Hepatitis Monthly 2009; 9(4): 305-309

REVIEW ARTICLE

Viral Hepatitis D among Hemodialysis Patients: A Worldwide Underestimated Problem

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Hepatitis D virus (HDV) infection is a major concern among hemodialysis (HD_i) subjects, particularly the hepatitis B surface antigen (HBsAg) positive patients; in HBsAg-positive subjects HDV can be transmitted at serum dilutions as high as 10^{-11} [(1)] and HBsAg-positive HD_i patients stand therefore a very high risk of becoming infected with HDV through blood contamination of the hemodialysis machinery or through transfusions. Despite the importance of the problem studies of HDV in HD_i are limited, the reported frequency of HDV infection among HD_i patients is different throughout the world and there is no definite standard protocol to manage disease in these patients. The following represent important issues when considering HDV infection among HD_i subjects: 1) High risk of HDV/ hepatitis B virus (HBV) transmission due to chronic transfusion or blood exchanges during dialysis 2) High mortality and morbidity rates 3) difficulties in the diagnosis of HDV in HD_i patients 4) Irreversible complications 5) Uncertain methods for treatments. Clearly the absence of a definite standard protocol for effective management of HDV infection in HD_i subjects stems from limited research on this matter. As HDV infection in HD patients has been largely neglected globally, in order to gain knowledge on this issue we carried out a world-wide investigation to determine the magnitude as well as the disease burden of HDV infection among HD_i subjects with the ultimate goal to provide guidelines to manage HDV infection in this setting. We reviewed all the related studies on "HDV and hemodialysis" "renal failure" by searching the MEDLINE. Forty-seven manuscripts were retrieved in total. After a preliminary evaluation, we found only 18 articles that seemed relevant. These articles were analyzed in detail and the relevant data were gathered and summarized.

Keywords: **Hemodialysis, Hepatitis D, Ultrafiltration, Hepatic Cirrhosis, Primary Prevention, Polymerase Chain Reaction**

Introduction

Viral hepatitis delta (D) is caused by the hepatitis D virus (HDV), a defective RNA agent which exists only in the presence of hepatitis B virus (HBV). Hepatitis D infection varies from a mild disease to chronic hepatitis or even fulminant hepatic failure (FHF). Epidemiological studies have shown that the prevalence of HDV infection among hepatitis B surface antigen (HBsAg) carriers is approximately 5% all over the world [(2, 3)]; however, the prevalence of hepatitis D infection in HBV

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Received: *24 Oct 2009*
Accepted: *27 Nov 2009*

Hepat Mon 2009; 9 (4): 305-309

carriers is different in various clinical settings and in different parts of the world [4-6].

Two forms of infection of HDV and HBV have been described: Co-infection and Super-infection. Despite evidence reflecting different pathophysiologic mechanisms of these two types of infection, both can potentially lead to severe and irreversible hepatic damage; super-infection with HDV is the most important reason for chronic hepatic failure, yet co-infection may not seldom lead to FHF [2, 7].

The risk of HBV/HDV transmission is a major problem in HD_i patients. Different rates of HDV transmission in HD_i patients were reported in previous studies [4, 6, 8], but these studies are too limited to provide a paradigm of the importance of HDV in HD_i patients. The high risk of HDV/HBV transmission in HD_i [9] stems from the possible contamination of the HD_i machinery with infected blood and from the many transfusions that these patients often receive, as well as from lack of adherence to universal precautions. Two other problems make the control of HDV infection a serious problem in HD_i patients: a) physicians do not usually bear in mind that HDV infection should be checked in the initial evaluation of HBV-infected patients as well as in surveillance protocol b) Diagnosis of HDV in HD_i patients face problems. The issue is complicated by the significant mortality and morbidity of hepatitis D related to complications such as hepatic cirrhosis or hepatocellular carcinoma (HCC) [10-12]. Furthermore, treatment protocols are controversial and there is no specific guideline to prevent, diagnose and control HDV infection in HD_i patients. As HDV infection in HD_i seems to be a relatively neglected issue, we gathered on the Medline all the findings of published reports on hepatitis D in HD_i patients. In this paper, we review all aspects of HDV infection in HD_i in order to assess the world-wide impact of the infection and the best way to manage hepatitis D in HD_i.

