Hepatitis D Virus

by S. Bennett Hooks, C. Julian Billings, Jorge L. Herrera

The hepatitis D virus (HDV) is a circular, single minus-stranded RNA virus which was first described in 1977 by Rizzetto. The original description suggested coinfection with hepatitis B virus (HBV) as it was found in the liver of patients with HBV and in the serum of HBsAg carriers (1). Coinfection is indeed necessary for HDV infection. This pathogen requires HBV’s presence for complete virus assembly and secretion. Parenteral and sexual transmission are routes of infection for this virus, identical to HBV. HDV is the least common of the infectious hepatitis viruses, but its virulence makes this an important public health concern. Hepatitis D remains an etiology for significant morbidity in patients with liver disease, often leading to decompensated liver disease and the need for liver transplantation.

VIROLOGY

HDV is the first animal virus that occurs from a circular RNA genome (2), and at 1,700 nucleotides in length it is one of the smallest viral genomes known. It shares similarities with both viroids and virusoids of plants in terms of structural characteristics of the RNA genome and mode of viral replication (3). The virus is folded into a rod shape and has a single structural protein, the hepatitis D antigen (HDAg). The two forms of HDAg include the long (HDAg-L) and short (HDAg-S) form. Both of these derive from the same open reading frame. The short HDAg particle binds to HDV/RNA and directs replication, while the long HDAg suppresses replication and directs packaging of the virion for export. The virion particle is encapsulated by an outer protein envelope made up of HBsAg. This outer protein binds to the hepatocytes via the same receptor used by HBV and the HDV genome is directed to the nucleus for replication. Because the lifecycle of the hepatitis D virus is dependent on the presence of HBsAg, HDV infection is always found in association with HBV infection.

Genetic variation of this RNA virus has lead to the discovery of three genotypes of HDV. Genotype I is the most common and is seen worldwide. It is most prevalent in the United States, Europe, and Middle East. This genotype carries an increased risk of a fulminant course. Once established, it usually exacerbates the pre-existing HBV infection and can rapidly progress to cirrhosis. Genotype II is predominant in the Far East and is less frequently associated with fulminant hepatitis or rapid progression to cirrhosis compared to genotype I. Genotype III is associated with severe outbreaks of acute HDV and has a high incidence of liver failure in Central and South America as well as Central Africa (4). Recently, four additional genotypes of HDV have been described; genotype IV is distributed in Taiwan and Okinawa, and genotypes V through VII are found in west and central Africa. The course of HDV/HBV co-infection also appears to be dependent on the HBV genotype. Coinfection with
genotype C of HBV and genotype I of HDV carries the worse prognosis with the highest risk of progression to cirrhosis and hepatocellular carcinoma (5).

**MODES OF INFECTION, SEROLOGIC MARKERS AND CLINICAL COURSE**

HDV requires presence of HBV for virulence, therefore in acute hepatitis there are two modes of presentation in the immunocompetent host. These include coinfection with HBV and HDV in a person naïve to both viruses or superinfection with HDV in someone with chronic HBV (Figure 1).

Simultaneous coinfection with HBV and HDV produces a clinical picture that is usually indistinguishable from acute HBV. It is transient, often self limited, although a higher incidence of liver failure has been reported in drug addicts (9). The rate of chronic infection is low (<5%), similar to acute HBV since the persistent presence of HDV is dependent upon chronic HBV infection. To diagnose HDV/HBV coinfection, one must demonstrate the presence of high titer HBcAb-IgM together with either HDV-RNA, anti HDV IgM, or HDVAg in serum. The diagnosis may be difficult, as HDVAg and HDV-RNA may be present only transiently in serum in cases of acute coinfection and often before clinical symptoms appear.

HDV superinfection occurs in the setting of chronic HBV infection. It may present as severe acute hepatitis in a previously unrecognized HBV carrier or as a hepatitis flare in someone with pre-existing chronic HBV (6). In acute HDV superinfection, serum HDAg appears early, but is short lived. It may escape detection if repeat testing is not performed (7). HDAg does last longer in patients with slow or weak immune responses to infection (8). The presence of anti-HDV IgM does occur, but titers peak after the peak of the ALT. It should be noted that HBcAb-IgM is negative in superinfection. In addition it has been noted that anti-HDV IgM can be detected in a number of patients with chronic HDV infection. Total anti-HDV appears late in acute HDV infection but persists in high titers with chronic infection (7).

In about 90% of patients with HDV superinfection chronicity develops and these patients go on to develop progressive hepatitis. This occurs because the presence of underlying HBV allows for ongoing repli-

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**Table 1**

Typical serologic patterns of HDV infection

<table>
<thead>
<tr>
<th>Setting</th>
<th>HBsAG</th>
<th>HBcAB-IgM</th>
<th>HDVAb total</th>
<th>HDVAb IgM*</th>
<th>HDVAg*</th>
<th>HDV-RNA PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coinfection**</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Superinfection</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Chronic Infection</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+/–</td>
<td>+/–</td>
<td>+</td>
</tr>
<tr>
<td>Recovered from HDV</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Latent Infection***</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–§</td>
</tr>
</tbody>
</table>

*HDV IgM antibodies and antigen are present early and transiently during acute coinfection or superinfection and may be missed.

