

Review article

A review on epidemiology, diagnosis and treatment of hepatitis D virus infection

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How to cite this article:

Hajiani E, Alavi SM. A review on epidemiology, diagnosis and treatment of hepatitis D virus infection. Jundishapur J Microbiol. 2011; 4(Supplement 1): S1-S8.

Received: August 2010

Accepted: January 2011

Abstract

Hepatitis D Virus (HDV) infection is a widespread disease that has affected a large number of population with hepatitis B Virus (HBV) infection in Iran. Disease is considered to be a major public health problem in Iran. Delta hepatitis is the least common form of chronic viral hepatitis and is the form most likely to lead to cirrhosis. Delta hepatitis is serologically complex, so effective therapy is difficult. The diagnosis is made on the basis of the presence of antibodies against HDV (anti-HDV) and hepatitis B surface antigen (HBsAg) in the serum of a patient with chronic liver disease. It is confirmed by the presence of the HDV antigen in liver or HDV RNA in the serum (by reverse-transcription polymerase-chain-reaction assay). It is important to determine whether delta hepatitis is present because the responses to therapy of patients with this disease are less satisfactory than those with hepatitis B, and the recommended regimen of interferon alfa is different. The optimal treatment of HDV is uncertain. Thus, patients should ideally be treated as part of a clinical trial. The only treatment approved for chronic HDV is interferon alfa. Treatment should be administered for one year; whether longer duration of treatment will improve response rates remains to be established. Available data have not demonstrated an advantage from the addition of a nucleos(tide) analogue.

Keywords: Hepatitis D Virus infection (HDV); Hepatitis B Virus infection (HBV); Chronic hepatitis; Khuzestan; Iran

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Jundishapur Journal of Microbiology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, Tel: +98611 3330074; Fax: +98611 3332036; URL: <http://jjm.ajums.ac.ir>; E-mail: editorial office: jjm@ajums.ac.ir

JJM. (2011); 4(Supplement 1): S1-S8.

Introduction

Hepatitis D Virus (HDV) is a satellite virus, which is dependent on hepatitis B virus (HBV) for the production of envelope proteins [1]. HBV/ HDV co infection most commonly occurs in the Mediterranean area and parts of South America. The availability of HBV vaccines and public health education on the prevention of transmission of HBV infection has led to a significant decline in the prevalence of HDV infection in the past decade [2].

HDV infection occurs into two forms. The first form is caused by the co infection of HBV and HDV; this usually results in a more severe acute hepatitis with a higher mortality rate than is seen with acute hepatitis B alone [3] but rarely results in chronic infection. A second form is a result of a super infection of HDV in a HBV carrier and can manifest as a severe “acute” hepatitis in previously asymptomatic HBV carriers or as an exacerbation of underlying chronic hepatitis B. Unlike co infection, HDV super infection in HBV carriers almost always results in chronic infection with both viruses. A higher proportion of persons with chronic HBV/HDV co infection develop cirrhosis, hepatic decompensation, and liver cancer compared to those with chronic HBV infection alone [4].

Virology

HDV is a small, 1.7Kb RNA virus contained in a protein envelope consisting of hepatitis B surface antigen (HBsAg) [5]. It was first described in 1977 [6]. HDV particle contains delta antigen that exists in two forms: a large delta antigen (LHDAg) of 27kDa and a small delta antigen (SHDAg). In virus-infected cells, HDAg is located exclusively in the nuclei. HDV envelope consists of all three protein species of HBsAg and as a result HDV probably utilizes the same cellular receptor

as HBV. Replication of HDV is restricted to the liver. Although replication of HDV can occur within hepatocytes in the absence of HBV, HBV is necessary for coating the HDV virions and allowing their spread from cell to cell.

Virus replication is helped by SHDAg but is inhibited by LHDAg. HBsAg and LHDAg are needed for HDV assembly. Envelope proteins derived from the pre-S and S antigens of HBV encapsidate HDV RNA and HDAg. HDAg is necessary for viral proliferation. HBsAg, HDAs, and HDV RNA are the main particles of HDV. Assembly can only occur in the presence of the helper virus HBV [7]. Based on the analysis of HDV genomes from various parts of the world, there are three genotypes of HDV [8]. Genotype 1, which is related to a wide variety of pathogenesis, is the most prevalent genotype. Genotype 1 is more prevalent in the United States, Middle East and the Europe with some geographically based subtypes. Genotype 2 is predominant in the Far East and associated with severe hepatitis in Northern South America [9]. Severe outbreaks of genotype 3 have been reported in Colombia and some remote areas of the Brazilian and Peruvian Amazon basin [9].

