Chronic hepatitis in Nigerian patients: a study of 70 biopsy-proven cases

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Summary

Background: **Liver cirrhosis and hepatocellular carcinoma are known sequelae of chronic hepatitis. Early diagnosis and treatment of chronic hepatitis could delay or even abort progression to terminal liver disease.**
Study design: **Prospective study of 70 consecutive patients with features of early liver disease or discovered with HBsAg (or anti-HCV) during pre-employment and/or pre-donation screening at Ile-Ife, Nigeria. All the patients had liver biopsy and the histology evaluated with the Knodell Histological Activity Index.**
Result: **Fifty-three patients had symptomatic disease (M: F ratio, 1.5:1) while 17 were asymptomatic (M: F ratio, 3:1). The mean ages were 49.04 (SD±16.78) and 29.82 (SD±6.13) for the symptomatic and the asymptomatic patients respectively (P< 0.005). Major symptoms were right upper abdominal pain (68%), weight loss (51%) and fatigue (41.5%). Alcohol consumption was significantly related to symptomatic chronic hepatitis (P< 0.01). Over 50% of patients with asymptomatic chronic hepatitis had abnormal liver scan and liver function tests. All the asymptomatic cases and 77.4% of the symptomatic group had HBsAg while only 1 patient (symptomatic) was anti-HCV positive. On liver histology, all the patients with asymptomatic chronic hepatitis had a Knodell score of ≤8 and none had fibrosis. Over half of the symptomatic patients had a Knodell score of ≥ 9 (56.6%) and stage 2 or 3 fibrosis (51%).**
Conclusion: **Asymptomatic chronic hepatitis patients tend to be younger and of the male sex. Symptomatic chronic hepatitis may signal the onset of significant fibrosis and alcohol abuse may accelerate this process. Serum ALT and liver scan are useful initial screening tests for asymptomatic patients with hepatitis B or C viral markers.**

Key-words: ***Chronic hepatitis, Asymptomatic, Symptomatic, Hepatitis B, Hepatitis C, Histology, Knodell score.***

Résumé

Introduction: Cirrhose du cullin foie, maladie du foie et le carcinome hépathocellulaire sont connus comme la séquelle de l'hépatite chronique. Un diagnostic précoce et traitement d'hépetite chronique pourrait retarder ou bien terminer la progression jusqu'au terminal de la maladie du foie.
Plan d'étude: Etude en perspective de 70 patients consecutifs avec les traits de la maladie du foie précoce ou découvert avec HbsAg (ou anti-HCV) pendant pré-emploie et/ou selection prédomination à Ile-Ife, Nigeria. Tous les patients avaient la biopsie du foie et on avait évalué l'histologie avec l'indice d'activité histologique de knodell.
Résultats: Cinquante trois patients étaient atteints de la maladie symptomatique (de proportion M: F 1, 5:1) tandis que 17 étaient asymptomatiques d'une proportion (M:F, 3:1). Les ages moyens étaient 49,04 (SD ± 16, 78) et 29; 82 (SD±6,13) pour des patients symptomatiques et asymptomatiques respectivement (P<0,005). Les symptoms principaux sont la douleur abdominale du côté droit superieur (68%), perte du poid (51%) et faiblesse (41,5%) consomption d'alcool était sensiblement liée au symptomatique hépatite chronique (P<0,01). Plus de 50% des patients avec l'asymtomatique hépatite chronique avaient subi l'examen de scan du foie anormal et fonction du foie. Tous les cas d'asymptomatiques et 77,4% du groupe de symptomatique avaient HbsAg tandis que un patient (symptomatique) seulement était anti-VCH positif. A travers l'histologie du foie, tous les patients atteints d'asymptomatique d'hépatité chronique avaient un score de knodell de ≤ et aucun cas de la fibrose. Plus d'un demi des patients symptomatiques avaient eu le score de ≥ 9 (56,6%) et 2me ou 3me étape de la fibrose (51%).
Conclusion: Les patients asymptomatiques avec hépatite chronique pourrait indiquer l'importance de la fibrose du début et excès d'alcool pourrait augmenter ce processus. Sérum ALT et scan du foie sont des selections de début très utile pour l'asymtomatique avec l'hépatite B ou marquers C viral.

Introduction

Chronic hepatitis has been defined as continuing inflammation of the liver without improvement for at least six months [1]. Aetiological agents include hepatitis B, C and D, drugs, autoimmune and genetic disorders. It is a recognised precursor lesion for cirrhosis, the final irreversible stage of chronic hepatitis, and ultimately, hepatocellular carcinoma (HCC). Unfortunately, the symptoms of chronic hepatitis are often non-specific and

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definitive diagnosis depends on histological confirmation. Hepatitis B virus (HBV)-associated liver disease is a common condition in Nigeria as in many other sub-Saharan African countries [2]. Most patients with HCC in this region are positive for HBV markers and do present with a short history of symptoms [3,4]. Diagnosis of chronic liver disease at a very early stage is therefore crucial if chances for cure are to be enhanced, a prospect now made brighter by the advent of specific chemotherapy of chronic viral hepatitis [5].

