Hepatitis B Serological Markers Among Asymptomatic, Treatment Naïve Patients With Chronic Hepatitis B Infection In Abeokuta, Nigeria

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Abstract

Background: Chronic hepatitis B infection is a public health challenge and the most common cause of chronic liver disease in Nigeria. The serological profile of hepatitis B virus has implications on chronicity, replication, choice of treatment and chances of chronic complications. This study determined the pattern of hepatitis B serological markers among asymptomatic treatment naïve patients with chronic hepatitis B in Abeokuta, Nigeria.

Methods: 300 chronic hepatitis B infected patients who met the inclusion criteria were recruited over 3 years. Hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), antibody to the e antigen (anti HBe), total and IgM antibodies to core antigen (total anti-HBc, IgM anti HBc), and antibody to the surface antigen (anti-HBs) were carried out on the sera of all the patients.

Results: 169 (56%) were male while 131 (44%) were female. Their ages ranged from 18 to 74 (mean 37± 10.5) years. All had HBsAg and total anti- HBc while 7 (2.3%) patients had HBeAg. 250 (83.3%) had anti HBe. 43 (14.3%) patients were negative for both the e antigen and anti HBe while no patient had both. 4 (1.3%) and 8 (2.7%) had IgM anti HBc and anti HBs respectively.

Conclusion: Most of the patients with chronic hepatitis B in Abeokuta, Ogun state, Nigeria were negative for e antigen and positive for anti HBe. Some were negative for both the e antigen and its antibody while few had both HBsAg and ant-HBs.

INTRODUCTION

Hepatitis B virus is one of the most common human viruses affecting about 2 billion people worldwide. The infection could be acute and self-limiting, but some will progress to the chronic form, depending on the age of acquisition. Chronic hepatitis B infection is a worldwide public health challenge affecting about 240 million people (1) This chronic infection is responsible for about 1 million death every year largely from long term complications of liver cirrhosis and or hepatocellular carcinoma (2). Having hepatitis B infection increases the chances of having hepatocellular carcinoma by hundred folds (3). Nigeria is endemic for hepatitis B with a pool prevalence of 13.6 % and it is the most common cause of chronic liver disease in the country (4-6).

The presence of various proteins that can stimulate the production of anti-bodies makes hepatitis B virus to have many serologic markers (7). These markers have implications on chronicity, replication, phase of the infection, choice, duration and response to treatment as well as chances of having chronic complications. The most abundant of these markers is hepatitis B surface antigen whose presence confirms hepatitis B infection (8). It appears between 1 and 3 months after exposure and Its persistence for more than six months implies chronic infection (7).

Hepatitis B early (e) antigen (HBeAg) is secreted from the pre-core part of the gene and it appears shortly after the infection. It is a marker of infectivity and replication (9). The loss of the e antigen and appearance antibody to e antigen (anti-HBe) is usually, though not always associated with low serum HBV DNA. Hepatitis B core antigen (HBcAg) is found in the infected hepatocytes. Antibody to this antigen (anti HBc) appears after the surface antigen. IgM class of the anti HBc is elaborated in the acute phase between the disappearance of HBsAg and appearance of the hepatitis B surface antibody (anti-HBs). IgG class of the anti HBc suggests a chronic infection and it persist for life. Anti HBS

suggest immunity against the virus and it can be acquired both post resolution of an acute infection or vaccination. Hepatitis B surface antibody usually but not always follows disappearance of the surface antigen (anti-HBs) (8).

Some workers have reported their findings on serological markers among patients with hepatitis B in in some parts of Nigeria. Most of them were either not complete or not done specifically in patients with chronic hepatitis B infection (10-14). It is important to determine the complete serological pattern in chronic hepatitis B patients because they are the ones at risk of long-term complications of the virus, which account for most of the mortality attributed to HBV. Moreover, to the best of our knowledge, there is paucity of data on the pattern of the serological markers of patients with hepatitis B infection in Abeokuta and indeed Ogun state. It is pertinent to know whether the pattern in Ogun state is the same as what others have reported.

We determined the pattern of the serological markers in asymptomatic treatment naive patients with chronic hepatitis B infection in Abeokuta, south west Nigeria.

METHODS

Study Design and site

This was a cross sectional study carried out at a hepatology specialist clinic in Abeokuta, Ogun between June 2015 and June 2018. Abeokuta is the largest and the capital city of Ogun state in south west Nigeria with a population of 593,100. It is on latitude 1.150 N and longitude 3.350 E. This clinic was the only hepatology specialist clinic in Abeokuta during the study period. Patients were referred from various hospitals in Abeokuta and its environs for various reasons including specialist consultation, investigations and endoscopy services.

