Original Article

Staging and grading chronic viral hepatitis: A teaching hospital experience using an objective histological activity index in a tropical population

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Abstract

Background: Chronic viral hepatitis (CVH) is the leading cause of chronic liver diseases (CLD) and exhibit diffuse parenchymal damage requiring a systematic assessment of disease extent and progression.

Aims: The aim of this study is to determine the epidemiological pattern and grade/stage all cases of CVH using Ishaq Modified Histologic Activity Index (HAI); then share and to compare our experience with similar works elsewhere.

Methods: Ten years (2006–2015) liver biopsies received in the Department of Pathology, Ahmadu Bello University Teaching Hospital Zaria, were fixed in formalin, embedded in paraffin and stained with routine and special stains were reviewed, graded and staged using Ishaq HAI. Data were analysed and presented in statistical frequency distribution tables and figures.

Results: CVH formed 55.2% was the most common of liver diseases. There were119 male and 47 female with male-to-female ratio of 2.5: 1 and peaked in the third decade of life. Nearly 42.2% had modified Ishaq HAI score of 4–8, while 28.3% and 27.1% had score 1–3 and score 9–12, respectively. Only 2.4% had score of 13–18. Nearly 70.5% of cases were between Stages 0 and 2, 25.9% of cases were Stage 3and 4 while only 6% were in Stage 5. Hepatitis B virus (HBV) was the most common aetiology and found in 77.7% of cases, 13.3% were associated with hepatitis C virus (HCV) and HBV/HCV co infection in 9.0%.

Conclusions: CVH was the most common form of CLD, peaked in the third decade of life. Nearly 42.2% were in mild grade disease while 70.5% had Stage 2 and below disease. HBV infection was the most common aetiology.

Keywords: Grading, hepatitis B viral hepatitis, hepatitis C viral hepatitis, staging

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Received: 28.06.2017, **Accepted:** 09.08.2018

INTRODUCTION

Viral hepatitis contributes significantly to the burden of liver diseases and over 2 billion living people have been infected with hepatitis B virus (HBV) while over 350 million of them are chronically infected carriers with no significant liver disease.[1] Majority of these infected carriers will progress to chronic hepatitis, cirrhosis and hepatocellular

Access this article online	
Quick Response Code:	Website: www.phmj.org
	DOI: 10.4103/phmj.phmj_24_17

How to cite this article: Bello U, Iliyasu Y. Staging and grading chronic viral hepatitis: A teaching hospital experience using an objective histological activity index in a tropical population. Port Harcourt Med J 2018;12:122-6.

carcinoma (HCC) thus representing a significant public health burden.[2] In Africa, at least 65 million people are chronically infected with HBV.[3] The seroprevalence of hepatitis B surface antigen (HBsAg) in Nigeria ranged from 10% to 40%.[4]

The World Health Organization (WHO) estimates that 170 million individuals were chronically infected with hepatitis C virus (HCV) globally with 75% developing chronic liver disease and of this 1.6% transformed to HCC.[5] Africa has the highest WHO estimated regional HCV prevalence of 5.3% while Egypt (17.5%) had the highest HCV prevalence worldwide.[6] The documented seroprevalence of hepatitis C viral antibody in Nigeria ranges between 4.5% and 5%.[4]

Liver biopsy has become central to the management of hepatic diseases despite being an invasive procedure and is widely used in clinical practice as the gold standard in assessing the nature and severity of liver diseases.[7] The first published qualitative classification of chronic hepatitis by an international group was in 1968 and codified terminologies such as chronic persistent hepatitis, chronic lobular hepatitis and chronic active hepatitis based on the degree of disease activity and to provide prognostic information and criteria for the use of immunosuppressive therapy.[8] Although these terminologies are currently obsolete, before this period, most hepatological examinations were descriptive and subjective that leads to interpretation discrepancies among clinicians.[9]

Objective Histological Activity Index (HAI) was established in 1981 by Knodell *et al*.[10] Subsequently, different modifications of the Knodell's (HAI) and scoring systems were introduced by Ishak,[11] Scheuer,[12] Batts-Ludwick,[13] and French METAVIR group [14] to ascertain the natural history, pathogenesis, correlate serological features and develop appropriate therapy for chronic hepatitis.[15] The advantage of these was to objectively enable statistical analysis of research result. Other international specialist bodies also brought some modifications such as World Congress of Gastroenterology, International Association for the Study of the Liver and the International Working Party.[16]

