained in the liver clinic of the Department of Gastroenterology.

Standard techniques were used for routine haematological and biochemical tests. Serum transaminases were estimated by the method of Reitman and Frankel (1957).

Australia antigen and antibody were studied by agar gel diffusion (AGD) counterelectrophoresis (CEP) and sandwich solid phase radio immunoassay (RIA), employing the techniques described by Blumberg *et al.* (1970); Pesendorfer *et al.* (1970); and Walsh *et al.* (1970) respectively. Test for LE cell was done in all the cases. Antinuclear factor was tested by immunofluorescence technique (Holborrow, 1970). Aspiration liver biopsy was carried out using Klatskin aspiration needle. Haematoxylin, eosin and reticulin staining were used for detailed morphological study. The histological criteria described by Degroote *et al.* (1968) were employed for the diagnosis of chronic hepatitis.

RESULTS

Age and sex distribution: There were 12 males and 4 females. Age at the onset of the disease varied from 28 years to 73 years. The disease was observed after the age of 50 in 8 cases. The onset of illness was abrupt resembling acute viral hepatitis in 6 cases, while in the remaining 10 cases the onset was insidious.

Clinical features: Varying degree of clinical icterus was present in all the cases. Other important clinical features were hepatomegaly, splenomegaly, ascites, bleeding tendency spider angiomas and encephalopathy (Table I).

Table I: Clinical features at the onset and during the course of illness

		Clinical features*	Percentage
Jaundice	Persistent	11	70
	Recurrent	5	30
Palpable liver		11	66.6
Splenomegaly		12	63.3
Ascites		8	56.6
Bleeding tendency		7	36.6
Hepatic coma		6	40.0
Spider angioma		4	33.3
Palmar erythema		3	30.0
Fever		3	40.0
Chronic diarrhoea		2	16.6

* Total No. of cases = 16

Past history of jaundice was recorded in 8 patients, history of injections in 11, blood transfusion in 4 and surgical interference in two cases. Hepatitis B antigen was positive in 6 cases who had past history of jaundice, 7 with history of injections and two each with history of blood transfusions and surgical interference.

History of Diabetes Mellitus was present in 2 patients and pulmonary tuberculosis in one case. Both the diabetic patients gave history of having taken oral hypoglycaemic drugs. The case of pulmonary tuberculosis was on anti-tubercular treatment *viz*. streptomycin and isonicotinic acid hydrazide. Hepatitis B antigen was positive in one of the patients of Diabetes Mellitus and also in the patient of pulmonary tuberculosis.

The biochemical profile is presented in Table II, which shows the mean value at the onset as well as the highest and lowest values during the course of the disease. Varying degree of hyperbilirubinaemia was noted in all the cases (over 20 mg. per cent during the peak period in 3 cases), Hypoalbuminaemia of less than 2.7 g per cent was noted during the course of the illness in 4 cases only. Serum globulin of more than 3.1 g per cent was observed in three fourth of the cases, but extreme degree of hyperglobulinaemia (serum globulin over 6.0 g per cent) was not seen in any of the patients. Serum transaminases were significantly elevated in all the cases at the onset of the illness which persisted in two thirds of them during the course of the disease. Mean highest value of

alkaline phosphatase during the course of the illness was 31.85 KAU, being more than 30 KAU, in 6 patients.

Table II: Results of conventional liver function tests

	At onset		During course of disease		
	No. of patients	Mean value	No. of patients	Mean highest figure	Mean lowest figure
Total serum bilirubin (mg%)	16	6.35	16	8.75	2.46
Serum albumin (g%)	16	3.13	16	4.17	3.95
Serum globulin (g%)	16	3.58	16	3.62	3.16
Serum alkaline phosphatase (KAU)	16	22.26	16	31.85	15.81

Results of Australia antigen study are shown in Table III. Persistent antigenaemia (HBAg beyond 14 weeks) was present in 10 cases and transient antigenaemia in 2 patients. Two cases were positive for antibody to HBAg. Hepatitis antigen was negative by the most sensitive techniques in the remaining four cases. Results of subtyping of antigen showed *ayw* subtype in 6 cases and *adw* in the remaining 3 cases. Antinuclear factor was positive in only 2 cases. Of which one was positive for HBAg as well. Test for LE cell was negative in all the cases. Histology of the liver showed features of chronic portal and lobular hepatitis (Plate CXXXVII, Fig. 1) in 4 cases; chronic periportal and lobular hepatitis (Plate CXXXVIII, Fig. 2) in 3 cases and active cirrhosis of the liver (Plate CXXXIX, Fig. 3) in 7 cases. In 2 cases it was difficult to categorise the hepatic lesions to any definite group (Table IV).

