Potential Applications of Serum HBsAg Level Measurement in Patients with Hepatitis B and D Co-Infection

Abstract

This study aimed to investigate the serum HBsAg level in patients with HDV co-infection, its relationship with HBV DNA and HDV RNA levels and with the fibrosis stage. 19 patients were considered. Patients with hepatitis C or HIV co-infection were excluded. HBV DNA and HDV RNA quantization was done using COBAS Taq Man HBV test (Roche Diagnostics) and AmpliSensHDV test (Inter Lab Service), respectively. The HBsAg level was measured by the Architect HBsAgQT (Abbott Laboratories) assay. Statistical relationships were estimated by the Pearson correlation coefficient r.

In patients with HDV co-infection no correlation between HBsAg level and HBV viral load was detected. The correlation between HBsAg and HDV RNA levels ($r=0.663$, $p=0.002$) as well as between HDV RNA level and fibrosis stage ($r=0.50$, $p<0.05$) was significant.

The correlation between HBsAg level and the fibrosis stage was less significant ($r=0.42$, $p=0.07$).

We conclude that in patients with HDV co-infection:

i. HBsAg level did not correlate with HBV DNA level.

ii. A high HBsAg level is usually associated with a high HDV RNA level, so it can be used for estimating HDV viral load.

iii. A severe fibrosis is usually associated with a high HDV RNA level and, to a lesser degree, with a high HBsAg level.

Keywords: Hepatitis D virus; Hepatitis B virus; HBsAg level; Viral load

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Introduction

Chronic hepatitis delta (CHD), caused by the hepatitis D virus (HDV), is a severe form of chronic viral hepatitis, which is associated with a frequent development of cirrhosis and hepatocellular carcinoma.

HDV is a small defective RNA virus that requires the hepatitis B virus (HBV) surface antigen (HBsAg) for its replication. Worldwide, 15–20 million of HBV infected patients are anti-HDV positive [1].

Pathogenesis of HDV infection is still insufficiently studied. Such marker of a HBV mono-infection disease activity as HBeAg rarely occurs in HDV co-infected patients. It is known that HDV infection is generally associated with a suppression of HBV replication [2]. In most cases the severity of CHD depends on the level of HDV RNA. A quantification of HDV RNA is done in specialized laboratories and this method is very expensive. Therefore, in clinical practice it is desirable to have some other markers which make it possible to estimate the HDV RNA level without measuring it directly.

Recent data show that the HBsAg level in patients with a HBV mono-infection correlates with the covalently closed circular DNA (cccDNA) level in the liver [3]. Furthermore, it correlates with the transcriptional activity of cccDNA and is considered as a surrogate marker for the amount of infected cells [4,5]. Several studies show that HBsAg and HBV DNA levels vary strongly between the phases of CHB [3,6,7]. Without treatment, the serum HBsAg level changes slower than the HBV DNA level [4,6]. Today HBsAg level is used to distinguish between inactive carriers and patients with an active disease. However, the relationship between the HBsAg level and other markers of HDV activity in co-infected patients is still insufficiently studied. The importance of the HBsAg level monitoring during the interferon treatment was demonstrated in several studies [8,9]. Long-term interferon therapy can be envisaged in patients who exhibit a significant decline of HBsAg levels during initial therapy [10].

The goal of our study was to investigate the quantitative level of HBsAg in HDV co-infected patients, its relationship to HBV DNA and HDV RNA levels and to the stage of fibrosis.

Materials and Methods

From 2012 to 2014, a total of 19 patients with CHD were included in the study, 10 males and 9 females. Exclusion criteria were: 1) any kind of antiviral therapy within the previous 12 months; 2) positive tests for HCV or HIV antibody. All data were collected during routine visits.

HBV DNA and HDV RNA levels were measured by real-time PCR. HBV DNA quantization was done using the COBAS Taq Man HBV test (Roche Diagnostics). HDV RNA quantization was done using the AmpliSens HDV test (Inter Lab Service). The lower limits of detection for the HBV DNA and HDV RNA assays were 150 IU/ml and 200 IU/ml, respectively.

