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Epidemiological, clinical and virological aspects of hepatitis B, C and D co-infection in individuals infected with human immunodeficiency virus type-1

Bogdan Ionescu [1]*, Grigore Mihaiescu[1]

ABSTRACT

After the introduction of the HAART therapy the spectrum of illnesses challenging HIV care providers has changed significantly. At present, end stage liver disease and cirrhosis caused by the coinfections with hepatitis C virus (HCV) and hepatitis B virus (HBV) cause more morbidity and mortality than any other conditions encountered in HIV infected patients. The number of people suffering from the coinfections with the hepatitis viruses has been steadily increasing over the last years. The shared routes of transmission have lead to 10% of HIV positive people becoming infected with hepatitis B and 15% to 30% with hepatitis C, resulting in over 4 milion HIV/HBV and respectively 10 milion HIV/HCV coinfected individuals around the world. The purpose of this paper is to review the main sources of transmission of the coinfections and the differences in their progress as compared to mono-infections.

Keywords: *HIV, hepatitis viruses, HAART, coinfection*

1. Introduction

Worldwide, 370 million people are suffering from chronic hepatitis B, 170 milion from hepatitis C, 15 milion from hepatitis D and over 40 million from HIV infection. Over the past several years, the HAART therapy has increased the life expectancy of HIV-infected persons, enabling a change in the HIV- associated opportunistic infections spectrum. Coinfections with the hepatitis B, C and D viruses have become widespread amongst the human immunodeficiency virus-1 (HIV)-infected patients resulting in over 14 milion coinfected people around the world, because of the common routes of transmission. As a result of this increasing frequency, conditions caused by the hepatitis viruses have become the leading health concern amongst HIV-infected people. According to the last statistics provided by the Romanian Ministry of Health, Romania is thought to be the country with the highest prevalence of chronic hepatitis C in the European Union (4.9%) and amongst the countries with a high prevalence of hepatitis B infection (6%). The purpose of this paper is to present the common routes of transmission for the hepatitis viruses and HIV and the effects of the coinfections on the normal progress of the hepatitis and HIV mono-infections.

2. HBV-HIV coinfection

HBV is the leading cause of chronic liver disease worldwide, including hepatitis, cirrhosis, and hepatocellular carcinoma affecting approximately 10% of HIV-infected individuals [1]. The shared routes of transmission with HIV include: sexual contact, the parenteral and percutanate ways.

[1] University of Bucharest, Faculty of Biology, Microbiology and Immunology Department, Bucharest, Romania
*Corresponding author e-mail address: ***bogdanionescu87@yahoo.com***

The global HIV/HBV-coinfected population is estimated to 4 million [2-3]. HBV infection was defined by a positive result for HBV surface antigen (HBsAg) [4]. A classification of specific markers present in different types of HBV infection is made in table 1.

Table 1. Serologic and Viral Markers in HBV infection

Stage of Infection	HBsAg	HBsAb	HBcAb IgG	HBcAb IgM	HBeAg	HBeAb	HBV Viral Load
Incubation	+	-	-	-	+ or -	-	Low
Acute hepatitis B	+	-	+	+	+	-	High
HbsAG-negative acute hepatitis B	-	-	+	+	+/-	-	High
Inactive HbsAg carrier	+	-	+++	+ or -	-	+	Low
Precore mutant	+	-	+ or -	+ or -	-	+	High
Occult infection[a]	-	-	+	+ or -	-	-	High or low
Chronic hepatitis B	+	-	+++	+ or -	+ or -	-	High or low
Resolved HBV infection[b]	-	++	++	+ or -	-	+	Undetectable
HBV vaccination	-	++	-	-	-	-	Undetectable