Table III: Hepatitis B antigen (HBAg) in chronic hepatitis (16 cases)

Technique used		No. of positive cases
CEP		9
RIA		12
Antibody to HBAg		2
Subspecificity of HBAg	ayw (YW)	6
	Adw (DW)	3

Table IV: Morphological findings in chronic hepatitis (16 cases)

Morphologic features	No. of cases	Percentage
Portal and lobular hepatitis	4	25.0
Periportal and lobular hepatitis	3	18.8
Chronic hepatitis type undetermined	2	12.5
Cirrhosis of the liver with activity	7	43.7

Follow-up study showed that all the four cases (25 per cent) with persistent hepatitis recovered completely within one to one and half years. While 6 patients (37.5 per cent) with chronic aggressive hepatitis, chronic hepatitis of undetermined type and active cirrhosis of the liver ended fatally. Three of them died within six months of their illness. The remaining 6 cases (37.5 per cent) who survived had good response to steroid therapy. In 3 cases azathioprine in dosage of 100 mg per day was used in addition to steroid and supportive measures. Of the two hepatitis B antigen and antibody negative cases, one had chronic persistent hepatitis and recovered within 9 months whereas the other one developed active cirrhosis of the liver within two and half years.

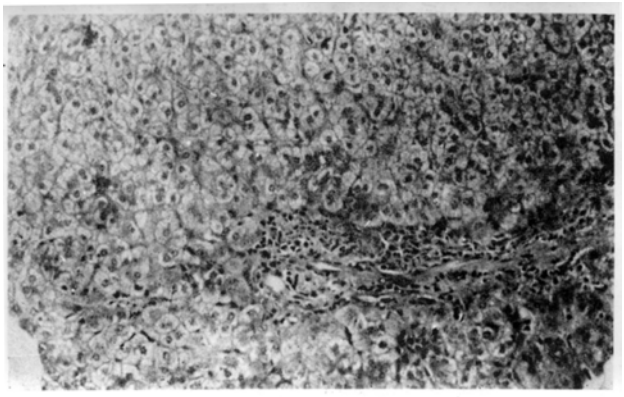

Fig. 1: Liver from a case of chronic persistent hepatitis showing mild degenerative changes, hypercellularity of portal tract with mononuclear cells and well preserved limiting plates x 10

DISCUSSION

The relationship between acute viral hepatitis, chronic hepatitis and cirrhosis liver has always been a controversial subject. Serial liver biopsy and autopsy data have shown progression from acute viral hepatitis to cirrhosis (Sherlock, 1948; Krarup and Roholm, 1941; Schaffer *et al.*, 1967; Kunkel and Labby, 1950; and Sherlock, 1970). The main argument against such a possibility is the reports of follow-up studies of epidemic hepatitis and acute infectious hepatitis, which fail to show progression to chronic liver disease (Zieve *et al.,* 1955; Neefe and Stokes, 1945; Chuttani *et al.,* 1966).

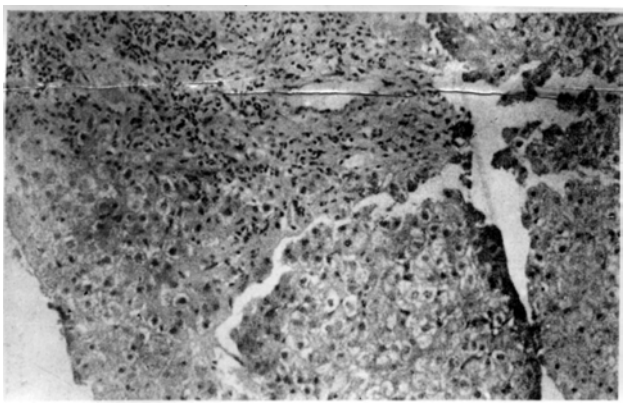

Fig. 2: Liver histology from a patient of HBAg positive chronic aggressive hepatitis showing lobular and periportal hepatitis, mononuclear cells infiltration of the portal tracts, disruption of limiting plates and piecemeal necrosis of the hepatocytes x 200.

