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Original Article

Diagnostic Accuracy of Serum Hepatitis B Virus DNA Levels and ALT for Liver Fibrosis

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Abstract

Background: To determine the diagnostic accuracy of combined serum HBV DNA and serum ALT levels for significant liver fibrosis in chronic Hepatitis B patients.

Methods: In this cross sectional study confirmed cases of Hepatitis B were enrolled. Inclusion criteria was age more than 20 and both genders, while those cases who had history of Hep C or were on treatment of Hep B were excluded. Patients'samples were taken for HBV DNA and ALT to predict the presence of liver fibrosis.

Results: Out of total 130 cases, there were 72 (54.5%) males with a mean age of 43.78± 10.28 years. The results of HBV DNA + ALT showed 51 (38.6%) patients to have fibrosis, whereas endoscopic diagnosis of esophageal varices was confirmed in 40 (30.3%) patients.Sensitivity of HBV DNA + ALT for diagnosis of fibrosis was found to be 55%, specificity 66.6%and diagnostic accuracy 65%.

Conclusion: Combined HBV DNA & ALT values can be advised as predictor of liver fibrosis.

Key Words: Chronic liver disease. HBV, ALT, Liver fibrosis,Biopsy

Introduction

There are about 350 to 400 million people who are infected with chronic hepatitis B worldwide.[1] The clinical course is marked by a wide range from asymptomatic carrier state to cirrhosis, hepatic decompensation and hepatocellular carcinoma[1]. In Pakistan, chronic Hepatitis B is a major problem and has intermediate Hepatitis B prevalence with a carrier rate of 4 to 5 %. [2]

Although high risk is attributed in patients who are HBsAg positive of developing sequel of disease but of these only minimal numbers of patients develop cirrhosis and hepatocellular carcinoma.[3] Recent development in techniques of genome detection has shifted the focus from serological studies to HBV detection for diagnosis and management.

Liver biopsy, which is the investigation of choice for inflammation and fibrosis, is strongly recommended in patients with persistent HBV DNA levels 2000 IU/ml and ALT 1 to 2 times the upper limit of normal.[1, 4] Few histological studies have demonstrated that HBV DNA levels 2000 IU/ml and upper limit of ALT to 90 U/L for women and 30 U/L for men are associated with high likelihood of severe fibrosis.

One of such study is REVEAL HBV study that showed that histological grades were significantly associated with serum HBV viral load.[5] A study showed sensitivity of 50% and specificity of 79.6 % of ALT >40 and HBV DNA more than or equal to 2000 IU/ml in predicting fibrosis and prevalence of 0.53.[6]

The latest EASL, AASLD, APASL and ASPA Guidelines recommend commencing of antiviral therapy in patients in whom significant fibrosis (i.e,METAVIR F2-F4) exists. These guidelines do not recommend Hepatitis B DNA and serum ALT to be used as a marker of underlying fibrosis. The liver biopsy is considered to be "gold standard" for diagnosis of fibrosis with sensitivity and specificity more than 90 %.[7, 8]

Patients and Methods

This study was conducted on 132 patients presenting with Hepatitis B. This cross sectional study conducted at Gastroenterology and Hepatology Division of Holy Family Hospital, Rawalpindi in a period of six months (April to October, 2015)..The patients included in this study were Hep B s Ag positive (by ELISA) and of 18 to 60 years of age. Patients who had Positive Hepatitis C status (by ELISA) or decompensated chronic liver disease or abnormal blood complete picture or deranged coagulation profile or were unfit for liver biopsy due to any reason were excluded from this study.

Detailed history and physical examination was carried out in standardized protocol. Complete blood count, liver function tests, HBV DNA was done. The liver biopsy was done after informed consent. The samples of liver biopsy were preserved in normal saline and formalin and were sent to histopathology laboratory of Pathology department of same hospital. Samples of ALT and HBV DNA were sent in serum bottles. HBV DNA levels >2000 IU/ml and ALT> 90 U/L for

women and >30 U/L for men are predictor for liver fibrosis. All the data was recorded on a specially designed performa separately for each case. Data was analyzed in SPSS version 18. The diagnostic accuracy was calculated for serum HBV DNA and ALT levels using 2×2 table keeping liver biopsy as gold standard.