Epidemiology

The epidemiology of HDV and HBV are very similar but with some differences. HDV is prevalent in many countries. Approximately 5% of HBsAg carriers are infected with HDV infection world wide [8]. The Mediterranean area, the Middle East, and parts of Africa are endemic for HDV infection [9]. HIV-infected persons in Iran, as a result of shared transmission routes, are highly prevalent groups for hepatitis viral infections [10-12]. HIV modifies the natural history of HBV, high rates of chronic HBV infection and progression to advanced liver disease [12].

However, the rate of HDV infection and HBsAg carriers has decreased in Iran due to the introduction of HBV vaccination. Besides, the rate of HDV infection and HBsAg carriers has decreased [10].

Socio-economic improvements and preventive activities applied in this country are the contributory factors in the decrease. However, the disease continues to be a public health problem in some parts of the world yet [13]. The decrease in the HDV prevalence in Iran may be due to the changes in the epidemiology of hepatitis B [14]. HDV is endemic in Iran but there is insufficient data to compare its rates in different cities. We have recently done an epidemiological study for determining the prevalence of HDV infection and its clinical impact in Khuzestan province [15].

Seroprevalence rate of HDV in the asymptomatic HBV chronic carriers in the south of Iran (1989) was 14% [16]. This rate decreased to 9.7% in a recently published report from Shiraz [17]. A low prevalence rate of 2.4% in 1989 was reported in HBV carriers in the Midwest of Iran [16]. It was estimated that the HDV prevalence rate during 1986-1988 was 2.5% in the asymptomatic HBsAg chronic carriers, 33.33% in haemophilic and 44.5% in HBsAg-positive hemodialysis patients. Anti-HDV positivity in hepatocellular carcinoma patients was 62.5% in this group [18]. In 2000, HBsAg was positive in 1.3% of blood donors and 25.2% of HBsAg positive hemodialysis patients were anti-HDV positive [16].

HDV prevalence was 5.7% in the chronic HBV patients of Tehran (the capital city of Iran) in 2004 [19]. In Golestan a province in the northeast of Iran, a new report has documented HDV prevalence of 5.8% in HBsAg carriers [16]. HDV prevalence in chronic HBsAg carriers in Babol, northern Iran was 2% in 2002 [20], in Kerman, in the south of Iran, this

prevalence rate was 20.7% [21] and in Tabriz, north-western Iran in 2000, this rate was 6.15% [22]. A recently published study (2008) has reported a high prevalence rate of 31.57% HDV infection in HIV/HBV co-infected cases in Kermanshah, Iran [23]. These studies suggest an increase in HDV prevalence over the past decade.

Diagnosis

The known clinical burden of the infection with the HDV and hepatitis B viruses, which can lead to cirrhosis, hepatocellular carcinoma and death, has led to the introduction of several diagnostic approaches for this infection. Recognition of this infection is very important because knowing the presence of the HDV infection in a HBV infected patient allows a more accurate prognosis. Moreover, patients with acute HDV infection are at a higher risk of development of fulminant /severe hepatitis, and chronic HDV infected patients are highly at risk of progression to cirrhosis and liver failure. HDV infection effects on the response of patients to antiviral therapy and a higher dosage of antiviral is needed than that of cases with chronic hepatitis B alone.

Anti-HDV presence in the serum is a reliable and specific marker of HDV infection. In the chronic HDV infected patients, IgM anti HDV is present early and remain in a variable titres for long times. IgM anti-HDV correlates to the levels of HDV replication but in the chronic HDV infected cases, an IgG anti-HDV titre higher than 1:1000 is a strong clue of persistent viral replication. HDV infection happens only in the HBsAg positive patients and is diagnosed by IgM- anti-HDV for acute or IgG anti-HDV for chronic infection. In fact HDV infection occurs only in the presence of HBV infection. In some patients, the markers of HBV infection may not be detected because of rapid HBsAg clearance in fulminant or acute hepatitis cases or due

to inhibitory effect of HDV on HBV replication.