Determination of the grade of activity in chronic viral hepatitis (CVH) was based on important histologic features including level of portal infiltrate, interface hepatitis, lobular necrosis and confluent necrosis. The stage of the disease is determined by the level of fibrosis that usually commences as short fibrous septae from portal areas to bridging fibrosis and subsequent formation of incomplete or complete nodules.[17] While other systems use one or two of these histologic features in determining the grade/stage of the disease, the Ishak system combined all the parameters to determine the grade of activity and stage the disease.[11]

In tropical populations, we are confronted with a lot of challenges related to healthcare delivery such as other sectors of the economy, related to workforce, the technology and facility and especially the political will in developing healthcare sector. The aims of this analysis are to determine the epidemiological pattern of CVH in our centre, grade and stage all cases that have fulfilled the laid down criteria such as specimen length and number of portal tracts using the Ishaq Modified HAI; then share and compare our experience with similar works elsewhere.

METHODS

This is a 10-year analysis of all the liver biopsies submitted to the Department of Pathology, Ahmadu Bello University Teaching Hospital (ABUTH) Shika-Zaria, between 2006 and 2015. Tissues were fixed in formalin, embedded in paraffin and stained with haematoxylin and eosin and special stains which were routinely used for all our liver biopsies including Masson's trichrome, reticulin, periodic acid–Schiff (PAS) with and without diastase digestion, Perls and Shikata orcein.

PAS was used to demonstrate the presence of mucin, extent of hepatocyte loss in the grading of necroinflammatory activity. Reticulin stain demonstrates Type III collagen and Masson trichrome stain demonstrates Type I collagen fibres, these highlight hepatic plate architecture and thin layers of these connective tissues and were used for accurate assessment of structural changes and grading fibrosis. Orcein stain was employed to demonstrate HBsAg material within hepatocytes while Perls' stain was used to highlights stainable iron to rule out the cases of haemochromatosis.

Patients' biodata, including age, sex, duration of symptoms, were extracted from the accompanying case cards and in some cases from patients' case folder. Other information on viral load and activity was also extracted from case cards.

Detailed histologic features were reviewed by all the authors and cases were graded and staged according to Ishak modified HAI;[11] the scores were categorised according to Desmet[18] interpretation as minimal (1–3), mild (4–8), moderate (9–12) and severe (13–18) diseases. Other features such as HBV viral cytoplasmic particles and lymphoid aggregates and steatosis associated with

HCV hepatitis were also noted. Alcoholic liver disease was excluded using history of significant alcohol consumption and histologic features such as Mallory hyaline bodies and megamitochondria. Collected data were analysed using summary statistics and presented in frequency distribution tables and figures. Ethical clearance for the study has been obtained from the Ethics and Scientific Committee of the Ahmadu Bello University Teaching Hospital, Shika-Zaria.

RESULTS

Three hundred and one liver biopsy specimens were received during the study and of these 166 cases (55.2%) were of CVH. There were 119 male and 47 female with a male-to-female ratio of 2.5:1. Their ages ranged from nine to 62 years and peaked in the third decade of life. Up to 82.5% of cases were between ages of 21 years to 50 years [Figure 1]. One hundred and forty-three cases (84.2%) were of chronic HBV infection, 8.4% (14 cases) were of HCV and 5.4% (9 cases) were due to co-infection with HBV and HCV.

Table 1 shows a review of previous qualitative diagnoses and corresponding disease grade. Overall, forty-seven cases (28.3%) had modified Ishaq HAI score of between 0 and 3 (minimal disease), 70 cases (42.2%) were mild grade disease, 45 cases (27.1%) were moderate-grade disease and 2.4% of cases only had severe grade disease [Figure 2]. The stages of disease progression is presented in Table 2 and showed that bulk of cases (70.5%) were between Stages 0and 2 and 25.9% of cases were Stages 3 and 4 while only 6% were in Stage 5.