Results

Out of 132 patients, there were 72 (54.5%) males and 60 (45.5%) females. The mean ± standard deviation age of study population was 43.78± 10.285 years. Results of HBV DNA + ALT showed 51(38%) patients to have fibrosis while it was absent in 81(62%), whereas endoscopic diagnosis of esophageal varices was confirmed in 40(30%) patients and absent in 92(70%)(Table 1).Based on these results, while taking biopsy as the gold standard, the sensitivity of HBV DNA + ALT for diagnosis of fibrosis was found to be 55%, specificity 66.6%, positive predictive value 43% and negative predictive value 78 % and diagnostic accuracy of 65% (Table 2)

Table 1: HBV DNA + ALT X Biopsy diagnosis of fibrosis

		Biopsy diagnosis of fibrosis	
		Yes	No
HBV DNA + ALT	Yes	22(16%)	29(22%)
	No	18(13%)	63(47%)

Table 2: Diagnostic accuracy of HBV DNA with biopsy for diagnosis of fibrosis

Sensitivity	55%
Specificity	67%
Positive predictive value	43.13%
Negative predictive value	77.77%
Diagnostic accuracy	65%

Discussion

In management of CHB patients, histological liver evaluation is an important part of the severity assessment and has importance for treatment decisions.[9] Although liver biopsy is a gold standard to determine the stage of fibrosis and degree of necroinflammation, it is an invasive procedure with minimal but significant risk of morbidity and mortality.[10] Therefore, many non-invasive methods have been applied to replace this invasive procedure.Similar results were seen in a study by Sanai et al .[11] In addition, the positive predictive value was found to be 81% and negative predictive value 91%. Another study showed that a serum HBV DNA would provide a theoretical sensitivity of 71.1%, with theoretical specificity of 73.4% in patients. [12]

There are three recognized phases of chronic hepatitis B infection: immune tolerant phase, immune clearance phase, and inactive or residual phase.[13] During the immune clearance phase, HBV DNA level is greater than 2,000/ml or 20,000 IU/ml depend upon the HBe Ag negative or positive status of the patient.[14] Acute flares of hepatitis activity with elevated levels of serum ALT may occur during this phase. Higher ALT levels, therefore, usually reflect the more vigorous immune response against HBV and more extensive hepatocytes damage.[15]On liver biopsy, nearly all of these patients have active hepatitis with variable degrees of fibrosis. All patients should be considered candidates for treatment.This phase is eventually followed by HBe Ag seroconversion to its antibody (anti-HBe) and/or undetectable or low HBVDNA < 2,000 IU/ml with normal ALT levels called inactive HBsAg carriers or low replicative phase.[16] On liver biopsy, they have no evidence of inflammation and in most cases no fibrosis. As a result, there is no reason why these patients require treatment for HBV.

Liver biopsy is most useful in these persons who do not meet clear cut guidelines for treatment.[17] These are the patients who are greater than 40 years of age, with ALT greater than the upper limits of normal but less than 2 ULN, HBV DNA levels > 2000 but < 20,000, and other clinical features suggestive of chronic liver disease and concomitant diseases. In the presence of moderate to severe necroinflammation and/or at least moderate fibrosis on liver biopsy, treatment of hepatitis B is warranted.[18]

One form of discordance is referred to as an immune tolerant phase.[19] Patients in the immune tolerant phase are usually young, Hepatitis B e Antigen (HBeAg) seropositive with high viral loads > 20,000 IU/ml but normal serum alanine aminotransferase (ALT). A recent study has confirmed that patients in the immune-tolerant phase show minimal disease progression. However, HBeAg positive subjects older than 40 years with persistent 'high normal' ALT may have significant hepatic necroinflammation or fibrosis.[20-21] Even with the current potent antiviral agents, it is difficult to completely suppress the high levels of HBV DNA found in these patients and treatment may significantly increase the risk of developing resistance over time. These patients should be kept under regular follow-up with ALT measured every 3 - 6 months. Performing a liver biopsy in these patients is often helpful to ensure that there is no on-

going inflammation and to confirm that the patient is indeed in an 'immune-tolerant state. [22]

Conclusion

Liver fibrosis prediction by measurement by HBV DNA + ALT can be considered as a simple non-invasive method to identify patients with fibrosis.

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