HBsAg level was measured by the fully automated Architect HBsAg QT (Abbott Laboratories) assay. This assay was calibrated against the WHO standard and allowed the quantization of HBsAg from 0.05 to 250 IU/mL. An HBsAg concentration higher than 0.05 IU/mL was considered as positive. Samples with an HBsAg level higher than 250 IU/mL required a 1:500 dilution with the diluent, as recommended by the manufacturer, and the exact concentration of HBsAg was measured.

Fibrosis stage was measured by transient elastography (Fibro Scan) only. No liver biopsy was performed.

Statistical relationships were estimated by the Pearson correlation coefficient *r*. Logarithmic values of HBsAg, HBV DNA and HDV RNA levels were used.

Results and Discussion

The baseline characteristics of the patients are summarized in Table 1.

Table 1: Characteristics of patients.

Age, mean ± SD, year	43,05 ± 5,92
Total bilirubin, mean ± SD, μmol/L	14,2 ± 3,5
ALT, mean ± SD, U/ml	87,38 ± 23,99
AST, mean ± SD, U/ml	65,06 ± 17,69
HBeAg positive	3 (16%)
HBsAg median (range), IU/ml	26306 (10634.75 - 43886.5)
HBV DNA median (range), IU/ml	150 (12.25 - 2980)
HDV RNA median (range), IU/ml	3010000 (623500 - 9412500)

In the HDV co-infected group, HBeAg-positive patients are rare. In the case of a HBV mono-infection, the presence of HBeAg is usually associated with a high HBV viral load. In patients with HDV co-infection this relationship has not been observed. This phenomenon can be explained by suppressive effects of HDV on HBV replication in all phases of HBV infection [11]. In our study, all three HBeAg positive patients (16%) had a low level of HBV DNA. It has also been shown that with HDV co-infection, the clinical long-term outcome of HBeAg-positive patients was similar to HBeAg-negative patients [11]. Only one of our HBeAg-positive patients had a severe degree of fibrosis (F4 (22,3 kPa)).

The distribution of patients depending on HBV (a), HDV (b) viral load, HBsAg level (c) and degree of fibrosis (d) is shown in Figure 1. A high level of HDV RNA (more than 10^6 IU/ml) was detected in 11 (58%) patients, while a high level of HBV DNA (more than 10^6 IU/ml) was detected in one patient only. A high HBsAg level (more than 2000 IU/ml) was detected in 15 (79%) patients.

Although all HBsAg positive patients should be screened for HDV antibody, in clinical practice CHD is often detected only several years after HBV infection has been diagnosed. In such cases, most of the patients already have an advanced fibrosis. In our study, 12 (63%) patients had a severe stage of fibrosis (stage F3-F4 in METAVIR score).

In our study a majority of the HDV co-infected patients had a high HDV RNA level combined with a low HBV DNA level. This correlates with the results reported in other studies. The inhibition of HBV replication by HDV is a well-known phenomenon [2,12]. However, one patient had both high HDV and HBV replication levels and three patients had both low HDV and HBV viral load. By contrast to HBV mono-infection, for which a significant correlation between HBsAg level and HBV viral load is typical [13,14], no correlation between these values was detected in patients with HDV co-infection. Instead, the correlation between HBsAg level and HDV viral load was significant (r=0.663, p=0.002).

The relationship between HBsAg level and HDV viral load is illustrated in Figure 2. In our study, all patients with a high HDV viral load had a relatively high HBsAg level. A low HBsAg level was detected only in two patients with a non-detectable HDV RNA level. As quantification of HDV RNA is expensive, a possibility to identify patients with a high probability of a low HDV RNA level without a direct quantification appears attractive. According to our study, detection of HBsAg level can be used for this purpose.

There is very little data available on how HDV viral load changes in the course of the disease [15]. Some studies demonstrate that serum HDV RNA level does not correlate with the stage of liver disease [16]. In our study, the correlation between HDV RNA level and fibrosis stage was significant (r=0.50, p<0.05). The correlation between HBsAg level and fibrosis stage was less significant (r=0.42, p=0.07).

Conclusion

Based on the results of our study, we conclude that in patients with HDV co-infection:

i. HBsAg level did not correlate with HBV DNA level. This can be explained by the inhibition of HBV replication in HDV co-infected patients.

ii. A high level of HBsAg is usually associated with a high HDV RNA level, so HBsAg level can be used for estimating HDV viral load.

iii. A severe fibrosis is usually associated with a high HDV RNA level and, to a lesser degree, with a high level of HBsAg.

