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Yet another cause of chronic viral hepatitis?

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YET ANOTHER CAUSE OF CHRONIC VIRAL HEPATITIS?

Pages with reference to book, From 281 To 284

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ABSTRACT

The clinical features, course and histology of liver in 20 patients; mostly middle aged to elderly females, closely resembling chronic Non A Non B hepatitis is presented. They presented quite late in their disease and therefore, complications such as variceal bleeds, ascites and encephalopathy were frequent. Our patients were negative for hepatitis B and C virus serology. Metabolic and immune causes of chronic liver disease were also ruled out. To the best of our knowledge, this is the first study of its kind elaborating the clinical features, course and histology of liver in chronic Non B Non C hepatitis and raises a number of questions as to the nature of the infecting virus and the epidemiology of disease (JPMA 41: 281, 1991).

INTRODUCTION

Parenterally transmitted viral infections, i.e., hepatitis B, Non A Non B, C and D are well established causes of chronic hepatitis and cirrhosis in this region. One study from Pakistan showed the prevalence of hepatitis B related cirrhosis to be just over 60%[1]. However, a number of patients seen at our institution have no serological evidence of hepatitis B, C or D or any autoimmune ormetabolib cause of cirrhosis. Such Non B, Non C chronic liver disease could also be prevalent in other parts of the world. A recent epidemiological suivey fromJapan showed a prevalence rate of 11.8-13% in Non B, Non C chronic hepatitis and cirrhosis[2]. Clinical features, laboratory data, course, histopathology and the results of various therapeutic modalities employed in the management of this disease are presented in this series.

PATIENTS AND METHODS

A total of 100 patients with chronic liver disease attending outpatient clinic or admitted through emergency room at the Aga Than University Hospital over a three months period from August, 1990 were screened for various causes of chronic liver disease. The following serological tests were done to screen for hepatitis B virus infection; HBs Ag, HBs Ab, HBc Ab (IgG type), hepatitis delta antibody (in HBs Ag positive cases only), HBe Ag and HBe Ab. Those patients who were negative for hepatitis B virus infection were screened for hepatitis C virus infection (enzyme linked immunosorbent assay kits manufactured by Abbott Laboratories was used. For HCV testing, second generation kit produced by the same manufacturer was used). Patients who were negative for HCV as well were then screened for autoimmune chronic liver disease, haemochromatosis, Wilson's disease and alpha-i antitrypsin deficiency by measuring anti-smooth muscle, anti-nuclear and anti- mitochondrial antibodies, serum ferritin levels, serum caeruloplasmin levels and alpha-i antitrypsin assays (serum ferritin was checked by DPC radioimmunoassay kit manufactured by Diagnostic Products Corporation, Los Angeles, CA 90045. Serum alpha 1 antitrypsin and serum caeruloplasmin assays were done by Nor-Partigen Immunodiffusion Plates for quantitative protein determination manufactured by Behring). Patients, who tested negative for all the above mentioned causes of chronic liver disease, were entered into the

study. Patients with a history of parenteral thug abuse, hepatotoxic thug exposure and heavy alcohol intake were also excluded. Follow up of patients entered into the study was done over a one year period. Patients were evaluated clinically and the following liver function tests were done regularly, at least at three monthly intervals; serum biirubin, SGOT, SGPT, alkaline phosphatase, serum albumin, serum alphafetoprotein and prothrombin time. Abdominal ultrasound to look at liver, spleen, pancreas and gall bladder were routinely done, at least once. Liver biopsies were done in all, to study the histological characteristics of this disease. Particular attention was paid to look at complications such as the development of ascites, portasystemic encephalopathy, spontaneous bacterial peritonitis, gastrointestinal bleeds and the development of hepatoma. Patients with established decompensated cirrhosis were treated with salt restriction, diuretics such as spironolactone and frusemide. Treatment of encephalopathy was done in the standard manner which included correction of fluid and electrolyte imbalance, protein restriction and lactulose where indicated. Exacerbations of hepatitis were treated with three courses of recombinant alpha interferon in one patient only.