In spite of the high prevalence of HBV-associated chronic liver disease in Nigeria, there is hardly any study in the country examining the clinico-pathological characteristics of chronic viral hepatitis. It is hoped that the information obtained from such a study may help in the early detection and treatment of chronic hepatitis so that progression to irreversible liver disease or malignancy can be averted.

Patients and methods

This was a prospective study of consecutive patients seen at the University Teaching Hospital (a tertiary health care centre) at Ile-Ife, Nigeria between 1987 and 2002. Patients with symptoms suggestive of liver disease and persons who either tested positive to viral hepatitis markers in their blood or had abnormal liver function tests during routine medical/blood donation screening were selected for investigation. As much as possible, patients with overt features of decompensated liver disease were excluded. Those selected were investigated with real time ultrasonography and liver biopsy after appropriate history and physical examination. Their serum biochemistry and haematology profile were also done. Screening for hepatitis B surface antigen (HBsAg) in the blood was done with Latex Kit, BIOTEC Laboratories Ltd., UK while ELISA test (2nd generation) was employed for the detection of antibodies to hepatitis C virus (anti-HCV). All asymptomatic subjects seropositive for either viral marker had a repeat serology after 6 months in order to eliminate cases of acute hepatitis. Regular liver ultrasound scan and serology for viral markers were only commenced in our hospital years into this study with anti-HCV test being the most recent (introduced only 3 years to the end of study). Therefore, not all the subjects selected could undergo these investigations. Screening for HBeAg and HBV-DNA, markers of HBV replicative activity, were not done due to lack of facilities.

Liver biopsy assessment

To obtain biopsies of the liver, the one-second Menghini technique[6] was adopted, using the trans-thoracic approach after securing informed consent. The liver tissue sample obtained averaged 1.84cm (SD ± 0.52) in length. In each case, the liver tissue specimen was fixed in buffered 10% formaldehyde, processed routinely within 24 hours and embedded in paraffin wax. Six 3 μm sections were cut from each block and subjected to the following stains: haematoxylin and eosin, reticulin (Gordon and Sweet) Masson's trichrome (for fibrosis assessment), Perl's Prussian blue (for iron), periodic acid Schiff (PAS) with diastase digestion (to check for α-1-antitrypsin) and the Shikata's orcein stain (for HBsAg). Only those subjects with histological features compatible with chronic hepatitis were included in the study. In all cases, two pathologists examined the stained tissue sections at different sessions. The histological grade (degree of necroinflammatory activity) and stage (degree of fibrosis) were scored using the Knodell Histological Activity Index (HAI)[7]. Grades of necroinflammation were grouped according to the proposal of Desmet *et al*[8], with slight modification.

Statistical analysis

Tests of statistical analysis were done using the Student's t-test and the Chi-Square test as appropriate. P value of < 0.05 was regarded as significant.

Results

A total of 70 patients, 45 males and 25 females (M:F = 1.8:1) were studied. Their ages ranged from 20 to 78 years with a mean of 44.37 (SD ± 17.02). Fifty-three (75.7%) of the 70 chronic hepatitis patients were symptomatic while 17 (24.3%) were asymptomatic. The symptomatic patients were made up of 32 males and 21 females with a mean age of 49.04 years (SD ± 16.78). The asymptomatic group consisted of 13 males and 4 females (M:F = 3:1) with an age range of 20 to 44 years and a mean age of 29.82 (SD ± 6.13) ($P < 0.005$). The asymptomatic subjects were detected at the time of attempted blood donation (n = 10) and during routine medical tests (n = 7). The most common symptom among the symptomatic group was right upper quadrant abdominal pain (68%) followed by weight loss (51%) and body fatigue (41.5%) (Table 1). History of jaundice in the past was positive in only 26.7% of the cases while 86.5% had no history of blood transfusion.