Studies conducted on HBV/HIV coinfection have shown that the HBV infection activates the host's immune response determining the proliferation of CD4 cells. As a result, a higher HIV multiplication and an increased HIV viral load is observed [5]. Results concerning the effect of HIV on HBV progress have shown that the level of seric HBV DNA is higher and the alanine aminotransferase (ALT) level is lower than the one observed in HBV mono-infection. In coinfected patients a decreased clearance of the hepatitis B surface antigen and a lower rate of HBeAg seroconversion were observed as well [6]. Most studies conclude that the increased rate of HBV multiplication caused by HIV infection accelerates the progression to liver fibrosis, cirrhosis, and hepatic failure-related deaths in patients with chronic HBV infection [2]. The risk of liver related mortality in HIV/HBV coinfected patients was found to be 13 times higher than HIV mono-infected patients. Studies conducted on the evaluation of treatment efficiency of HBV-HIV coinfection cases have revealed that the decision to treat one or both infections is of paramount importance in choosing a regimen for the HIV/HBV-coinfected patients. The most recent guidelines suggest that HBV should be treated if there is any evidence of liver disease (including isolated HBV PCR > 10^4copies/mL) regardless of CD4+ cell count [7-8]. The treatment of the coinfection includes two categories of medication, the difference being in their capacity to suppress the HIV infection. In the category of the HIV non-suppressive medication there are included: interferon and pegylated interferon. The efficiency of interferon is poorly studied, but however a poor tolerance (many side effects) has been reported and a proportional relationship between its efficiency and the level of CD4+ cell counts [5]. Concerning the pegylated interferon, different studies are considering it a better therapeutic solution than the conventional interferon in HIV-negative patients [6], but data in coinfected subjects are lacking.With reference to the category of HIV suppressive medication, lamivudine is considered to have lower efficacy as monotherapy given the relatively rapid resistance rates occurred during the treatment, but it remains an option as part of a combination regimen [3].

3. HCV-HIV coinfection

HIV and HCV are seen as major health concerns at the moment, with 15 to 30 % of HIV positive people being infected with HCV, summing up to 10 milion coinfected people worldwide [9]. Both are RNA viruses and both have similar blood-to-blood transmission routes [10]. The main

sources for transmission include intravenous drug use, transfusion of blood products prior to screening, and to a lesser extent, sexual intercourse [11].

Most studies have associated the HIV/HCVcoinfection with a faster rate of hepatitis C progress, higher HCV viral loads, and a greater risk of developing severe liver damage. The impact of hepatitis C on HIV disease is less clear [10].

Studies conducted on this coinfection have concluded that the more rapid progression of HCV in coinfected patients is due to an inadequate immune response. IL-10 has been proposed to decrease inflammation in HCV patients. It also should be noted that patients with HIV naturally have lower levels of IL-10, which may explain the observed accelerated liver disease in co-infected patients [11].

Higher concentrations of HCV RNA are found in coinfected individuals than in HIV-negative patients with hepatitis C. These increased levels usually correlate with the CD4 count. Viral load is considered to be a predictor of response to therapy [12]. Interestingly, recent data from a cross-trial comparison showed that HIV-positive patients were less likely to present elevated levels of serum ALT and clinical symptoms of hepatitis than HIV-negative patients [13].

Numerous large cohort studies have demonstrated that once chronic hepatitis C is established the presence of HIV leads to a faster HCV clinical progression due to the lack of critical CD4-positive T cell responses against HCV [14]. Furthermore, the time interval between HCV exposition and development of cirrhosis was found to be shortened in coinfected subjects. Indeed, within 10-15 years of initial HCV infection, 15-25% of HIV-coinfected patients develop cirrhosis compared with 2-6% of HIV-negative patients [15]. HIV can be successfully treated in most people with hepatitis C. Some experts consider that it would be better to begin HIV treatment first in order to control HIV replication and increase the CD4 count, since hepatitis C treatment works better in people with stronger immune systems [13].

Regarding the HCV treatment, most coinfected people should be treated with pegylated interferon plus ribavirin combination therapy. Because hepatitis C can progress faster in people with HIV, it is best to begin hepatitis C treatment as early as possible in coinfected people [10]

The HAART therapy is thought to have a dual effect in the case of coinfected patients. Some studies have concluded that it can improve the immune response, which might reduce the rate of HCV-associated liver disease progression. In contrast other studies have stated that the hepatoxicity associated with this treatment might accelerate the HCV progress. Several recent studies suggest that a good response to HAART with good CD4 count and low or undetectable HIV RNA may slow HCV disease progress to a rate on par with HCV mono-infected individuals [16].

4. HIV/HBV/HDV coinfection

Hepatitis delta is considered the most severe form of viral hepatitis in humans. The hepatitis delta virus (HDV) is a defective RNA virus which requires the hepatitis B virus (HBV) surface antigen (HBsAg) for complete replication and transmission, while the full extent of the HBV helper function is unexplored [17].