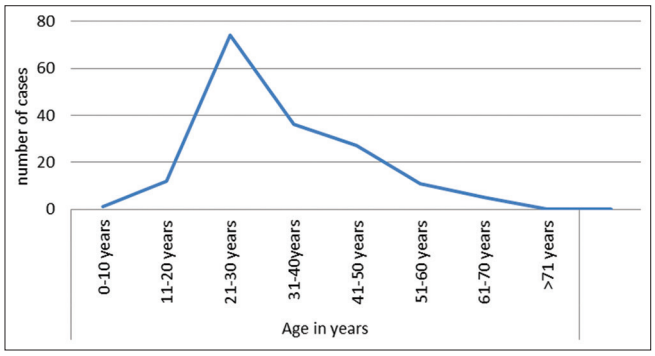

Figure 1: Line graph showing age distribution of cases of chronic viral hepatitis in the study

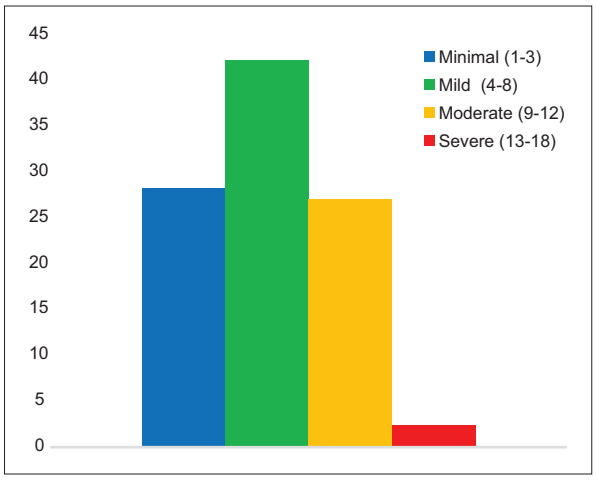

Figure 2: Histogram showing Grading of Chronic Viral Hepatitis Using Ishaq's Modified Histologic Activity Index

DISCUSSION

CVH was the predominant liver pathology in our settings affecting younger age groups predominantly male. Hence, many reasons to explain this trend; the high prevalence of HBV infection, higher rate of foetomaternal transmissions, the promiscuous behaviour of the young populations, the rising markets of traditional concoctions, improved awareness and accessibility to medical facilities. Similar reports from Nigeria show chronic hepatitis to predominate among different liver diseases. David *et al*, in their study of the safety of liver biopsy in the same center as the index study also reported chronic viral hepatitis as the predominant liver pathology.[19] Chronic viral hepatitis accounted for 55.2% of all the liver diseases recorded in this study. This is slightly higher though comparable to the frequency distribution of 40.5% and 45.7% respectively from Kano (north west) and Maiduguri (north east).[20,21] In Jos, north central 31.7% was reported,[22] while the highest

Table 1: Chronic viral hepatitis review and grade Using the Ishaq Modified Histologic Activity Index

Qualitative diagnoses		Disease grade				Total
Diagnosis	Frequency	Minimal	Mild	Moderate	Severe	
Chronic persistent hepatitis	63	40	30	3	0	63
Chronic active hepatitis	21	0	5	14	2	21
Chronic lobular hepatitis	14	2	6	6	0	14
Chronic hepatitis	15	2	8	5	0	4
Chronic viral hepatitis	30	0	17	12	1	30
Chronic HBV hepatitis	22	3	14	4	1	22
Chronic HCV hepatitis	1	0	0	1	0	1
Total	166	47	70	45	4	166

HBV: Hepatitis B virus, HCV: Hepatitis C virus

Table 2: Grading and staging of chronic viral hepatitis by sex using Ishaq Modified Histologic Activity Index

Disease grade	Stage														Total
	0		1		2		3		4		5		6		
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	
Minimal	18	14	7	2	3	0	2	0	0	0	1	0	0	0	47
Mild	9	4	18	5	17	3	11	2	1	0	0	0	0	0	70
Moderate	0	0	3	2	7	5	10	5	7	4	2	0	0	0	45
Severe	0	0	0	0	0	0	1	0	0	0	2	1	0	0	4
Total	28	17	28	9	27	8	24	7	8	4	5	1	0	0	166
Grand total (%)	45 (27.1)		37 (22.3)		35 (21.1)		31 (18.7)		12 (7.2)		6 (3.6)		0		166 (100)

rate of 62.5% was reported by Ugiagbe *et al* in Benin, south-south Nigeria.[23] However, a study from Lagos (Southwest) documented lower rate of 17.7%.[24]