Subjects and data collection

Using a proportion of 20% for frequency of e antigen among patients with hepatitis B infection (10), precision of 5% and confidence interval of 95%, a minimum sample size of 246 was obtained.

Chronic hepatitis B infection was defined as being aware of one's hepatitis B status for at least 6 months.

Selection criteria

1. Patients who have known their hepatitis B status for at least 6 months
2. Patients that were 18 years and above
3. Patients who had no symptoms suggestive of a liver disease
4. Patients with normal liver examination
5. Patients with normal liver ultrasound
6. Patients who were treatment naive

Consecutive patients who met the inclusion criteria were recruited for study.

About 5 mls of blood was drawn from each patient and was immediately centrifuged. The plasma was harvested into a cryovials and labelled with a serial no that was unique to each patient. The plasma was kept in a -400c refrigerator at the Sacred Heart Hospital, Lantoro, Abeokuta until analysis. HBsAg, HBeAg, anti HBe, IgM anti HBc, Total antibody to hepatitis B core antigen (Total anti-HBc), and anti HBsAg were done on each patients' sample using LUMIQUICK® Diagnostics (California, USA) immunochromatography test kits with accuracy of between 97.4 and 99.6 for the different components. The tests were done following the manufacturer's instructions.

Ethical Consideration

Ethical approval was obtained from the ethics committee of Sacred Heart Hospital, Lantoro, Abeokuta and informed consent was taken from each of the patients recruited.

Data analysis

The data was analyzed using Statistical Package for Social Sciences version 23. A total of 300 subjects were recruited for the study: 56 (19%) in 2015, 108 (36%) in 2016, 75 (25%) in 2017 and 61(20%) in 2018. Data was summarized using frequency tables and means. Association were tested for between the presence of each serological marker and sex and age using chi square, fisher's exact and independent students t tests. P value less than 0.05 was considered significant.

RESULTS

Out of the 300 patients recruited for the study, 169 (56%) were male while 131 (44%) were female. Their age ranged from 18 to 74 with a mean of 37 (± 10.5) and median of 36.5 years. All the patients were positive for HBsAg and total anti HBc. Seven patients (2.3%) were positive for HBeAg while 293 (97.7%) patients were negative for it. Out of the positive seven patients, one was a female while six were male (P value= 0.11). 250 (83.3%) patients were positive for the antibody to e antigen (anti -HBe) while 50 (16.7%) were negative for it. Of the 250 positives for anti HBe, 139 were male while 111 were female (p=0.64). All the patients that

had e antigen were negative for anti HBe while 43 (14.3%) were negative for both e antigen and anti-HBe. Four (1.3%) patients were positive for the IgM anti-HB core while 296 (98.7%) were negative for it. Out of the 296 that were negative, 167 were male while 129 were female (p=0.59). Eight (2.7%) patients were positive for anti-HBs while 292 (97.3%) were negative for it. Out of the 292 that were negative for anti-HBs, 163 were male while 129 were female (p=0.47). The relationship between the different serological markers and sex are as shown in table 1.

Table 1

Relationship between sex and serological markers

		Male	Female	P value
HBeAg	Positive	6	1	0.11*
	Negative	163	130	
Anti-HBe	Positive	139	111	0.34c
	Negative	30	20	
IgM anti HBe	Positive	2	2	0.55*
	Negative	167	129	
Anti HBS	Positive	6	2	0.47*
	Negative	163	129	

Tests [c] = chi square [*] = Fisher exact test

The mean age of parents with e antigen was 32 ± 7.5 years while that of those that were negative for the e antigen was 37 ± 10.2 years with a p value of 0.38. The relationship between other serological markers and age are shown in table 2.

Table 2

Relationship between age and different serological markers of the subjects

		Means of age in years	P value
HBeAg	Positive	32 ± 7.5	0.38
	Negative	37 ± 10.5	
Anti HBe	Positive	37± 9.9	0.13
	Negative	36± 12.8	
IgM anti HBc	Positive	45.5± 7.6	0.38
	Negative	36.8± 10.5	
Anti HBS	Positive	41± 8.1	0.34
	Negative	37 ±10.5	