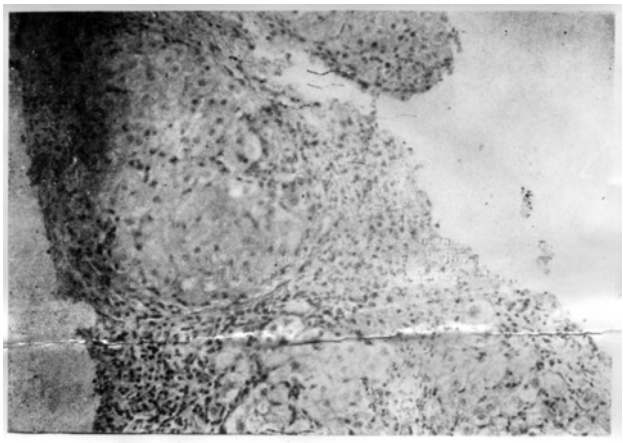

Fig. 3: Second liver biopsy 4 months after the first biopsy from a patient of HBAg positive chronic aggressive hepatitis showing well formed pseudolobules, thick fibrous band with active liver cell necrosis and degeneration. These findings are typical of cirrhosis of liver with chronic hepatitis x 100.

Past history of jaundice in patients of cirrhosis liver suggested the role of antecedent acute viral hepatitis in the aetiology of chronic liver disease. However, in the absence of definite serological and virological studies, it was not possible to document that the hepatitis was viral in aetiology. Study of Australia antigen, an immunological marker of virus B antigen (HBAg), is a distinct advancement in the field of hepatology. The association of hepatitis B antigen with chronic hepatitis in ¾ cases observed in this study, very strongly suggests that majority of the cases of chronic active liver disease in India are due to virus B hepatitis.

Past history suggestive of viral hepatitis in 50 per cent cases, history of injections or inoculations in 68.7 per cent and blood transfusion in 25 per cent in this study also support the etiological relationship between virus B hepatitis and chronic liver disease in tropics. Moreover, liver biopsy showed changes of hepatitis in all the patients. In the present series, serial liver biopsies showed progression from acute viral B hepatitis to active cirrhosis of the liver within four months to one and half years after the initial observation in 3 cases (Plate CXXXIX, Fig. 3).

There are some differences between HBAg positive chronic hepatitis seen in the present study in Delhi and autoimmune chronic active hepatitis reported from the West. Hepatitis B antigen (HBAg) positive chronic liver disease is common in males of older age group, often have acute onset like viral hepatitis, and the systemic manifestations, auto-antibodies and extreme hypergamma-globulinaemia are rare. Similar observations have been made by Sherlock (1972); Wright (1970), Hadziyannis (1970); Bulkley (1970); Finalyson *et al*. (1972); Vischer (1970) and Grob *et al.* (1971). However, Bianchi *et al.* (1972) from Italy observed no significant difference between HBAg positive and negative chronic active hepatitis.

Hepatitis B antigen positive and HBAg negative chronic hepatitis might be aetiologically distinct entities. The study of auto-antibodies in relation to HBAg in chronic hepatitis patients also support this hypothesis. While smooth muscle antibodies and anti-nuclear antibodies have been reported in over 50 per cent cases of chronic hepatitis from Great Britain, and U.S.A. in the present study only one case had both positive antinuclear factor and HBAg. Similarly, the rarity of auto-antibodies in antigen positive chronic liver disease have been published from USA, Great Britain, Greece and Switzerland (Prince *et al.,* 1970; Blumberg *et al.,* 1970; Fox *et al.,* 1969; Hadziyannis *et al.,* 1970; and Reinicke and Nordenfelt, 1970).

While the role of steroids and immunosuppressive drugs like 6 mercaptopurine (6 M.P.) and azathioprine (imuran) is well established in chronic active hepatitis (Mistilis, and Blackburn, 1967; Cook *et al.,* 1971), its value in HBAg positive chronic hepatitis needs to be evaluated by prospective double blind trials. Persistent antigenaemia beyond 12 weeks observed in this study appears to be the most important antecedent factor in predicting chronic course in patients of acute viral B hepatitis.

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