HBsAg is not detectable in the serum of 10% of patients on the early phase of acute hepatitis. In such cases, the presence of IgM against to HBcAg in serum helps to diagnose acute hepatitis B. As mentioned before, because of the suppression effect of HDV on HBV replication, HBV markers may resemble a carrier state of HBsAg, HBeAg negative, anti-HBe positive, and HBV DNA negative. Although detection of HDAg in the liver by immunostaining is the gold standard of diagnosis of HDV infection, this test is not used for routine practice. Serum HDAg is usually detected by micro plate-based, enzyme-linked (EIA) or radioimmunoassay (RIA). At present, these assays are not available for clinical diagnosis in Iran.

In approximately 20% of cases HDAg is present in the serum of the late incubation period of acute infection and remains unchanged in the symptomatic phase. Since HDAg is often present transiently and there are no commercial assays to detect HDAg, it is only a research test. HDV RNA is a useful marker of HDV replication in patients with chronic infection. It is also an early marker of acute infection. HDV RNA detection in the serum is made by either molecular hybridization or reverse transcriptase-polymerase chain reaction (RT-PCR). RT-PCR is assays based techniques and are more sensitive and have a lower limit of detection, as few as 10 genomic copies.

HDV RNA, besides diagnostic usage, may be useful for antiviral therapy monitoring. With the use of PCR, more than 90% of hepatitis patients with chronic HDV have HDV RNA detectable in the serum [7]. The relation between the hepatocellular carcinoma (HCC) with HDV and HBV has been shown in some published studies [24]. A rise in the serum alfa feto protein (AFP)

in a HDV infected patient should raise in the mind this concern that HCC has developed [25].

Treatment of hepatitis D virus infection

The aim of treatment of hepatitis D is to eradicate or to achieve long-term suppression of both HDV and HBV. The primary endpoint of treatment is the suppression of HDV replication, which is accompanied by normalization of the serum alanine transferase (ALT) level and amelioration of necroinflammatory activity on liver biopsy. Suppression of HDV replication is documented by loss of detectable HDV RNA in serum and of HDAg in the liver.

A secondary endpoint is the eradication of HBV infection, with HBsAg to anti-HBs seroconversion. There is very little information to support that current treatment is effective in achieving this goal. Eradication of HBV infection with development of anti-HBs will protect the individual from reinfection with HBV as well as HDV. Patients who have cleared HDV but who remain HBsAg positive are still at risk of reinfection with HDV.

Interferon alfa

The only drug approved at present for the treatment of chronic hepatitis D is interferon alfa (IFNa). Pegylated interferon appears to be more effective than standard interferon but the data are limited. Unfortunately, only a minority of patients treated with interferon clear HDV infection. Early attempts to treat hepatitis D with immunomodulatory drugs, such as corticosteroids or levamisole, were unsuccessful [26].

The mechanism of action of IFNa in hepatitis D is unclear. IFNa does not have any antiviral activity against HDV when tested *in vitro*. Thus, the efficacy of IFNa in patients with chronic hepatitis D may

depend upon its antiviral effects on the helper virus (HBV) or its immunomodulatory effects. Interestingly, *in vitro* studies have found that HDV subverts the effect of IFN α signalling, possibly contributing to viral persistence and treatment resistance [27].

The absolute number of reported patients with chronic hepatitis D who have been treated with standard IFN α is small and the available data have shown mixed results [28]. Eradication of HDV infection and resolution of liver disease after IFN α treatment have been reported anecdotally in uncontrolled studies. In one of these reports, long-term therapy with high doses of IFN α permanently suppressed HDV replication in some patients and dramatically improved liver fibrosis [29]. However; the favourable effects of IFN α have not been confirmed in all controlled trials. In view of the poor overall response, it is difficult to identify factors that predict response. The only feature that may be associated with an increased likelihood of response is a short duration of disease.

Pegylated interferon

There is little published experience with pegylated interferon in the treatment of chronic hepatitis D. The largest published study included 38 patients who were treated with pegylated IFN α -2b (1.5MU/kg per week) alone or in combination with ribavirin for 48 weeks [30]. Most patients had previously failed treatment with standard IFN. All patients were maintained on pegylated IFN for an additional 24 weeks, and then followed off therapy for 24 weeks. At the end of follow-up, HDV RNA was undetectable in eight patients (21%). Treatment had to be discontinued in the 25% of patients while 58% required dose modification. The response rate was similar in the monotherapy and combination

therapy groups suggesting that ribavirin had no effect on the viral clearance rate.