Test: Independent t test

DISCUSSION

The main aim of this study was to determine the pattern of serological markers in asymptomatic treatment naïve patients with chronic hepatitis B infectin in Abeokuta. The 2.3% frequency of e antigen in this study is the same as what Otegbayo et al reported among blood donors in Ibadan (15). It is however lower than 8.6% and 18.2% reported in Enugu and Ibadan respectively (10,11). The relative low frequency of e antigen in this study is not surprising as the study was done among subjects that have had hepatitis B infection for at least six months i.e. patients with chronic hepatitis B infection. Other studies did not state whether their subjects were just those with chronic hepatitis. Early (e) antigen appears early in the course of the infection and usually disappears later with subsequent development of anti- HBe (8). Therefore, the frequency of hepatitis B e antigen tend to be higher in acute infection than in chronic infection when some might have achieved e seroconversion. The absence of e antigen does not always mean low replication and infectivity of the virus (9). Some HBV variants have mutation (s) in the pre-core and or basal core promoter region which prevent the production of HBe antigen (16). We are no aware of any report of the frequency of such mutations in the population of Nigerian patients with chronic hepatitis B infection. Infection with core mutant variants of hepatitis B have been associated with more severe liver disease including liver cancer. A study from South Africa reported higher frequency of core promoter mutations in patients with hepatocellular cancer (66%) than asymptomatic hepatitis B infected patients (11%) (17). This might explain why HBV induced hepatocellular carcinoma is still common in Nigeria even though majority of our HBV patients are e negative.

There are possible explanations for the 14.3% of the subjects that were negative for both HBeAg and anti HBe. It is possible that these patients recently lost the e antigen and were yet to develop the anti HBe. Another possibility is that these patients might have core mutant variant of HBV de novo and so could not produce both the e antigen and of course the antibody to it. In a similar study in Enugu, Nigeria, 14% of their subjects were negative for both HBeAg and anti-HBe (11).

The mean age of those patients with e antigen was lower than that of those without e antigen. Conversely the mean age of those with anti-HBe was higher than that for those without the antibody to the e antigen though, it did not attain statistical significance. This is what is expected since the longer the infection in the body, the more the chances of seroconversion. Most of the HBV infection in our population are acquired in childhood (18).

Four of the subjects were positive for the IgM class of the anti-HBc even though these patients had harbored HBV for at least six months. Though IgM anti-HBc is believed to be a marker of acute infections, it may persist sometimes for up to 2 years after the initial exposure (9). Studies from Lagos, Enugu and Benue reported frequencies of IgM anti-HBc of 10%, 0% and 12% respectively in their subjects (19-20).

Other reasons why IgM anti HBc could be present in chronic setting include acute flare of a chronic hepatitis B, superinfection with hepatitis D or C (21). Distinguishing between acute and acute flare of chronic infection can thus become a challenge. Maruyama et al had proposed an additional serology marker called antibody to woodchuck hepatitis Virus to help in distinguishing between acute hepatitis B and acute exacerbation of hepatitis B infection (21).

Anti- HBs is usually elaborated after the disappearance of HBsAg with a short interval when the two might not be detectable(22).The Society of Gastroenterology and Hepatology in Nigeria's (SOGHIN) guideline for the management of hepatitis B and indeed most international guidelines, advocate screening for hepatitis B surface antigen before vaccination of those that are negative against hepatitis B in areas of high prevalence like Nigeria(23-25). However, some people get vaccinated without first screening for hepatitis B surface antigen, thereby increasing the chances of having both the surface antigen and the antibody, if the individual was already positive for HBsAg. This might be the reason for the 2.7% who had both HBsAg and anti HBs. Other reasons for concomitant HBsAg and anti HBs include infection by multiple subtypes of hepatitis B viruses, chronic renal failure patients on hemodialysis and those that abuse heroine (22). In a study of 63 patient with HBsAg in Makurdi, Nigeria, none of their patients had anti- HBs (20).

CONCLUSIONS

In conclusion, most of the patients with chronic hepatitis B in Abeokuta, Ogun state, Nigeria are negative for e antigen, positive for anti-HBe. Some are negative for both the e antigen and antibody while few have both HBsAg and ant-HBs.