**HDV serologic markers during acute coinfection may be positive only transiently and can be missed.

***Latent infection has been described only in posttransplant patients.

§HDV-RNA PCR is positive only in liver tissue in cases of latent infection.
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C: cation of HDV. In the remaining 10%, the superinfec-
: tion may resolve, either with persistence of the origi-
: nal HBV infection or with clearance of the HBsAG.
: Chronic HDV infection is typically associated with
: persistent anti-HDV IgG as well as anti-HDV IgM
: titers. Reverse transcription polymerase chain reaction
: (RT-PCR) for HDV-RNA has played a role in deter-
: mining persistent infection as antibodies may last
: longer than presence of the actual disease. In a study
: by Huang and others in China they found that among
: patients with chronic anti-HDV positive but HDV-
: RNA negative (RT-PCR) hepatitis B and C were the
: major causes of persistent ALT elevations (10). The
: typical serologic patterns of HDV infection are shown
: in Table 1.

Reference laboratories in the United States have
assays commercially available to detect the presence
of the HDVAg, HDVAb (total titer), and HDVAb-IgM.
While assays to determine and quantify HDV-RNA in
serum have been developed, their commercial avail-
bility is restricted to very few reference laboratories
and availability is limited only to qualitative poly-
merase chain reaction (PCR) tests. The available sero-
logic tests for HDV are listed in Table 2.

In general, the absence of HDV-Ab total titer in a
patient with chronic HBV excludes the diagnosis of
HBV-HDV coinfection. Those patients testing positive
for HDV antibodies should be tested for HDV-RNA to
confirm viremia. Although the presence of HDVAb-
IgM usually suggests ongoing viral replication, some
investigators have found poor correlation between
IgM antibodies and HDV-PCR in serum. Conversely,
absence of detectable HDVAb-IgM does not reliably
indicate absence of viral replication.

**EPIDEMIOLOGY**

It is believed that over 300 million people in the world
harbor HBV, and 5% of them are coinfected with HDV,
leading to a total of 15 million people infected with
HDV. The prevalence of HDV does not mirror that of
hepatitis B and there are considerable geographic dif-
fferences in epidemiology. In the western countries the
route of transmission is most often from intravenous
drug abuse (IVDA). The transmission from blood
transfusions has decreased sharply since the routine
screening of blood for HBsAg and the development of
HBV vaccination. Recent outbreaks of viral hepatitis
including southeastern Russia are typically linked to
the increased use of illicit parenteral drugs (11).

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Endemic areas including those in the Mediterranean basin have HDV infection early in life often found in low socioeconomic areas. In these areas permucosal route of transmission (for example, sexual transmission) is more common. Hepatitis B vaccination, measures to control the spread of HIV, and socioeconomic improvements all likely play a role in the decreased incidence of HDV in these endemic areas (12).

WHEN TO CONSIDER HDV TESTING?

In patients with acute hepatitis B, consideration for HDV testing should be made if the patient is having a protracted course or is moving toward fulminant hepatic failure. Patients acquiring acute hepatitis B in endemic areas such as the Mediterranean Basin should be routinely tested for HDV coinfection.

An acute flare of known chronic hepatitis B infection could be the presenting feature of HDV superinfection, particularly among IVDA. In this case, HDV testing should be performed, ideally with HDV-PCR testing as HDVAg and HDVAb may only be present transiently during acute superinfection. Some recommend that all chronic HBV patients (even those without detectable DNA) should be tested for HDV coinfection with total anti-HDV, particularly those who are being considered for antiviral therapy or liver transplantation.

TREATMENT

The goal of treatment is primarily aimed at suppressing the HDV replication. When this occurs, it is usually accompanied by normalization of ALT and resolution of necroinflammatory activity on liver biopsy. A secondary endpoint is eradication of HBV with seroconversion to HBsAb. This will prevent reinfection of both HBV and HDV. If the patient clears HDV, but remains HBsAg positive reinfection with HDV appears to only cause a mild and self-limited hepatitis (13). The only drug currently approved for treatment of chronic hepatitis D is interferon alfa. Other potential treatments including acyclovir, ribavirin, famcyclovir, steroids, thymosin and levamisol have been evaluated and failed to suppress HDV (14). Suramin, a compound that in-vitro blocks entry of HDV virions into hepatocytes proved to be too toxic for longer term use in humans.

Lamivudine has been evaluated for treatment and has failed despite significant suppression of HBV. This may be secondary to the lack of HBsAg seroconversion as HBsAg is used in packaging HDV (15). Combination of interferon alfa with lamivudine and with ribavirin have not been proven to be more efficacious than with interferon alfa monotherapy (20–22).