RESULTS

Our series of twenty patients with chronic liver disease was picked up because of abnormal liver function tests or as a result of complications such as decompensated cirrhosis, bleeding esophageal varices or portasystemic encephalopathy. Seven (35%) patients presented with gastroesophageal variceal bleed, nine (45%) with decompensated cirrhosis with or without encephalopathy and one with spontaneous bacterial peritonitis. Three (15%) were diagnosed at cholecystectomy where a liver biopsy was taken. Five (25%) were males giving a female preponderence of 75%. The age ranged between seven to seventyone years with a mean of 52.3 years. The peak incidence occurred in the 6th and 7th decades. Nineteen (95%) patients were urban dwellers. Three (15%) patients had a history of travel outside the Indian subcontinent and 3 patients had a history of blood transfusions in past. A family history of liver disease was available in two patients, one patient's father died of carcinoma of liver and the other had a sister who had hepatitis at the same time as the patient. Ten (50%) had a past history of jaundice. On examination majority were well nourished and only nine (45%) had a mild jaundice. Signs of chronic liver disease such as spider angiomata were present in three (15%) and palmar erythema in four (20%) patients. Hepatosplenomegaly was present in twelve (60%) patients. Six (30%) had encephalopathy due to their liver disease. Serum bilirubin ranged between 0.6-6.5 mg/dl (mean 2.1 ± SD 1.44 mg/dl). SGOT between 18-596 T.U./L (mean 147± SD 165.3 I.U./L); SGPT 16-248 I.U./L (mean 114±SD 183.03 I.U./L) and serum alkaline phosphatase 5 1-525 I.U./L (mean 189±161.83 I.U./L Serum albumin level of less than 208g/dl was observed in fourteen (70%) and hyperglobulinaemia in twelve (60%) patients. Serum alphafetoprotein level was greater than 363/4/nil in only one patient with hepatoma. Serum anti-nuclear antibody was positive in three patients in a strength of + +. Serology for hepatitis B and C was negative in 14, while in 6 patients anti HBc (IgG) was positive. Liver biopsies were done in all patients. In seventeen patients the biopsies were done by us and tissue was available for detailed examination. The remaining three liver biopsies were done elsewhere. The histological features of liver biopsies are shown in Table I and histology in Figures1a, 1b, 2 and 3.

TABLE I. Histological features of liver.

Histological features		No. of cases
Cirrhosis with chronic active hepatitis		14
Chronic active hepatitis only		2
Cirrhosis with hepatocellular carcinoma		1
Bridging necrosis		13
Piecemeal necrosis		17
Fatty change	None	7
	Mild	6
	Moderate	2
	Severe	2
Kupffer cell hyperplasia		17
Lymph follicle aggregates in portal tracts		14
Sinusoidal lymphocytosis		17
Bile duct proliferation		1
Focal necrosis		1
Lobular necrosis		1
Bile duct necrosis		1
Cholestasis		1
Pigments	Iron	0
	Copper	0
	Acidophilic bodies	1
	Mallory hyaline	0
Ground glass cells		1
Stain for hepatitis B surface antigen		Negative in all cases

