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REVIEW PAPER

HEPATITIS D IN HEMODIALYSIS SETTING: A SHORT REVIEW

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ABSTRACT

Hepatitis D virus (HDV) infection in hemodialysis (HD) patients has remained as a serious worldwide problem for health care system for many years. High probability of HDV/HBV transmission in HD patients due to chronic transfusion, high mortality and morbidity rate of hepatitis D, diagnostic problems of HDV in HD patients, irreversible complications of HDV infection and uncertainly difficult and controversial treatments have made HDV infection a major concern in HD patients. Considering that there is not efficient treatment for HDV infection, prevention and early detection seems to be the best solution for limiting the rate of transmission of HDV. A short review of the literature was made in order to guide for control of this important infection in HD patients.

Keywords: *hepatitis D, hemodialysis, prevalence, epidemiology*

INTRODUCTION

Hepatitis Delta Virus (HDV) is a small defective RNA virus that replicates and always exists only in the presence of hepatitis B virus (HBV).[1] The epidemiology of HDV infection is similar to HBV but with notable exceptions. Evidence of HDV infection was found all around the world and epidemiological studies have revealed that the prevalence of HDV infection among HBsAg carriers is approximately 5% worldwide.[2,3] On the other hand, the prevalence of hepatitis D infection in HBV carriers seems to be different in various setting of patients and different parts of the world.[4-6] HDV infection occurs worldwide but incidence and prevalence data are limited due to inaccurate reporting and delayed detection. It is more difficult to determine the number of cases of acute or fulminant hepatitis related to HDV infection, as the incidence varies among continents, countries, and regions. Hepatitis D infection varies from a mild disease to chronic hepatitis or even fulminant hepatic failure (FHF). Currently, two forms of simultaneous infection of HDV and HBV have been described: co-infection and super-infection. In spite of evidences reflecting different pathophysiologic mechanisms of these two types of HBV/HDV infection, both of these entities can potentially lead to irreversible hepatic damage. Although super-infection with HDV is one of the most important reasons for chronic hepatic failure, co-infection may lead to FHF.[2,7]

Hepatitis B Virus (HBV) infection in hemodialysis (HD) patients varies among different localities and

correlates with the endemicity in the general population of the region. HBV prevalence has decreased in many countries in general population and dialysis patients after improvement in people's knowledge about risk factors, national vaccination programs for neonates and vaccination of high risk groups.[8] The overall incidence and prevalence of HBV infection in dialysis patients has decreased over the years as a result of routine screening of blood products for HBsAg, the advent of recombinant human erythropoietin, HBV vaccination and the implementation of infection control measures. However, the prevalence and incidence rates of HBsAg positivity are still high among patients undergoing maintenance hemodialysis in the less developed countries.

HBV/HDV transmission with different rates has been reported as a major problem in HD patients previously.[4,6,9] High probability of HDV/HBV transmission in HD patients seems to be related to transfusion and lack of adherence to universal precaution.[10] Unfortunately the physicians in dialysis centers do not usually check the HDV infection in their HBV-infected patients and diagnosis of HDV infection faces with some problems. In addition, HDV/HBV infections are associated with significant mortality and morbidity.[11-13] Controversy regarding management of hepatitis D in HBs Ag-positive HD makes the treatment protocols a major concern.[2,11] There are limited studies that have been conducted on HDV infection in HD individuals. Transmission of HDV is similar to HBV, via blood and blood fluids containing the virus, and infection spreads by parenteral routes.[14] Dialysis patients may acquire HDV infection as they are at risk of hepatitis B infection. In European countries, South Asia countries and the USA, HDV infection is restricted to high risk group of drug addicts and has decreased during the recent years .[15] It is believed that the reduction in hepatitis D incidence is largely due to the reduction in incidence of HBV.[16] There are some reports of acute and fulminant hepatitis or symptom-free transmission in dialysis patients with HBV and HDV infections.[17-19] The prevalence varies from zero to 44.5% in hemodialysis patients.[6,20] Also, the prevalence of HDV in different groups is related to routes of transmission. In Iran, the main route for HBV transmission was vertical in the past[8] and the difference between the prevalence of HDV infection in hemodialysis patients (44.5%) and asymptomatic carriers (2.5%) is significant.[20]

However, it appears that there is no specific protocol to prevent, diagnose and also to control HDV infection in HD patients, that has been introduced globally. Consequently, HDV infection seems to be a relatively neglected issue, especially in HBsAg-positive HD subjects. In order to emphasize the importance of HDV infection in hemodialysis setting and its control a short review of literature was done.