Several authors performed controlled trials in the 1990’s with interferon alfa demonstrating that viral response was directly proportional to duration of treatment and dose of medication (16–19). In a trial by Farci and others, higher doses (9 MU three times weekly) of interferon alfa given for up to one year resulted in ALT normalization in 71% of patients. Of those who responded, 50% of them maintained normal ALT six months after treatment was stopped. Although HDV-RNA was still detectable in all of these patients, the high dose group had significantly lower levels of detectable virus at the end of treatment. Follow up on this study was provided in 2004 when regression of hepatic fibrosis was reported by Farci, et al. Patients were followed up to 12 years after the initial trial and those who received high dose interferon had a significantly higher survival and documented absence of fibrosis in the final biopsy of four patients with long term biochemical response and documented cirrhosis at initiation of the study (23). These data suggests that in a subset of patients, interferon therapy may induce a long-lasting biochemical remission resulting in improved outcomes despite continued HDV viremia in some.

Pegylated interferon has been used to treat chronic hepatitis delta in two studies published in 2006. Castelnau, et al studied 14 patients who were treated with 1.5 mcg/kg of weekly peginterferon alfa-2b injections for 12 months. Forty-three percent of this group achieved a SVR (negative HDV-RNA at six months post treatment). In the virological responder group, between six and eight patients had previously been unsuccessfully treated with standard interferon (24). Niro and others (25) treated 27 patients for 48 weeks with peginterferon alpha-2b alone or in combination with ribavirin, followed by an additional 24 weeks of peginterferon monotherapy; for a total duration of therapy of 72 weeks. Response to treatment was determined at 24 weeks after completion of antiviral therapy. At the end of follow up HDV-RNA was negative.
in 21% of patients, but the addition of ribavirin did not affect the viral clearance rate and increased the toxicity of the treatment regimen. Of note, in some cases patients cleared HDV only after therapy was discontinued, a pattern that had also been described during treatment with conventional interferon therapy. In these studies, the seroconversion of HBsAg to HBsAb was not necessary to achieve clearance of HDV-RNA, however, patients who clear HBsAg with interferon therapy no longer have HDV-RNA or HDVAg detectable in serum or liver. Further studies into the treatment of HDV are needed as current therapy with interferon yields substandard results.

The mechanism of action of interferon in chronic HDV infection is poorly understood. The modest effect of interferon has recently been investigated. Pugnale and others believe that the decreased efficacy of interferon in the treatment of HDV infection may be partially explained by in-vitro findings demonstrating that the hepatitis delta virus inhibits intracellular interferon-induced signaling resulting in decreased interferon-mediated antiviral efficacy (26).

Parameters predictive of response to therapy in HDV are lacking. Response to therapy in HDV infection can take up to 10 months. Treatment should be continued for at least 12 months in order to determine if a patient is a true non-responder. It is not clear when therapy can be safely stopped as recurrence is common, even in patients who clear HDV-RNA during treatment. In contrast, those who clear HBsAG and acquire HBsAB while undergoing interferon therapy can safely stop, as recurrence of HDV in this situation will not occur.

Novel therapies based on the knowledge of HDV structures are being developed and explored. The HDV-RNA contains a ribozyme whose activity is important to the viral life cycle, suggesting that this may be an attractive target for therapeutic intervention. Prenylation is a chemical reaction that is essential in HDV assembly. Mice have been successfully treated with prenylation inhibitors resulting in clearance of HDV viremia depending on the duration of treatment (27).

**LIVER TRANSPLANTATION**

As HDV leads to a more virulent course of patients infected with HBV, a larger percentage of coinfectected patients will need transplantation as compared to those monoinfected with HBV. Liver transplantation is a viable option for patients with HDV associated liver failure. While most cases transplanted as a result of severe acute HDV-HBV coinfection have no recurrence of disease after transplant, those transplanted for chronic coinfection are at higher risk of recurrence. The rate of reinfection with HDV is lower than that of HBV and Hepatitis C virus (HCV) (14). If reinfection occurs, the clinical course is milder in the transplanted liver than in the native liver.

The administration of HBIG long term with or without oral nucleoside or nucleotide analogues after transplantation can help to extend this mild clinical course postoperatively by preventing recurrence of HBsAG. This led to the recognition of a latent HDV infection pattern (28). In this situation, HDV can be detected in the liver, but not in serum, within a few days of transplantation despite no evidence of HBV infection. In these patients the aminotransferase levels remain normal and there is no hepatitis on liver biopsy. If HBV recurs, then the risk of significant hepatitis and graft damage is heightened with a high risk of developing severe hepatitis accompanied by HDV and HBV viremia.

**SUMMARY**

Delta hepatitis coinfects about 5% of patients with hepatitis B virus and remains a source of significant morbidity and mortality. Current treatment of HDV consists of prolonged courses of interferon alfa, with relatively low yield of sustained remission, although there is a suggestion that a 48 week course of interferon therapy may improve the long-term clinical outcome in some patients. New knowledge regarding the steps involved in viral replication may allow for the development of therapies specifically targeted against HDV. Oral agents that inhibit HBV replication such as nucleoside and nucleotide analogues have proven ineffective in the treatment of HDV. Because HDV is dependent on HBV for its virulence, advances in public health initiatives including widespread vaccination against HBV will help to decrease the overall impact of HDV. In the care of patients with HBV, an evaluation for delta hepatitis should be considered in those who acquired HBV in an area known to be endemic for...
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References