Materials and Methods

We gathered all reports on HDV infection in HD_i patients by an integrative search of MEDLINE from 1985 to August 2008. The search was conducted using the following key words and MeSH terms: "hemodialysis" or "dialysis" in combination with "HDV" or "hepatitis D". We limited the search results to the reports published in English. We reviewed the epidemiologic aspects as well as the clinical course of HDV infection. Two of the authors carried out independent reviews to identify the relevant manuscripts. One of the authors reviewed the whole articles to get the most relevant data and to consider the reliability, validity and relevance of the manuscripts; then, reviewed the articles and the information extracted from the reports. We gathered a total of 47 reports that were relevant. Of these, 15 did not focus on viral hepatitis in HD_i patients but provided information on hepatitis D in HD_i centers. Altogether, we found a total of 32 reports that specifically focused on hepatitis D in the setting of HD_i. Following discussion on the findings of the reports, we achieved a consensus on 18 articles as the most relevant.

Results

The frequency rate of HBV infection in HDi patients is significantly higher than the general population [7, 9, 13] and HDV infection seems also more prevalent in HD_i patients. However, worldwide estimates on the frequency of HDV infection in HD_i patients are inadequate in different parts of the world. Although few studies were carried out in this field, some have shown that HDV is a major medical problem in developing countries [8, 14]. Nevertheless no serious attempt to conduct further investigations or propose a protocol to reduce the incidence of HDV in HD_i patients has been performed.

European reports have suggested that HDV infection is rare or absent in HD_i patients [6]; however, other studies have shown that even in Europe HDV remains a major problem in HD_i patients [4]. HDV seems to be a serious problem in western Asian countries. A study in Turkey in 1993 reported that the frequency rate of HDV in HD_i patients was higher than 8% [15]. A research in Oman in 1994 demonstrated that the 7.7% of HD_i patients were HDV-infected [14] and a case-control study in Saudi Arabia in 1992 revealed that 11.4% of patients in control group and 12.5% of patients in case group (HD_i patients) had evidence of HDV infection [8]. Despite the concern raised by these studies which suggested that the prevalence of HDV in HDi was higher than the average global prevalence (5%), no other specific research has been carried out since 1994 in HD_i patients in Middle East.

Transmission of HDV is similar to HBV [10]; and exposure to infected blood is the main vehicle for HDV as well as HBV acquisition. It appears that hemodialysis is a high-risk procedure that can potentially lead to transmission of HDV at young ages; as a consequence, HD_i patients may become HDV carriers for a long period of time. Some etiologies of end stage renal disease such as chronic glomerulonephritis, congenital malformations in

urologic system, urolithiasis, hereditary nephropathy and systemic diseases such as diabetes mellitus type 1 and hemolytic uremic syndrome are more prevalent in children and adolescents than in adults [16]. Therefore, it is reasonable to conceive that a significant number of HDi patients who need regular hemodialysis are children and young adults; the majority of these patients can be identified from young ages as an epidemiologic core for HDV in the society.

Previous studies indicate that there is no age limit for HDV infection among HBsAg-positive subjects [17]. Overall, two forms of acute HDV infection may occur: Co-infection (simultaneous acquisition of HBV and HDV infection) and super-infection (acute HDV infection in a chronic HBsAg carrier). In patients with co-infection, the rate of progression to chronic hepatitis seems similar to acute HBV infection, but these subjects are at a significant risk of FHF [2, 7]. In contrast, patients with super-infection almost always progress to chronic hepatitis D; thus, in this setting, cirrhosis due to chronic progressive liver disease is a major concern [10-12]. Early diagnosis of cirrhosis should alarm physicians to complications such as esophageal varices or hepatic encephalopathy.