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References

1. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, and Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. The Lancet. 2015;386 (10003): 1546–1555.
2. Ferenci P, Fried M, Labrecque D, Bruix J, Sherman M, Omata M, et al., "Hepatocellular Carcinoma (HCC): A Global Perspective," J. Clin. Gastroenterol. 2010; 44(4): 239–245.
3. Beasley R, Hwang L, Lin C, and C. Chien, "Hepatocellular carcinoma and hepatitis B virus: A prospective study of 22707 men in Taiwan. Lancet. 1981; 2: 1129–1133.
4. Musa BM, Bussell S, Borodo MM, Samaila AA, Femi OL. Prevalence of hepatitis B virus infection in Nigeria, 2000-2013: a systematic review and meta-analysis. Niger. J. Clin. 2015; 18(2): 163–172
5. Soyemi OM, Otegbayo JA, Ola SO, Akere A, Soyemi T. Comparative diagnostic efficacy of serum squamous cell carcinoma antigen in hepatocellular carcinoma. BMC Res. Notes. 2012; 5 (403).
6. Ojo OS, Thursz M, Thomas HC, Ndububa DA, Adeodu OO, Rotimi O, et al., Hepatitis B virus markers, hepatitis D virus antigen and hepatitis C virus antibodies in Nigerian patients with chronic liver disease. East Afr. Med. J. 1995; 72(11): 719–721.
7. D. R. Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seeff LB. Diagnosis and Monitoring of Hepatic Injury. I. Performance Characteristics of Laboratory Tests. Clin. Chem.2000; 46(12): 2027–2049.
8. Tong S, Kim KH, Chante C, Wands J, and Li J.Hepatitis B Virus e Antigen Variants. Int. J. Med. Sci. 2005; 2(1): 2–7.
9. Mauss S,Berg T, Rockstroh J, Sarrazin C, Wedemeyer H. Hepatology, 7th ed. 2016.
10. Akere A, Akande KO, Oke TO, Fakoya T. Hepatitis B Virus Infection: Characteristics of Patients, Frequency and Significance of Viral Markers. J. Hepat. Res.2015; 2 (1): 1021
11. Ijoma UN, Nwokediuko SC, Onyenekwe B, and Ijoma, C.K. Low prevalence of hepatitis B 'E' antigen in Asymptomatic Adult subjects with Hepatitis B infection in Enugu, South East Nigeria. Internet journal of Gastroenterology.2009;10(1).
12. Aba HO, Aminu M. Seroprevalence of hepatitis B virus serological markers among pregnant Nigerian women. Ann. Afr. Med.2016;15 (1): 20–17.
13. Emmanuel MM, Iroegbu CU, Ike AN. Hepatitis B Virus (HBV) serological patterns in Benue state, Nigeria. Open J. Med. Microbiol.2014; 4: 1–10.
14. Ola SO, Olaleye DO, Olubuyide IO. Serology of HBV and its clinical implications among Nigerian subjects. Trop. Gastroenterol. 2008; 29(3): 163–166.
15. Otegbayo JA, Fasola FA, Abja A. Prevalence of hepatitis B surface and e antigens, risk factors for viral acquisition and serum transaminase among blood donors in Ibadan, Nigeria. Trop. Gastroenterol. 2003;24(4):196–197.
16. Carman WF, Hadziyannis S, Mcgarvey MJ, Jacyna MR, Karayiannis P, Makris A, et al. Mutation preventing formation of hepatitis b e antigen in patients with chronic hepatitis b infection. The Lancet. 1989; 334 (8663): 588–591.
17. Kao J, Chen P, Lai M, Chen D. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. Gastroenterology. 2003; 124(2): 327–334.
18. Fakunle YM, Abdurrahman MB, Whittle HC. Hepatitis-B virus infection in children and adults in Northern Nigeria: a preliminary survey. Trans. R. Soc. Trop. Med. Hyg. 1981; 75(5): 626–629.
19. Akinbami AA, Oshinaike OO, Dosunmu OA, Adeyemo TA, Adediran A, Akanmu S, et al. Seroprevalence of hepatitis B e antigen (HBe antigen) and B core antibodies (IgG anti-HBcore and IgM anti-HBcore) among hepatitis B surface antigen positive blood donors at a Tertiary Centre in Nigeria. BMC Res. Notes. 2012; 5(1):167

20. Odimayo M, Nwadioha S, Ajayi AO. Hepatitis B serologic markers among individulas with hepatitis B surface antigen seropositivity in Markudi, Nigeria. Int. J. Med. Med. Sci 2016; 6(5): 340–344
21. Maruyama T, Schodel F, Lino S, Koike K, Yasuda K, et al. Distinguishing between acute and symptomatic chronic hepatitis B virus infection. Gastroenterology. 1994;106 (4):1006–1015.
22. Foutch PG, Craey WD, Tabor E, Cianflocco AJ, Nakamoto S, Smallwood LA, et al. Concomitant Hepatitis B Surface Antigen and Antibody in Thirteen Patients. Ann. Intern. Med. 1993; 99 (4); 460.
23. Malu OA, Borodo MM, Ndububa DA, Ojo OS, Anomneze EE, Lesi OA, et al. Hepatitis B and C Treatment Guidelines for Nigeria. Nigerian Journal of Gastroenterology. 2015; 7(2): 63–75
24. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HL, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J. Hepatol. 2017; 67(2): 370–398.
25. Sarin SK, Kumar M, Lau GK, Abass Z, Chen HLY, Chan CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol. Int. 2016; 10 (1): 1–98.

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