Ethics

The study was approved by the Ethical Committee of the Botkin Infectious Diseases Hospital.

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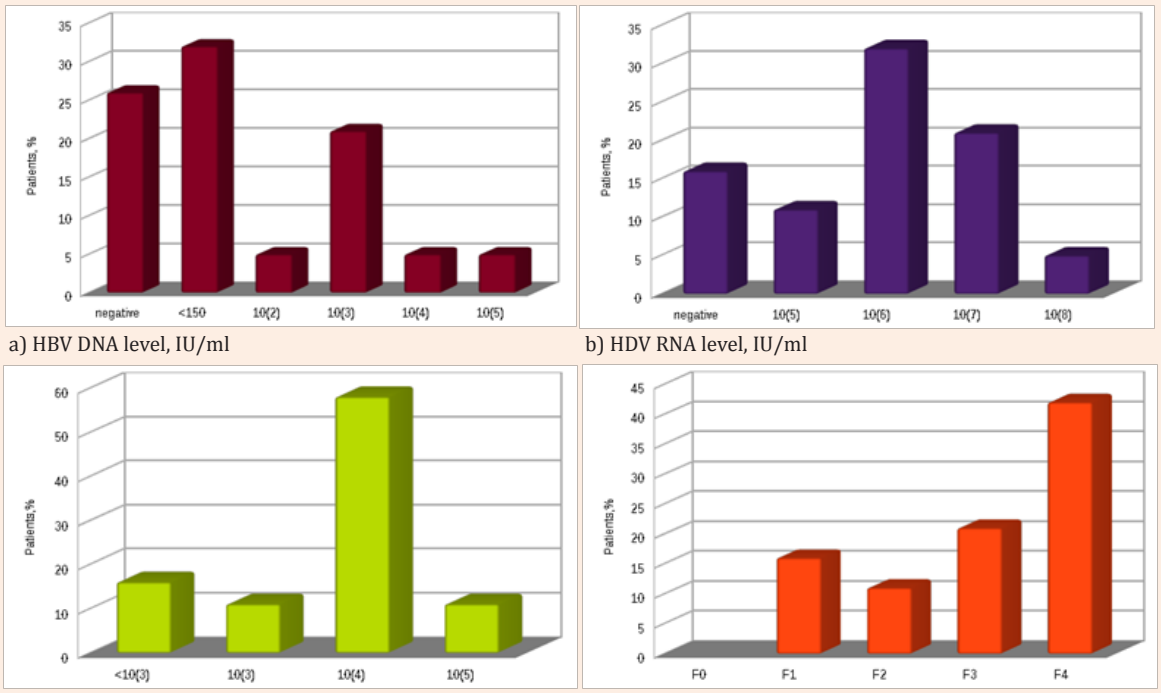

a) HBV DNA level, IU/ml

b) HDV RNA level, IU/ml

c) HBsAg level, IU/ml

d) Fibrosis

Figure 1: Virologic characteristics and fibrosis.

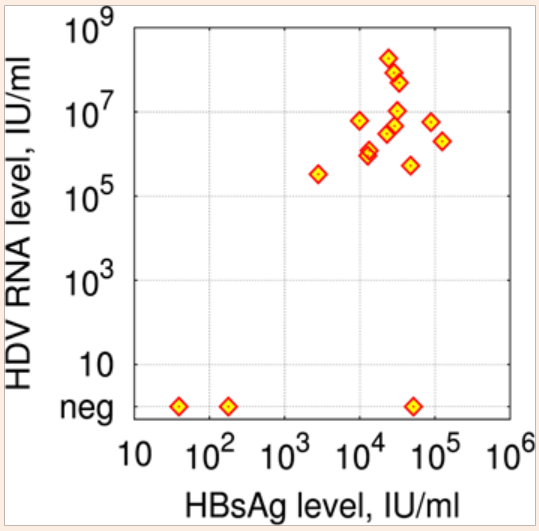

Figure 2: Relationship between HBsAg and HDV RNA levels.

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