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Original Research Article

Chronic Hepatitis and Knodell Score Analysis in Jos, Nigeria

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ABSTRACT

Introduction: Liver biopsy is the key to the definitive diagnosis of chronic hepatitis. Hepatitis B virus infection is prevalent in resource poor sub-Sahara Africa. The objective of this research was to evaluate the occurrence of chronic hepatitis in our institution and correlate the histological activity with associated factors.
Methodology: This is a retrospective study and involved the evaluation of microscope slides made from archival formalin fixed paraffin embedded blocks of liver biopsy tissues obtained over a ten year period.
Results: A total of 374 liver biopsy specimens were evaluated. Chronic hepatitis constituted 61% while 7.8% had progressed to cirrhosis. HBV was responsible for 96% of chronic hepatitis. Knodell score of 5-8 points was found in 51.1% chronic hepatitis and 13.8% cirrhosis. There was no statistical gender difference in Knodell scores in both chronic hepatitis and cirrhosis. A weak correlation occurred between Knodell scores and age (Pearson's r, 0.0067).
Conclusion: There is a heavy burden of histologically diagnosed chronic liver disease in north-central Nigeria. The Knodell scoring system is a valuable tool for evaluating disease severity and monitoring therapy.

Key words: Liver; hepatitis; chronic hepatitis; hepatitis B virus; Knodell score; cirrhosis.

INTRODUCTION

Histological examination following a liver biopsy is the traditional gold standard for the evaluation of liver diseases. Liver biopsy was first described by Ehrlich in 1883 but it gained wider acceptance after Menghini again described the procedure in 1958. [1] The last 50 years has witnessed a dramatic change in the indications for performing a liver biopsy because of better understanding of liver diseases, new disease entities and the ever increasing availability of advanced radiological, immunological, biochemical and genetic techniques. [2] The common indications for requesting a liver biopsy include abnormal liver function tests, fever of unknown origin, and evaluation of chronic liver diseases for diagnosis, grading, staging and assessment of therapy. [1] Chronic hepatitis is a symptomatic, biochemical or serological evidence of continuing or relapsing hepatic disease for more than six months with histologically documented inflammation and necrosis. [3] Aetiological agents of chronic hepatitis include hepatitis B, C, and D, drugs, alcohol, autoimmune and genetic disorders. And this disease is a precursor lesion for cirrhosis and

hepatocellular carcinoma. The high prevalence of hepatitis B virus infection in Nigeria has been demonstrated by many studies. [4-6]

The clinical features of chronic hepatitis are extremely variable and are not predictive of outcome. [3] The severity of the disease is assessed by several scoring systems. These include the Knodell, Ishak, Scheuer, METAVIR, Batts-Ludwig and the Laennec. The Knodell score, also known as the histological activity index (HAI), is generic, the most comprehensive and evaluates four parameters, viz: periportal/bridging necrosis, interlobar degeneration and focal necrosis, portal inflammation, and fibrosis. The Knodell score is useful for assessing the baseline level of histological damage to the liver and monitor improvements with therapy. [7] The scoring of fibrosis is modified in the Ishak method to document smaller changes in fibrosis and this is particularly helpful in monitoring progression to cirrhosis. [8] Ndububa et al studied seventy chronic hepatitis patients at Ibadan and observed 57 (75.7%) to be symptomatic while 24.3% were asymptomatic. The asymptomatic cases were found during tests before blood transfusion or routine medical tests. They were all positive for hepatitis B surface antigen (HBsAg) and negative for anti- hepatitis C virus (HCV) antibody. Only one of the six symptomatic patients tested positive for anti-HCV. All of the asymptomatic cases studied had a Knodell histological grade of ≤ 8 and none with fibrosis. On the other hand, 56.6% of the 53 symptomatic patients with a histological grade of ≥ 9 had stage 3 or 4 fibrosis. Severe necro-inflammation (HAI score ≥ 14) was found in 11 (20.8%) of the symptomatic patients demonstrating a direct correlation between occurrence of symptoms and severity of disease. [9] This study aimed to document the occurrence of chronic hepatitis from the liver biopsies obtained in Jos, north – central Nigeria and correlate the Knodell scores obtained with gender and age of patients with this disease.