Prevention of HDV infection is usually concentrated on the reduction of hepatitis B virus transmission in seronegative individuals as well as decrease of HDV acquisition in HBsAg-positive patients [13, 18]. Vaccination against HBV has a pivotal role in prevention of HDV infection and appears to be the best current method to decrease the incidence of HDV infection in HD_i patients [13].

The treatment of choice in cases with super-infection or co-infection of HBV and HDV remains to be determined. No optimal treatment has been identified for hepatitis D, however, high dose interferon alpha (IFN-α) and some other antiviral drugs may play a role [10, 13]. The issue needs to be confirmed in randomized clinical trials with a high number of subjects.

Different HDV genotypes might be associated with specific clinical outcomes. Although eight different HDV genotypes have been isolated so far, the genotype assessment is usually limited to determining genotypes 1 to 3 [7]. In a global view, genotype 1 seems to be the most common [7]. The frequency of HDV genotypes is different in the Western *vs.* Eastern world. Genotype 1 is the predominant genotype in the Unites States as well as Europe and the Middle East, genotype 2 prevails in the Far East [7]. HDV genotype 2 has been correlated with mild forms of hepatitis D with a low rate of progression to chronic liver disease or FHF. [7, 13] Genotype 1 has variable pathogenicity but often results in a severe HDV infection with high probability of arising serious hepatic damage [7]. While in the western countries the rate of HDV infection is lower than the other parts of the world, HDV infection is considered as the main cause of irreversible hepatic disease, presumably because of the high incidence of HDV genotype 1 [7, 13]. As a consequence, determining the HDV genotype may help the physicians to predict the ultimate outcome. Genotyping HDV, specifically in the risk groups such as HD_i patients, is not a routine and in fact we found no report on using HDV genotype assessment in nosocomial outbreaks of HDV infection.

Virological assays as well as serological studies to detect HDV-RNA and antibody to HDV (anti-HDV Ab) are the most important diagnostic tests to determine HDV infection [19, 20]. Generally, all HBsAg-positive subjects should undergo anti-HDV Ab enzyme linked immunosorbent assay (ELISA) studies to determine the evidence of HDV infection. While anti-HDV Ab is an appropriate test for screening, a positive anti-HDV Ab report does not necessarily demonstrate ongoing HDV infection. Thus, polymerase chain reaction (PCR) for HDV-RNA should be utilized to confirm the diagnosis.

In spite of this laboratory diagnosis algorithm, the diagnosis of HDV infection in HDi patients remains difficult. Firstly the clinical presentations of HDV infection are remarkably variable and non-specific [17]; there is no specific sign or symptom alerting to a diagnosis of the HDV superimposition on HBV infection. Considering that all patients with HDV infection are HBV-infected, physicians are not able to differentiate super-infection or co-infection of HDV from exacerbation of hepatitis B based on clinical findings and no sign or symptom of hepatitis delta is distinctive to allow an early diagnosis of HDV infection among HBV carriers.

Secondly, ultrafiltration of plasma in HD_i patients during dialysis can theoretically result in a decrease or disappearance of antibodies from the serum; therefore, serum level of anti-HDV Ab may decline below the detection limit of the anti-HDV Ab assay, missing the diagnosis of HDV infection. Thirdly, the presence of HBsAg and HDV in super-infection may result in an acute hepatitis in healthy carriers [7, 13]; more intriguing, a significant decrease in HBV replication may be observed after acquisition of HDV instead of the florid HBV-DNA positive infection expected in typical hepatitis B. HBV-DNA may often be negative in acute Hepatitis D even by the most sensitive HBV-DNA PCR test [20]. Another problem with diagnosis of HDV infection is the delay in the production of anti-HDV Ab [20]. Since

anti-HDV Ab is usually detectable some weeks after HDV infection, it might not be detected in patients suffering from FHF and physicians should rely on PCR studies in seronegative subjects. Consequently, a high level of suspicion is required for the diagnosis of HDV infection in high-risk groups. Since the rates of HDV infection among HD_i patients are not precisely known, interest of health Authorities to deliver diagnostic and management protocols for this disease is unexpected; devising protocols to control the rate of HDV infection among HD_i patients depends primarily on acquiring detailed knowledge on the rates and trends of HDV infection.