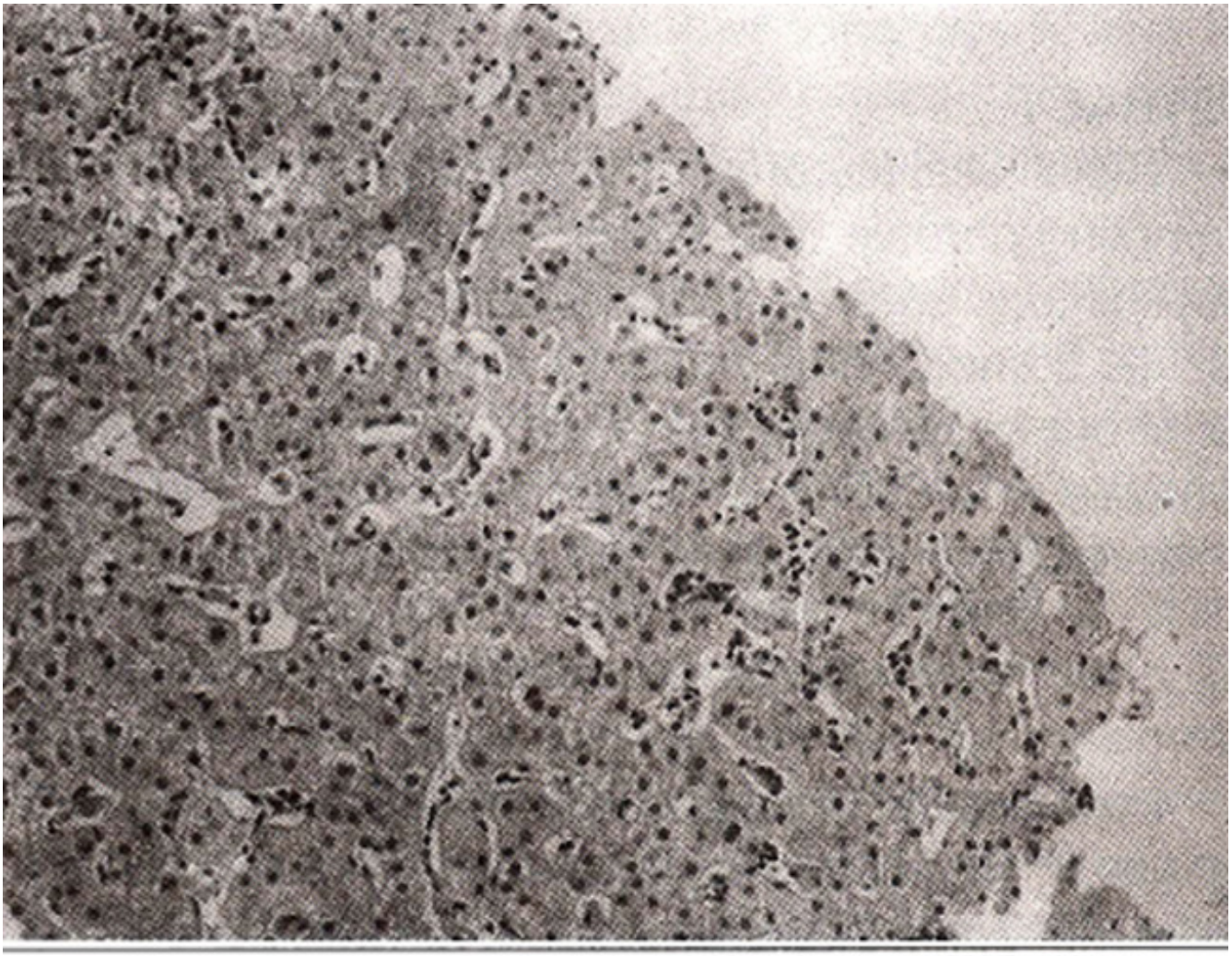

Figure 1a. Liver biopsy showing sinusoidal lymphocytosis (H&Ex100).