Significant alcohol consumption defined as ≥ 60g/day for males and ≥ 40g/day for females for not less than 10 years was found in only 18 patients. Of these 18 cases,

Table 1 Main symptoms among chronic hepatitis patients (n = 53)

Symptoms	No.(%)
Abdominal pain (right upper)	36 (68)
Weight loss	27 (51)
Body fatigue/weakness	22 (41.5)
Jaundice	18 (34)
Abdominal swelling	16 (30.2)
Fever	15 (28.3)
Anorexia	14 (26.4)
Leg oedema	14 (26.4)
Early satiety	10 (18.9)
Diarrhoea	10 (18.9)

Table 2 Serum *ALT, liver ultrasound scan and viral hepatitis markers in chronic hepatitis patients

	Serum *ALT			Liver Ultrasound Scan			HBsAg					Anti-HCV				
	Normal	Abnormal	Total	Normal	Abnormal	Total	Neg.		Pos.		Total	Neg.		Pos.		Total
							M	F	M	F		M	F	M	F	
Asymptomatic	7	8	15	7	8	15	–	–	13	4	17	7	4	-	-	11
Symptomatic	9	26	35	5	18	23	2	5	19	5	31#	2	3	1	-	6
Total	16	34	50	12	26	38	2	5	32	9	48	9	7	1	-	17

**ALT = Alanine transaminase #For 6 of these patients the HBsAg was positive only in the liver tissue*

however, 15 (83.3%) belonged to the symptomatic group ($P < 0.01$). Serum alanine transaminase (ALT) could only be done in 50 patients (35 symptomatic and 15 asymptomatic) as reagents were occasionally out of stock. Thirty-four (68%) of them had abnormal serum ALT levels while they were normal in 16 (32%). The 34 patients consisted of 26 symptomatic (74.3%) and 8 asymptomatic patients (53.3%). Seventy-eight percent of the symptomatic and 53.3% of the asymptomatic patients had abnormal liver scan. All of the asymptomatic patients were HBsAg positive but all of the 11 of them tested for anti-HCV were negative. Of the 31 symptomatic patients tested for HBsAg, 18 (58%) were positive. However, HBsAg was stained in the liver tissue of 6 additional patients bringing the total HBsAg positivity rate among them to 77.4%. Ten out of the 21 female symptomatic patients had HBsAg screening done out of whom 5 (50%) were positive. Anti-HCV screening could only be done in 7 of all the 25 female patients and all were negative. Only 1 of the 6 symptomatic patients tested was positive for anti-HCV (see Table 2).

Of the 18 patients with significant alcohol consumption, 10 were screened for HBsAg and of these, 7 (70%) were positive. None of the asymptomatic patients had hepatomegaly or splenomegaly. On the other hand, 42 (79.2%) and 18 (34%) of the symptomatic patients had hepatomegaly and splenomegaly respectively.

Correlation of histological findings with clinical features

The histological evaluation of the liver tissues from all the 70 patients was based on the histological activity index (HAI) of Knodell or Knodell score. All of the asymptomatic patients had a histological grade of ≤ 8 (maximum score = 18) with 11 (64.7%) of them below grade 5 (Table 3). None of the members of the asymptomatic group had fibrosis on histology (stage 0). On the contrary, 30 (56.6%) of the 53 symptomatic patients had a histological grade of ≥ 9. Eleven (20.8%) of them scored a grade of ≥ 14 demonstrating severe necroinflammation and early cirrhosis (stage 4). All the patients with histological stage 3 or 4 were symptomatic. Features of liver cell dysplasia (LCD) were seen in 4 cases (1 asymptomatic, 3 symptomatic). All the 4 cases (3 males and 1 female) with LCD were positive for HBsAg and had a histological grade of ≤ 9. The female patient returned 3 years after the diagnosis of chronic hepatitis was made with evidence of neoplastic transformation as shown by increased hepatomegaly and the development of hepatic arterial bruit.

Discussion

Chronic hepatitis can present with or without symptoms. Even when it is symptomatic, the symptoms can be non-specific[8]. This study confirms this observation and it also shows that symptomatic chronic hepatitis is significantly related to age ($P < 0.005$), as has been reported elsewhere[9]. Hepatitis B virus (HBV) infection is usually acquired in childhood in sub-Saharan Africa. If the mean period of exposure to HCV to the development of cirrhosis (i.e. 21 years)[10] is applicable to HBV infection, clinical disease would therefore be expected to begin to manifest by middle age. For the same reason, asymptomatic patients are younger and, as also shown by this study, predominantly males. The male sex is a recognised risk factor for chronic HBV carrier state[11].