Triple infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis D virus (HDV) is rare [18]. It has been estimated that ~5% of HBV carriers are also coinfected with HDV, resulting in ~15 million persons infected with HDV worldwide [19-20]. Most

studies suggest that the majority of HDV infections are acquired through parenteral and sexual routes [19-22], which are also important routes for HIV transmission.

Regarding the interaction with HBV, HDV coinfection was shown to significantly suppress HBV replication, which might ameliorate the damage incurred as a result of HBV infection. However, HDV coinfection may lead to exacerbation and rapid progression of chronic liver disease, hepatic failure, and death in patients with HBV infection [23-24].

Clinical studies regarding the impact of HDV infection on patients with HBV-HIV coinfection were limited and yielded inconsistent results before the introduction of HAART [21]. Some authors suggested that HIV coinfection might worsen chronic liver damage caused by HDV [22-23], and patients with long-term HDV infection were more likely to develop cirrhosis than were patients with HBV infection alone [22].

The only approved treatment for HDV infection is IFN-α, but without satisfactory results. Nevertheless, in one study high-dose IFN (9 MU three times per week) was used, with better biochemical, virological and histological results than 3 MU three times per week. The most important finding is that in the patients who responded, histological improvement was maintained even after 10 years [24].

The improved survival rate among HIV-infected patients since the introduction in 1996, of HAART has allowed complications and liver-related diseases involving chronic hepatitis infections to emerge as the main causes of death in HIV infected patients.

Many studies have been conducted on the hepatitis viruses-HIV coinfections due to their association with unfavorable outcomes and failure of antiretroviral therapy. The concern regarding these coinfections has stared interest in Romania as our country ranks amongst the countries with high prevalence of HBV infection and is considered the country with the highest prevalence of HCV infection in the European Union.

In the case of the HVB-HIV coinfections, both viruses determine widespread infections worldwide and their shared routes of transmission including: sexual contact, the parenteral and percutanate ways has lead this coinfections to become a topic of interest for every researcher.

Studies conducted on the effect of HBV on HIV progress have shown that the HBV infection determines the proliferation of CD4 cell leading to higher levels of HIV multiplication. In regard to the influence of HIV on HBV development studies demonstrated that the level of seric HBV DNA is greater and the alanine aminotransferase (ALT) is lower in comparison to the ones observed in mono-infections. Other studies determined that HIV infection leads to a decreased clearance of the hepatitis B surface antigen and determines a lower rate of HBeAg seroconversion.

Regarding HIV and HCV, both are RNA viruses and their main routes for transmission include intravenous drug use, transfusion of blood products prior to screening, and at a smaller scale sexual intercourse.

Most studies have associated the HIV/HCV coinfection with a faster rate of hepatitis C progres, higher HCV viral loads, and a greater risk of developing severe liver damage. The impact of hepatitis C on HIV disease is less clear. The inadequate immune response characterized by the lack of critical CD4-positive T cell responses against HCV was found to be the cause of the rapid progress of the hepatitis C infection in HIV infected people. Higher levels of HCV RNA and serum ALT were found in coinfected individuals. These increased levels were correlated with the CD4 count. In addition, studies regarding the effect of HIV on hepatitis evolution have found that the time between HCV exposition and development of cirrhosis was found to be shortened in coinfected

subjects. In the case of the HBV/HDV-HIV triple infection is rare. Most studies suggest that the shared routes of transmission by all three viruses include the parenteral and sexual routes.

Studies regarding the effect of HDV on HBV progress have shown that HDV suppresses HBV replication, which might lead to an amelioration of the damage incurred as a result of HBV infection. Other studies have concluded that the HDV infection may lead to exacerbation and rapid progression of chronic liver disease, hepatic failure, and death in patients with HBV infection.

4. Conclusions

The effects of hepatitis viruses on HIV progress remain to be revealed by future studies. The majority of the studies conducted on the hepatitis viruses and HIV coinfections conclude that HIV accelerates the progression of liver disease and increases the hepatocyte apoptosis worsening the liver fibrosis. As a result end-stage liver disease and cirrhosis have become the leading cause of death in HIV positive patients. It is therefore of great importance that a suitable therapy is used in combating this emerging health threat to HIV positive people.

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