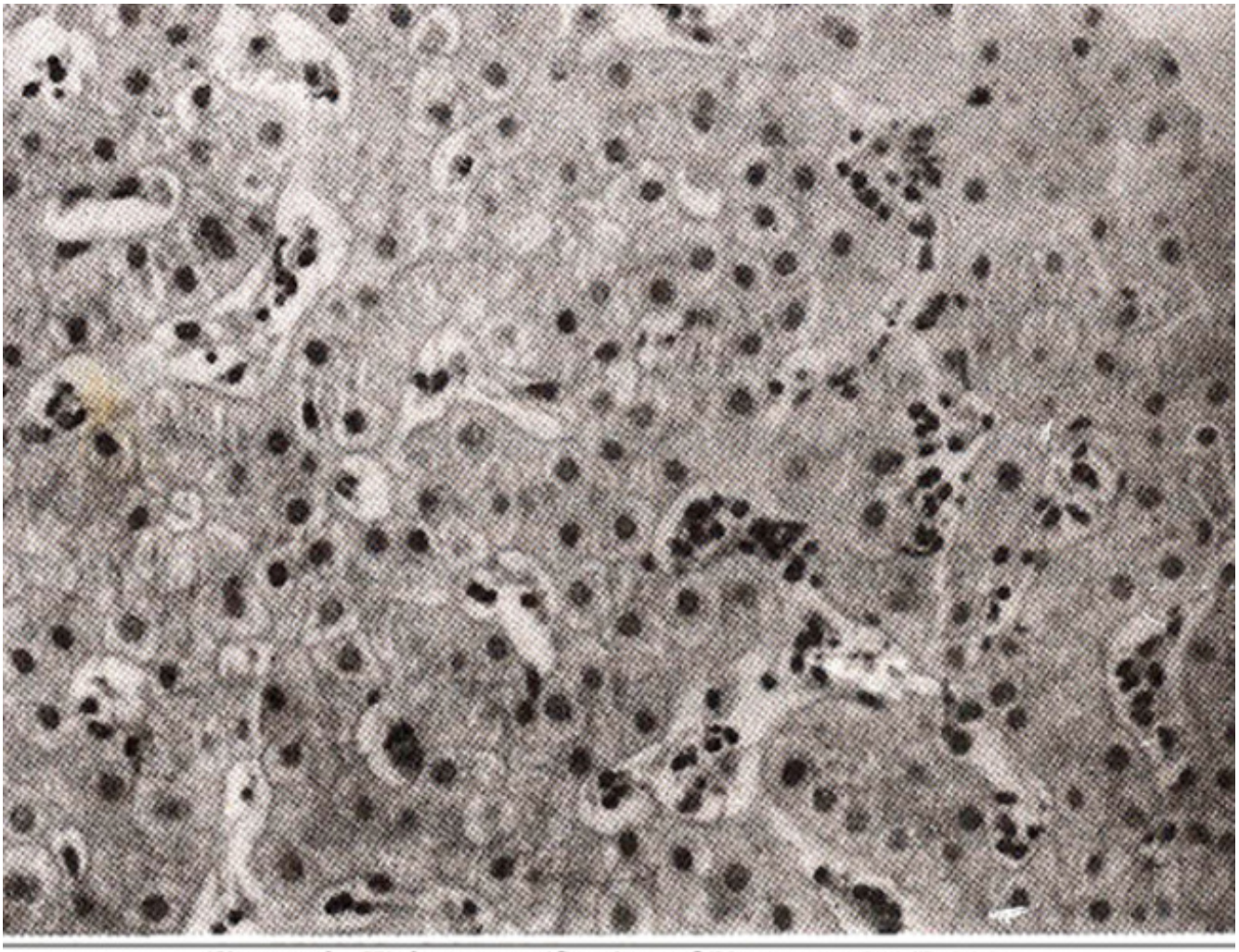

Figure 1b. Higher magnification of Figure 1a (H&Ex200).