METHODS

The literature search for HDV infection in hemodialysis patients was done by using electronic database MEDLINE (1985 to Dec 2008), EMBASE (1988 to July 2008), OVID (1976 to July 2008), Google Scholar (for local websites and medical journals). The search was conducted using the following key words "hemodialysis" or "dialysis" in combination with "HDV" or "hepatitis D". Manual search by using citation in previous publication was performed and we tried to find the full text or abstract by another search in Google. Our search was restricted to papers in English language.

DISCUSSION

There are three patterns of transmission of HDV infection in the world. In Italy and Greece, the infection is endemic, In Latin America countries such as Venezuela, the infection has epidemic pattern and finally in Western countries it occurs in high-risk groups such as intravenous drug users. Vaccination against HBV and decrease in HBV infection in hemodialysis patients has changed the epidemiology of HDV infection. However, it still continues to represent a public health problem in some parts of the world.[21-24] It is clear that the rate of HDV positivity in HD patients appears to be significantly higher than in HBV-infected general population.[7,10,25] Although a few studies have been carried out in this field, some studies have revealed that HDV is still a major medical problem in HD patients especially in developing countries.[9,26] There is a certain controversy regarding the prevalence of HDV infection in HD patients in European countries. Some European reports have shown that HDV infection is extremely rare or absent in HD patients;[6] but other studies have revealed that even in Europe, HDV might be a major trouble in HD patients.[4] Despite these controversies, no further detailed studies have been conducted in Europe to clarify the frequency rate of HDV in HD patients.

It seems that HDV infection is a serious problem in Asian countries. The prevalence of HDV infection in HD patients have reported to be more than 8% in Turkey,[27] 7.7% in Oman,[26] 12.4% in Saudi Arabia.[9] Although the prevalence of HDV in HD patients reported in these studies seems to be more than the global prevalence (5%), no other specific researches have been carried out since 1994 regarding the frequency rate of HDV in HD patients in Middle East.

The higher risk of HBV infection makes HD patients as a potential main source of HDV infection in the society. Transmission of HDV has been demonstrated to be quite similar to HBV.[10] It appears that HD patients are acquiring the HDV infection soon after start

of hemodialysis. As a consequence, HD patients may become HDV carriers for a long period of time. As already mantioned, two forms of the 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 to be 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 experience chronic hepatitis D; so, in this setting, cirrhosis due to chronic progressive liver disease is a major concern.[11-13] Although cirrhosis is known as an irreversible phenomenon, early diagnosis of cirrhosis could be an alarm for physicians to be prepared for the following complications such as esophageal varices or hepatic encephalopathy. Unfortunately the success rate of therapy with unique approved drug, alpha interferon in HD patients with HDV infection is disappointing.[11,25] This fact emphasizes prevention strategies for control of HDV infection in HD patients. The best strategy for prevention of HDV infection in HD patients is focused on reduction of HBV infection by vaccination and health precaution.[25,28] Serological test for anti-HDV antibody by ELISA and detection of HDV RNA, are the main used tests in HDV infection diagnostics.[29,30]

Theoretically, it seems that ultrafiltration of plasma in HD patients during dialysis process can result in a decrease or disappearance of antibodies from the serum. This makes the diagnosis of HDV infection in HD patients more difficult. The other conflict with diagnosis of HDV infection is the delay in production of HDV-Ab.[30] Since HDV-Ab is usually detectable several weeks after HDV infection, it might not be detected in patients suffering from FHF and physicians should rely on PCR studies in seronegative subjects. For diagnosis of infection, the high level of suspicious is necessary. Unfortunately until now, there is not any guideline for diagnosis of HDV infection in HD patients. However, in asymptomatic patients, the anti-HDV antibody before dialysis session is recommended.

Segregation of HDV-positive subjects among HBsAg positive individuals has not been addressed in any published article. Hower, it may be better to dedicate the dyalisis machine(s) to HDV/HBV infected HD patients and separate them from those with HBV infection.[31]

CONCLUSION

There are few published articles about prevalence of HDV infection in HD patients, especially in developing countries. Neverthelss, it is an important cause of fulminant hepatitis in HD patients in developed countries.[18] Periodic testing for HDV infection by anti-HDV antibody in HBsAg positive carriers on chronic hemodialysis treatment is recommendable. All HD patients should vaccinate against HBV infection and follow up for anti-HBs antibody screening. Reduction of HBV infection in HD patients would be the best solution to control the HDV infection in HD patients. Dedication of HDV/HBV machines and infected patients in HD centers is also a prudent strategy. Emphasizing the adherence to universal precaution should not be forgotten, also. It is obvious that the HDV infection in HD patients has been forgotten! There is an apparent lack of attempts to conduct more investigations and create definite protocols to reduce the incidence of HDV infection in HD patients. The global attempt should start soon. Tomorrow is too late!

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