Alcohol consumption was also shown by this study to be significantly associated with the development of symptomatic chronic hepatitis ($P < 0.01$). Symptomless HBsAg carriers drinking ethanol have been shown to be

Table 3 Correlation of clinical status of chronic hepatitis with liver histological grading and staging scores

*HAI	Grading Score (over 18)						Staging Score (over 4)				
Clinical Status	3–4	5–6	7–8	9–13	≥14	Total	0	1	3	4	Total
Asymptomatic	11	4	2	–	–	17	14	3	–	–	17
Symptomatic	3	16	4	19	11	53	19	7	16	11	53
Total	14	20	6	19	11	70	33	10	16	11	70

**Histological Activity Index*

more susceptible to liver damage than HBsAg negative subjects[12]. This study therefore lends support to the advice that HBsAg carriers should abstain from alcohol. The importance of screening high-risk patients with serial liver scans among other tools for the early detection of chronic liver disease has been well recognised[13]. Over half of the asymptomatic patients in this study had abnormal liver scan and impaired liver function tests. Arico *et al*[14] reported that impaired liver biochemical tests occurred mainly in symptomless HBsAg carriers with positive antibodies to hepatitis D virus (anti-HDV). The anti-HDV status of patients in this study was not determined but a previous study from our centre showed a low seroprevalence for HDV antigen in our patients with chronic liver disease[15]. Further studies are needed to determine if there are specific factors associated with deranged liver function tests in Nigerians who are asymptomatic HBsAg carriers.

Viral hepatitis is the most common cause of chronic hepatitis worldwide with HBV predominating in South-east Asia and sub-Saharan Africa and HCV more prevalent in the United States, Japan and Europe. Expectedly, a large majority of our patients had HBV-associated disease while only one patient out of 17 tested positive to anti-HCV. This result suggests that HCV infection plays a very minor role in the pathogenesis of chronic liver disease in our patients, as an earlier study from our centre also showed[16]. However, more studies with larger sample size are needed before firm conclusions can be drawn.

Autoimmune hepatitis (AIH) is characterized by the absence of hepatitis seromarkers, female predominance and circulating autoantibodies among others[17]. Half of our female symptomatic patients tested for HBsAg and all those tested for anti-HCV were negative. This raises the possibility that AIH may have accounted for the chronic hepatitis seen in some of them. Facilities for the assay of autoantibodies and HLA typing were not available for the diagnosis to be confirmed.

In 1981 Knodell *et al*[7] introduced a semi-quantitative analysis of liver histopathology. Liver biopsy specimens were divided into four groups and each group was assigned a numerical score depending on the extent of necroinflammation (grade) or fibrosis (stage). A summation of the scores for the four categories formed the Histological Activity Index (HAI) for a particular specimen. The maximum HAI score for necroinflammation is 18 while that for fibrosis is 4, representing the worst lesion in the scale of severity. A suggestion for the modification of the Knodell's necroinflammatory and staging scores has been made[18]. Since its introduction, the Knodell score has gained popularity and is presently the most applied of all the scoring systems for chronic hepatitis. One important drawback of the Knodell score is the intra- and inter-observer variation that can occur in the interpretation of lesions. This can, however, be minimized by arranging for more than one pathologist to assess slides[19]. Desmet *et al*[8] proposed a correlation between Knodell's HAI score and the old description of necroinflammatory activity in chronic hepatitis. HAI score of 1-3 showed minimal chronic hepatitis consistent with chronic lobular hepatitis (CLH) or chronic persistent hepatitis (CPH) and 4-8 was mild chronic hepatitis consistent with severe CLH, CPH or mild chronic active hepatitis (CAH) in the old nomenclature. HAI score of 9-12 showed moderate chronic hepatitis representing moderate CAH while a score of 13-18 was indicative of severe chronic hepatitis consistent with severe CAH with bridging necrosis. Asymptomatic chronic hepatitis patients tend to have features of CPH on histology. Symptomatic patients, on the contrary, tend to have significant necroinflammation and established cirrhosis[20]. This agrees with the findings in this study where all the asymptomatic patients had a Knodell score of ≤ 8 and none of them had fibrosis. On the other hand, majority of the chronic hepatitis with symptomatic disease had a score of ≥ 9 and stage 3 or 4 fibrosis. The presence of symptoms in a chronic hepatitis patient is therefore a manifestation of advanced disease. Weissberg *et al*[21] obtained a 5-year survival rate of 55% for patients with CAH and cirrhosis compared to 97% for those with mild disease and no fibrosis. Eleven (20.8%) of our patients, all symptomatic, had severe necroinflammation (HAI score ≥ 14) and evidence of early established cirrhosis (stage 4) on histology. These patients represent the group with the worst prognosis and it is noteworthy that most of them had no antecedent history of jaundice or clinical illness. The risk to develop HCC has been found to be extremely high in them[22].

Liver cirrhosis is known to be a notable risk factor for the development of HCC. However, in 10% or more cases, the tumour may arise in non-cirrhotic liver. Such cases have been shown to have histological abnormalities such as liver cell dysplasia (LCD)[23]. The cases of LCD seen in this study occurred in patients with a Knodell score of ≤ 9 (i.e. mild to moderate disease). This further highlights the need for early diagnosis of chronic hepatitis and as shown by one of the LCD cases in this study, the condition may not necessarily reach the cirrhosis stage before malignant transformation occurs.

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