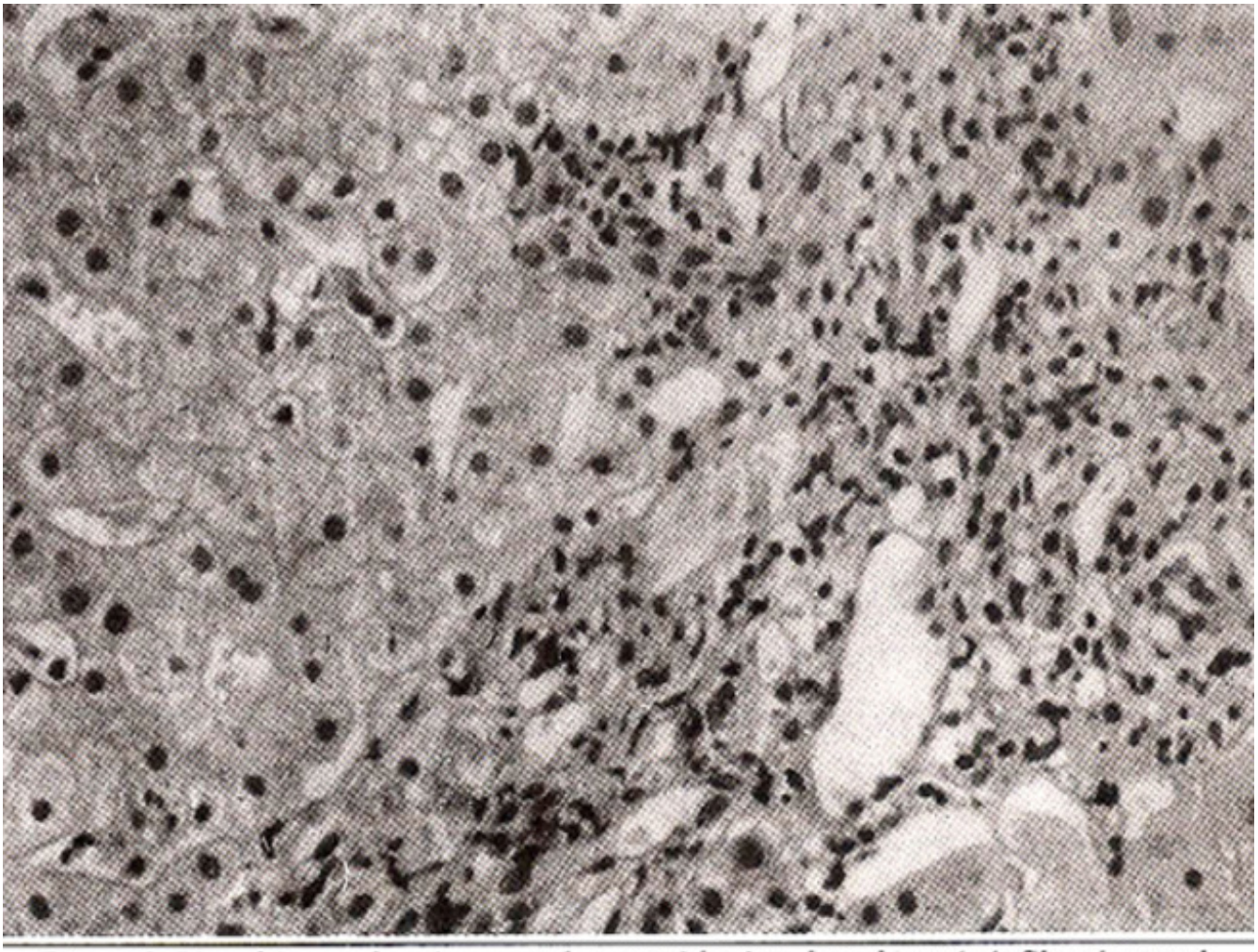

Figure 2. Liver biopsy showing portal tract widening, lymphocytic infiltration and moderate bile ductular proliferation (H&Ex200).