The response rate was somewhat higher in a subset of patients who had not previously received interferon-based therapy (three of eight patients). A higher virologic response rate (43%) was found in another study involving 14 patients treated with 12 months of pegylated IFN [31]. The higher response rate may have been due to a lower proportion of patients with cirrhosis in the second study (28% versus 74%).

Pegylated interferon plus adefovir dipivoxil

Few studies have evaluated combination therapy for HDV using nucleoside analogues. One of the largest controlled trials (published as an abstract) included 90 patients with compensated chronic HDV infection who were randomly assigned to pegylated interferon alone or in combination with adefovir, or adefovir monotherapy [32]. After 48 weeks, both pegylated interferon groups demonstrated significant suppression of HBV DNA (25% becoming undetectable).

Combination therapy appeared to offer no advantage while adefovir monotherapy had no effect on HDV replication. Patients receiving combination therapy had a significant decline in HBsAg levels with two clearing HBsAg; further studies are needed to better characterize the clinical significance of this benefit [33].

Alternative treatments

Several drugs have been evaluated as alternatives to interferon. Overall, the results are discouraging. Ribavirin inhibits HDV replication *in vitro*. It has been tested in two small trials in humans without any biochemical or virological response [34]. The addition of ribavirin to pegylated IFN α did not improve response.

Foscarnet and acyclovir have a paradoxical stimulatory effect on HDV replication, at least *in vitro*. However, anecdotal reports suggest that foscarnet may be beneficial in fulminant liver failure due to HBV/HDV coinfection [35]. Suramin inhibits HDV infection *in vitro*, possibly by blocking virus uptake or uncoating [36]. When administered *in vivo*, suramin was effective in preventing HDV infection in the woodchucks only when they were inoculated with a low infecting dose. THF gamma 2, a synthetic octapeptide of thymic origin, has been shown to have some efficacy in HBV infection. However, a pilot study in 11 patients with hepatitis D found that it was ineffective [37].

Lamivudine, a potent inhibitor of HBV replication, had little or no effect on HDV replication in two series [38]. Antisense oligonucleotides are nucleic acid sequences that bind to RNA or DNA with a high degree of specificity, and can thereby block expression of a specific protein. Antisense therapy is being developed for treatment of HDV, but its efficacy has not yet been established [39].

"Prenylation" involves the covalent addition of a farnesyl or geranylgeranyl isoprenoid molecule to a conserved cysteine residue at or near the C-terminus of a protein. This link promotes membrane interactions with the prenylated protein, since the isoprenoid chain is hydrophobic. Specific inhibitors of HDV prenylation have been developed. In particular, the farnesyltransferase inhibitor FTI-277 prevented the production of complete infectious HDV virions of different genotypes, including the genotypes associated with most severe disease [40]. The prenylation inhibitors FTI-277 and FTI-2153 were highly effective in clearing HDV viremia in the mice. Famciclovir, an acyclic deoxyguanosine analogue, was of no benefit in a pilot study [41].

Treatment of acute hepatitis D

There is no specific treatment for acute hepatitis D. In one report, all three patients treated with foscarnet for fulminant hepatitis due to HDV recovered, as did two additional patients with fulminant hepatitis due to HBV alone [42]. Although these results are encouraging, they need to be confirmed. Foscarnet is an inhibitor of some viral DNA polymerases. However, it was shown to have a paradoxical stimulatory effect on HDV replication *in vitro*. Thus, the efficacy of foscarnet in fulminant hepatitis due to HBV/HDV coinfection may be secondary to its inhibition of HBV.

Conclusion

In conclusion, delta hepatitis is serologically complex, hence effective therapy is difficult. It is important to determine whether delta hepatitis is present because the responses to the therapy of patients with this disease are less satisfactory than those with hepatitis B. The optimal treatment of HDV is uncertain. Thus, patients should ideally be treated as part of a clinical trial. The only treatment approved for chronic HDV is interferon alfa. Treatment should be administered for one year; whether longer duration of treatment will improve response rates remains to be established. Available data have not demonstrated an advantage from the addition of a nucleos/tide analogue.

Acknowledgements

This work was supported by Tropical and infection Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. We are grateful to Research deputy of Ahvaz Jundishapur University of Medical Sciences for his encouragement, and constructive advice during the preparation of the manuscript.

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