No specific treatment has been identified to be successful in the majority of patients with hepatitis D [4, 10]. There are anecdotal reports on the use of multiple antiviral drugs for the management of HDV infection. In HD_i subjects, alpha interferon was shown to provide some success; it is not clear whether the positive effect of alpha interferon on HDV is a result of direct antiviral effect against HDV or decrease of HBV replication.

No effective treatment is available for the treatment of acute hepatitis D in HD_i subjects [10].

Segregation of HDV-positive subjects among HBsAg-positive individuals has not been addressed in existing guidelines; therefore it cannot at present be determined whether HDV-infected cases should be isolated, and dedicated HDV machines should be considered in HD_i centers providing services for HBsAg-positive patients.

Discussion

Hepatitis D in HD patients has been and remains a serious worldwide health problem. The high risk of HDV/HBV transmission in HD_i patients [9], the high mortality and morbidity rate of hepatitis D, the problems of diagnosis of HDV in HD_i patients, the irreversible complications of its infection [10-12] and the difficult and controversial treatments [2, 10] have made HDV infection a major concern in HD_i patients.

HD_i patients are highly at risk of blood-borne diseases such as HBV and HDV infection. Considering that HDV can lead to chronic liver disease or FHF [2, 7, 10-12] and no efficient treatment has been identified for HDV infection [10, 13] prevention and early detection seems to be the best solution for limiting the rate of transmission. On this basis, designing an integrative protocol appears to play a vital role in lowering the morbidity and mortality among HBsAg-positive HD_i subjects. This aim could be achievable if some principles were considered in HD_i units.

These are:

1) primary prevention such as vaccination against hepatitis B is the best solution to control HDV transmission in HD_i patients. Unfortunately, due to immunocompromission these patients may not be responsive to the vaccine. There is no effective treatment for acute hepatitis D. The efficiency of current antiviral drugs including alpha interferon and of antivirals against the HBV is limited and controversial [10, 13]. Overall options for secondary and tertiary prevention are limited and primary prevention plays the major role in the control of HDV infection in HD_i patients.
2) Performing proper screening tests is a must for the diagnosis of HDV infection among HBsAg-positive individuals. All HBsAg-positive subjects should undergo anti-HDV Ab Elisa test. In HD_i there are nevertheless diagnostic problems of major practical concern. In HD_i patients, repeated plasma ultrafiltration may decrease the level of anti-HDV Ab in the serum. Therefore, a negative anti-HDV Ab test may not be reliable and HDV-RNA PCR should be requested even in anti-HDV Ab negative HBsAg-positive HD_i patients, to determine whether HDV infection is ongoing.
3) Segregation of infected patients with HDV could be considered in HD_i units to prevent the dissemination of HDV infection among HBsAg-positive HD_i patients, yet the role of adherence to universal precaution should not be underestimated; in other words, in HD_i units providing services for HBV-infected subjects, HDV-infected patients could be segregated to dedicated HBsAg-positive, HDV-positive machines, if possible, in order to prevent the transmission and occurrence of nosocomial outbreaks. The cost-effectiveness and ultimate usefulness of this precaution remains unknown.
4) Periodic sonographic evaluation of cases with chronic hepatitis D seems to play a vital role to uncover occult cirrhosis as well as hepatocellular carcinoma.

Conclusions

In conclusion, despite all aforesaid problems regarding HDV infection in HD_i subjects, few studies have been carried out in developing

countries to determine the prevalence of HDV in HD_i patients. In addition, even in developed countries the amount of information regarding HDV infection in HD_i patients is limited. The conclusion that HDV infection in HD_i patients has been largely neglected worldwide, has prompted us to carry out a wide-spectrum investigations to determine the magnitude as well as disease burden of HDV infection among HD_i subjects. Hepatitis D and its complications need considered for incorporation into universal guidelines in the management of HD_i patients.

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