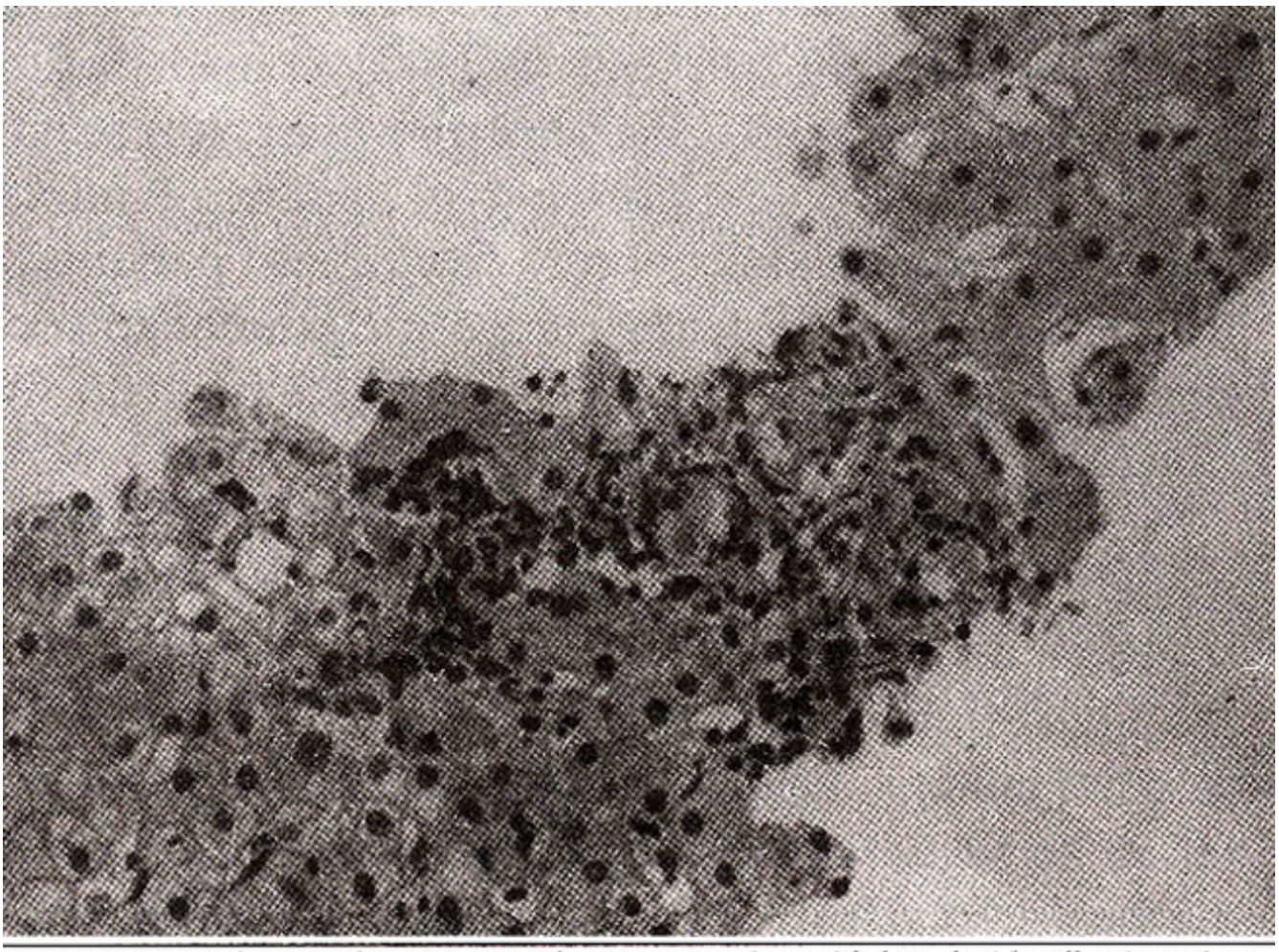

Figure 3. Liver biopsy showing portal tract expansion with lymphoid collection piece meal necrosis (H&Ex200).

The significant clinical manifestations that developed during the follow-up are shown in Table II.

TABLE II. Clinical manifestations during followup (20 patients).

Clinical manifestation	No. of cases
Fatigue, weight loss and anorexia	15
Abdominal pain/discomfort	15
Swelling of legs and abdomen	12
Spontaneous bacterial peritonitis	10
G.I. blood loss (esophageal varices)	7
Encephalopathy	6
Jaundice	5
Other symptoms (diarrhoea = 2; pruritus = 2; joints pain = 1; diabetes mellitus = 5)	

Differences in the clinical features, biochemical profile and auto-antibody screen between our patients

with chronic Non B Non C hepatitis and those of chronic Non A Non B hepatitis described in literature are presented in Table III.

TABLE III. Differences in the clinical features, biochemical profile and autoantibody screen between our patients with chronic Non B Non C hepatitis and of chronic Non A Non B hepatitis is described in literature[10].

	Non A Non B chronic hepatitis as described in literature	Our patients with chronic Non B Non C hepatitis
Age	Any age	Mostly middle aged to elderly
]		
Sex	No particular sex predilection	Mostly females
Biochemical profile:		
Serum globulin levels	Normal in majority	Increase in majority
Serum albumin levels	Usually well preserved	Low in majority
Autoantibody screen:		
Antinuclear antibody	Negative	Positive in 3/20 patients

During follow-up two patients died from complications of porta systemic shunt surgery. One patient with .hepatoma had local injections of absolute alcohol into the tumour and is doing well. The serum alpha-feto protein levels have come back to normal and the tumour has shrunk in size considerably on ultrasonic examination. One patient received interferon therapy for her chronic active hepatitis. She responded well to this therapy initially but later became refractory to this form of treatment and developed porta systemic encephalopathy and esophageal variceal haemorrhage. She is awaiting liver transplantation. One patient who has had liver transplant, a young man, banker by profession is doing well and his liver function tests are within normal limits one year after liver transplant.