Majority (82.5%) of our cases were clinicopathologically due to hepatitis B viral infection. The carrier rate of HBsAg varies worldwide; from 0.1% to 0.2% in Britain, the United States of America and Scandinavia to 3% in Greece and southern Italy. In Africa and Far East, it ranges between 10% and 15%.[2] Higher rates are also documented in isolated communities of Alaskan Eskimos (45%) and Australian Aborigines (85%).[2] The HBV hepatitis is highly endemic in Africa with prevalence of 8% and at least 65 million people chronically infected.[3] The seroprevalence of HBsAg in Nigeria ranges from 10% to 40%.[6] In 2014, Mbaawuaga *et al*. reported a 12.0% seroprevalence of HBsAg in Northcentral Nigeria.[25] Musa *et al*. also studied 46 published articles in a 13 years systematic review and meta-analysis of the prevalence of HBV infection in Nigeria and reported ranges of between 0.5% and 46.8% and a pooled prevalence of 13.6% among Nigerians.[26]

The CVH cases were reviewed based on Ishaq modified HAI, a comprehensive quantitative numerical assessment. One-hundred and seventeen cases (70.5%) had minimal and mild grade diseases with scores of 1–3 and 4–8, respectively according to Desmet,[18] also 70.5% of the cases had fibrosis score of 0–2, a non-progressive disease while only 3.6% had a score of 5 which is an advanced stage that may progress to cirrhosis. However, adequate treatment at this stage can still reverse the process with promising results.[27] Our finding is comparable to the report by Okafor and Olusegun in Ile-Ife whom in comparing the various systems of grading/ staging, used similar grading and staging criteria in their study of chronic viral hepatitis and documented 46% for minimal and 38% for mild grade diseases with respective scores of 1-3 and 4-8 and a fibrosis score of zero in 70% of cases). In that report only single case had Stage 5 disease.[28] Ananya *et al*. in their study of chronic HCV hepatitis reported that 60.5% of their cases had Ishaq HAI score of <8, a minimal to mild grade disease, 33.3% had fibrosis Stage 0–2 disease and 66.7% had fibrosis Stage 3.[29] Similarly, a prospective study of 344 cases of chronic HCV patients in Pakistan by Anwar *et al*., reported 54.9% patients with minimal to mild disease activity. In the later study, they also reported that 69.0% of their cases had Stage 0–2 disease,[30] a finding which is similar to 70.5% recorded in this study for Stage 0–2. Again only 8.7% of their patients were Stage 4 diseases. The finding of 70.5% for minimal to mild grade in this study also concur with reports from Brazil and Dhaka, Bangladesh by Atique *et al*. where they recorded 63% for Stages 0–2 though with wide disparity in the disease grades.[31,32] The low rate of progression of disease in this study may be due to the fact that the majority of cases were HBV-associated chronic hepatitis with only few cases of HCV hepatitis. According to the WHO reports, 75% of adult infected with HCV progress to chronic disease while only 5.5%–10% of HBV-infected patients progress to chronic disease.[6] The fibrosis stage of CVH determined progression to cirrhosis and possible transformation to HCC, in our series 10.8% of cases had modified Ishaq HAI Stages 4–5 and these are likely to progress to cirrhosis with significant percentages transforming to HCC.

Grading and staging of liver biopsies are central to the management of patient with CVH though in most centres in the tropical settings is not routinely done. In the few centres, where this important aspect of hepatologic examinations is routinely undertaken, there seems to be no uniform system adopted. The new approach to histopathologic hepatic tissue examinations requires comment on aetiology, severity and distribution of necroinflammatory activity and degree of fibrosis. Aetiology in most cases cannot be determined on the basis of histological examinations alone; but combination of clinical features, serologic evidence as well as characteristics histopathologic findings. For grading and staging of chronic hepatitis biopsy specimen the minimum criteria include specimen length of at least 20-25mm long and 11 or more complete portal tracts avoiding supcapsular specimen as this may affect staging fibrosis. The specimen should be accompanied by complete, adequate and relevant clinical informations.

The most important challenges in evaluating hepatic biopsy specimen in most centres in developing nation including ours relates to specimen adequacy, fragmentations, lack of relevant clinical information, properly processed tissue with ancillary stains, number of pathologist and especially only few show interest in hepatopathology. The limitations of this study include inadequate quantity of tissues, some with <6 portal areas and fragmentation of the tissues. In addition, the study is hospital based; on selected patients attending the hospital and therefore cannot represent the generality of the populace.

CONCLUSIONS

Grading and staging of liver biopsy specimen in chronic hepatitis are an integral part of the histopathologic interpretations. A standard reproducible system of grading and staging with clinical relevance in a particular locale should be adopted in reporting such specimen by the attending pathologist. This is eased by complete relevant clinical information from the gastroenterologist and or hepatologist.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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