MATERIALS AND METHODS

This is a hospital based retrospective evaluation of the liver biopsy specimens accessioned in the histopathology laboratory of Jos University Teaching Hospital, Jos, Nigeria within a period of ten years, from January, 2000 to December, 2009, inclusive. Demographic data and clinical details were obtained from the clinical records. Serological test results for hepatitis B surface antigen were obtained from the clinical records. In diagnosed cases where additional information was needed, like in the cases of chronic hepatitis and cirrhosis without staging and grading, the tissue blocks were retrieved, re-sectioned and stained with haematoxylin and eosin. Special stains such as Masson's trichrome, Gordon and Sweet's silver impregnation and Perls' Prussian blue were also employed. World Health Organisation histological classification of tumours of the liver and intra-hepatic bile ducts (2000) was used in this study. [10] The histological activity in hepatitis and cirrhosis was assessed with the Knodell scoring system. All statistical computations were performed using Microsoft Excel (2007 version). Ethical clearance was obtained from the Ethical Committee of Jos University Teaching Hospital.

RESULTS

There were three hundred and ninety one liver biopsy specimens accessioned in Jos University Teaching Hospital from January 2000 to December 2009. Seventeen of them were assessed to be inadequate and were not included in this analysis. These included specimens which were necrotic, not properly fixed or processed, or with less than five portal regions. Therefore, three hundred and

seventy-four specimens were analysed in this study.

Liver diseases were generally observed to be more common in males than females. There were a total of 245 (65.5%) males and 129 (34.5%) females with a male to female ratio of 1.9:1.

The most frequently diagnosed liver disease was chronic viral hepatitis with 228 (61%) out of the total of 374 liver disease specimens. Cirrhosis was significantly noted to be much less frequent with 29 (7.8%) cases seen during this ten year period.

Chronic hepatitis

Chronic hepatitis occurred most frequently in the fourth decade with 87 (38.2%) out of 228 biopsies from patients within this age group (Table 1). Chronic hepatitis occurred predominantly in males with a male: female ratio of 1.9:1. The peak occurrence was in the 31-40 years age group. Hepatitis B virus (HBV) infection was responsible for 219 (96.1%) cases of chronic hepatitis. All the hepatitis B virus cases were also positive for hepatitis B surface antigen on serological testing. This information was obtained from the clinical records. There were five cases of hepatitis C viral infection while co-infection with hepatitis B virus was present in four (1.8%).

Distribution of Knodell scores in chronic hepatitis.

The histological activity index in chronic hepatitis and cirrhosis was assessed using the Knodell scoring system. The age and sex distribution of the Knodell scores obtained in the slides diagnosed with hepatitis B virus infection is presented on Table 2. The scores were arbitrarily grouped into 1-4, 5-8, 9-12, 13-18 and 19-22 points based on previous studies. [9,11] The highest frequency (51.1%) was obtained in those cases with scores between the ranges of 5-8 points. This was followed by Knodell scores of 1-4 points, constituting 29.2%. Only two (0.9%) out of the 219 histologically diagnosed cases of chronic hepatitis B virus infection were scored 13-18 points.

Cirrhosis

There were 29 cases of liver cirrhosis and their peak incidence paralleled that of chronic hepatitis. Fourteen (48.3%) of them occurred within the 31-40 age bracket and this was followed by the third decade (20.7%) similar to what was observed in chronic hepatitis.

Distribution of Knodell scores in cirrhosis

Slightly more than half (51.7%) of the cirrhosis cases had Knodell scores between 13 to 18 points. Thirty-four point five per cent were scored 9-13 points while 13.8% were scored 5-8 points. In this study, there was no case of cirrhosis with a Knodell score beyond 18 points (Table 3). Higher scores were obtained in the cases of cirrhosis with a mean of 13.7±3.2 when compared with non-cirrhotic cases which had a mean of 6.6±2.6.