DISCUSSION

Non A Non B hepatitis is a well recognized and important cause of chronic liver disease[3]. Worldwide Non A Non B hepatitis seems to represent 15 to 25% of clinical cases of viral hepatitis[4]. One of the agents thought to be responsible for Non A Non B hepatitis has been cloned and sequenced in 1989[5] and has been termed hepatitis C virus. This and the subsequent development of an ELISA antibody tests[6] have been major break throughs in the study of Non A Non B hepatitis. However, as more and more patients with chronic Non A Non B hepatitis are tested for anti-HCV with this ELISA test, it has become clear that a proportion of these patients tested negative for HCV C100-3 antibody. Serological evidence for HCV infection can be detected in 60 to 84% of post-transfusion chronic Non A Non B hepatitis and approximately 58% cases of sporadic or "community acquired" chronic Non A Non B hepatitis[6-8]. We have described a series of twenty patients presenting to our hospital with chronic liver disease in which serology for hepatitis B and C was negative. Except the three patients with a history of blood transfusions, all patients would be categorized as having sporadic Non A Non B hepatitis. This observation concurs with data from the Centre for Disease Control Atlanta which shows that only upto

10% of the reported patients with Non A Non B hepatitis have a history of blood transfusion and that in at least 40% of patients there is no known source of infection[9]. The clinical profile of our patients resembled that of patients with Non A Non B chronic hepatitis, in particular the sporadic variety[10]. The infection is frequently asymptomatic and anicteric. Most prominent symptom is mild fatigue and stigmata of chronic liver disease are rare[11]. The elevation in serum transaminases is generally mild and there is waxing and vaning pattern of activity during follow-up, a pattern usually seen in chronic Non A Non B hepatitis[1]. However, our patients presented quite late in the course of their disease and complications of portal hypertension such as variceal bleeds and ascites seemed to be setting in. Spontaneous bacterial peritonitis and encephalopathy were also frequent symptoms. The development of hepatoma also suggests that the disease had been present for quite a while and gone unnoticed. The female preponderance (75%) of the disease is noteworthy. This and antinuclear antibody positivity in three patients could mean a chronic lupoid type of reaction induced by the infecting virus in the liver in some patients. False positive serological test for hepatitis C virus in patients suffering from autoimmune chronic active hepatitis has been reported[12]. The histological features of liver show cirrhosis with varying degrees of chronic active hepatitis in fourteen (82%) out of seventeen patients, chronic active hepatitis without cirrhosis in two and hepatoma in one patient with a well established cirrhosis. Histological features of chronic Non A Non B hepatitis as described by Sherlock[13] include the occurrence of fatty change, kupifer cell hyperplasia, the presence of lymph follicle aggregates in portal tracts, a disproportionate degree of sinusoidal cellular infiltration occasional damage to bile duct epithelium and the absence of ground glass cells. Most of these features were present in the majority of our patients. Negative stain for hepatitis B surface antigen (Shikata) in all the seventeen liver biopsy specimens is also noteworthy. Many possible explanations have been advanced for the absence of anti HCV in our patients diagnosed as Non B Non C chronic hepatitis. Firstly, that the disease may be of a nonviral origin. This seems unlikely as the nonviral causes of chronic liver disease were excluded as far as possible. Secondly that the sensitivity of the HCV assay may be less than optimal. We used the second generation of HCV antibody test which tests for not one but two epitopes on the C100-3 part of HCV antigen. Thirdly, that there may be inadequate sampling for anti HCV, particularly the absence of late sampling. The great majority of our patients presented quite late in the course of their disease as evidenced by the presence of chronic hepatitis and cirrhosis on liver biopsy and therefore this explanation seems unlikely. However, serial testing of these patients for HCV antibody is underway. Lastly, is the possibility that there exists another Non A Non B hepatitis agent. This has been suggested by the occurrence of multiple episodes of Non A Non B hepatitis in a single patient[14], by cross challenge studies in the chimpanzee[15] and by inactivation studies that distinguished chloroform sensitive hepatitis agent and a chloroform insensitive[16] agent by testing the sera and liver biopsy specimens of these patients for hepatitis C RNA polymerase chain reaction, for HBV DNA to detect evidence of hepatitis B infection and animal inoculation of sera from these patients. The transient response of disease in one patient to recombinant alpha interferon therapy requires further evaluation in controlled trials. The absence of known risk factors for the development of chronic hepatitis and denial of a history of blood transfusions/parenteral drug use in the vast majority (85%) of our patients brings to one's mind the possibility of other modes of transmission of infection, which could either be sexual or be arthropod borne or be passed on via the orofecal route. This could be a significant problem in the community and needs to be evaluated further.

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