Analysis of effect of gender on Knodell Scores in chronic hepatitis and cirrhosis

The Knodell scores in males with chronic hepatitis B virus infection averaged 6.6 ± 2.5. There was a slightly higher mean of 6.8 ± 2.6 in females. Similarly, males had lower mean scores (13.0 ± 3.4 S.D.) than females (15.3 ± 2.3) in cirrhosis. In chronic hepatitis B infection, the calculated variance ratio, F (0.23) was less than the critical F value (6.75). In addition, the p-value computed, 0.63 is more than the significance level for alpha (α), 0.01. Therefore, there was no statistically significant difference between the male and female scores in chronic hepatitis B viral infection. Similarly, in cirrhosis, the calculated variance ratio, F (0.99), was less than the critical F value (7.68) and the p-value, 0.033, is more than the alpha level of significance (α) of 0.01, and the null hypothesis (Ho: μ male Knodell scores = μ female Knodell scores) was not rejected. Hence, there was no

statistically significant difference between the male and female scores in cirrhosis.

Correlation analysis of Knodell scores and age in chronic hepatitis

Pearson's correlation analysis of age and all the Knodell scores in chronic hepatitis B viral infection returned the value, r = 0.0067. With a degree of freedom (df) of 217, there was a two tailed P-value of 0.9218 and one-tailed value of 0.4609. The Pearson's r value is much less than both the two-tailed and one-tailed P-values. The scatter -plot of this analysis demonstrated a positive, though, weak, linear correlation between the age of the patient and the degree of liver damage.

Table 1: Age and sex distribution of chronic hepatitis.

Age (Years)	Male	Female	Total	Percentage (%)
0-10	1	0	1	0.4
11-20	8	6	14	6.1
21-30	51	22	73	32.0
31-40	56	31	87	38.2
41-50	23	10	33	14.5
51-60	6	7	13	5.7
61-70	4	3	7	3.1
Total	149	79	228	100.0

Table 2: Distribution of Knodell scores in chronic hepatitis B infection

	Knodell Scores (HBV)								Total	Percentage (%)
	1-4		5-8		9-12		13-18			
Age (Years)	M	F	M	F	M	F	M	F		
0-10	0	0	0	0	1	0	0	0	1	0.5
11-20	3	1	1	4	3	1	1	0	14	6.4
21-30	16	5	28	12	6	5	0	0	72	32.9
31-40	19	8	24	15	11	6	1	0	84	38.4
41-50	4	4	12	2	4	3	0	0	29	13.2
51-60	1	3	3	4	1	0	0	0	12	5.5
61-70	0	0	3	3	0	0	0	0	6	2.7
71-80	0	0	1	0	0	0	0	0	1	0.5
Total	43	21	72	40	26	15	2	0	219	100.0
Percent (%)	19.6	9.6	32.9	18.3	11.9	6.8	0.9	0	100	
	29.2		51.1		18.7		0.9			
M: male, F: female										

Table 3: Age and sex distribution of Knodell scores in cirrhosis

	Knodell scores									
	1-4		5-8		9-12		13-18			
Age (Years)	M	F	M	F	M	F	M	F	Total	Per cent (%)
0-10	0	0	0	0	0	0	0	0	0	0.0
11-20	0	0	0	0	0	1	0	0	1	3.4
21-30	0	0	2	0	1	0	2	1	6	20.7
31-40	0	0	0	1	6	1	4	2	14	48.3
41-50	0	0	0	1	1	0	1	2	5	17.2
51-60	0	0	0	0	0	0	0	2	2	6.9
61-70	0	0	0	0	0	0	1	0	1	3.4
71-80	0	0	0	0	0	0	0	0	0	0.0
Total	0	0	2	2	8	2	8	7	29	100.0

Table 4: Sex and age distribution in chronic hepatitis C infection

Age (Years)	Male	Female	Total	Percentage (%)
31-40	1	2	3	33.3
41-50	3	1	4	44.4
51-60	1	-	1	11.1
61-70	1	-	1	11.1
Total	6	3	9	100

DISCUSSION

The liver biopsy specimens used in this study cut across the different age groups, in both sexes. The ratio of adults to children is 49:1. This is higher than the finding in previous liver biopsy reports both in Jos, Enugu and Lagos, large cities located at different zones of Nigeria. [12-14]

The incidence of liver diseases in males has been noted to be higher than in females. In this study, the male to female ratio is 1.9:1. This ratio compares favourably with the observations of Ndububa et al and Abdulkareem et al who both reported 1.8:1 and significantly less than 3:1 reported by Osuafor and colleagues. [9,12,13] The peak incidence of chronic hepatitis occurred in the 31-40 years age group in Jos. This observation is consistent with reports by other workers. [13,15]

Chronic hepatitis formed 31.7% of liver biopsies has previously been reported

in Jos. [15] This is less than 38.2% found in this present work. Osuafor et al found chronic active hepatitis to constitute only 6.5% of a series of 154 liver biopsies histologically analysed at Enugu. [12] In a similar study in Kano, chronic hepatitis was the commonest histological diagnosis (40.5%). [16] It is pertinent to note that these are hospital based studies and give only a glimpse of the real burden of this disease. Poverty, ignorance, lack of access to health care and a pervading belief in traditional healers in African communities are obvious impediments to accurate data mining.

Most of the patients are males and had Knodell scores ranging from five to eight points signifying mild necro-inflammatory activity (Table 2 and Table 3). The older patients did not demonstrate a greater degree of liver damage and Pearson correlation analysis returned a weak linear relationship between Knodell scores and age. We could not determine the duration of illness in these cases and besides, many cases of chronic infection with hepatitis B virus are asymptomatic. Perhaps, a further study with a larger sample size, correlating the scores with duration of illness will give a significant statistical result and computing with the duration of infection may predictably yield the strongest positive correlation. Poynard et al had found acceleration of fibrosis with increasing age in a series of 4,852 patients with chronic liver diseases. [17] Older age at diagnosis appears to be an important determinant of progression to cirrhosis and hepatocellular carcinoma. This may be caused by the aging of the immune system which can no longer contain the disease or simply because of the longer duration of infection. [18] Hepatitis B virus infection in endemic regions is often of a long standing duration because most infections occur in childhood. We found hepatitis B virus associated chronic hepatitis in 96% of all cases of this disease. Although this is a hospital based research, this figure represents the very heavy burden of this virus in sun-Sahara Africa. There is a low incidence of hepatitis C virus infection in most of Africa. Nwokedi et al observed a seroprevalence of 6.2% in a series of 1007 patients. [19] In our research, the histologically diagnosed cases of hepatitis C virus chronic hepatitis constituted only 3.9% (9) of the 228 patient biopsies. The peak incidence of cirrhosis occurred in the fourth decade. This is lower than the fifth decade reported in Jos and Lagos, and sixth decade observed at Illorin. [13,20]

Fibrosis appears to progress more slowly in females than in males with chronic hepatitis B infection, suggesting that oestrogens have a protective effect on fibrogenesis. [21] Rigamonti and colleagues demonstrated the effect of gender on necro-inflammation. They conducted a univariate and multivariate analysis of the prognostic variables in chronic hepatitis C and found that gender modulates the progression of chronic hepatitis C only in younger patients. Women $\leq$ 50 years showed lower necro-inflammatory and fibrosis scores than men of comparable age while men and women >50 years did not exhibit any difference in the severity of the disease. [21] In contrast to the observations of these researchers, the analysis of variance (ANOVA) of the scores obtained from males and females with chronic hepatitis B, in this study, failed to demonstrate a significant statistical difference suggesting an insignificant influence of gender on histological activity index. There has actually been contrasting data on the influence of gender on the risk of progression of chronic hepatitis. [18] Considering the needed for greater control and prognostication, especially for chronic hepatitis related events such as de-compensation, hepatocellular carcinoma and liver related death, the duration of infection and effect of gender may be factored into the scoring systems in the

future. Liver biopsy is under still largely under-utilised in Nigeria because, besides establishing diagnosis and determining baseline histological activity, patients are hardly ever monitored with serial biopsies.

CONCLUSION

Sub- Sahara Africa still bears the heavy burden of chronic hepatitis, cirrhosis and hepatocellular carcinoma. There is an insignificant modulating effect of gender on necro-inflammatory activity and progression of fibrosis in chronic hepatitis. However, a weak positive correlation exists between disease progression and age. The Knodell scoring system is a comprehensive method of assessing the level of severity and monitoring therapy in chronic hepatitis and cirrhosis and should readily be employed by pathologists and clinicians.

Disclosure

The authors declare that there is no conflict of interest regarding the publication of this paper.

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