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Hepatitis Delta Virus

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Introduction

Hepatitis Delta virus (HDV) is a hepatotropic single-stranded RNA virus. It is one of the smallest viruses (36 nm in diameter) that can infect humans. It was first identified in Italy in 1977 in patients with chronic hepatitis B virus (HBV) disease and severe hepatitis. HDV is a helper-dependent virus as it requires the concomitant presence of hepatitis B surface antigen (HBsAg) to infect and replicate in hepatocytes. Eight genotypes have been identified; globally genotype 1 is the most ubiquitous genotype, while genotype 3 is associated with the most severe forms of HDV infection.[1]

Epidemiology and transmission

The precise prevalence of HDV remains unknown due to the use of different testing strategies in various parts of the world. According to two meta-analyses published in 2020, 12 – 48 million people, or 4.5 – 13.0% of people who are HBsAg positive are also anti-HDV positive. Higher prevalence rates were noted in western and central Africa, China, Mongolia, Moldova, and certain indigenous communities in South America. The studies noted that there was limited data available from north and central America, and southern Africa.[2,3]

HDV is transmitted through the same routes as HBV, i.e. parenteral and sexual. Mother-to-child transmission is possible, but rare, as the infant of an HBsAg-positive mother will either receive HBIG and the first dose of HBV vaccine within 24 hours of birth, or the mother is likely to have been treated for HBV during the pregnancy followed by the previously mentioned postpartum treatment of the infant.[4]

Clinical features

There are two presentations of HDV infection (please see Figure 1):

- An acute **co-infection** with HBV in which both viruses are acquired at the same time, resulting in acute viral hepatitis. Signs and symptoms typically appear 3 – 7 weeks after infection and are indistinguishable from other causes of acute viral hepatitis. The majority (95%) of patients will clear both viruses spontaneously.
- A **superinfection** in a patient who is already chronically infected with HBV. The majority of these patients (80 – 90%) will fail to clear HDV and will be chronically infected with both HBV and HDV.

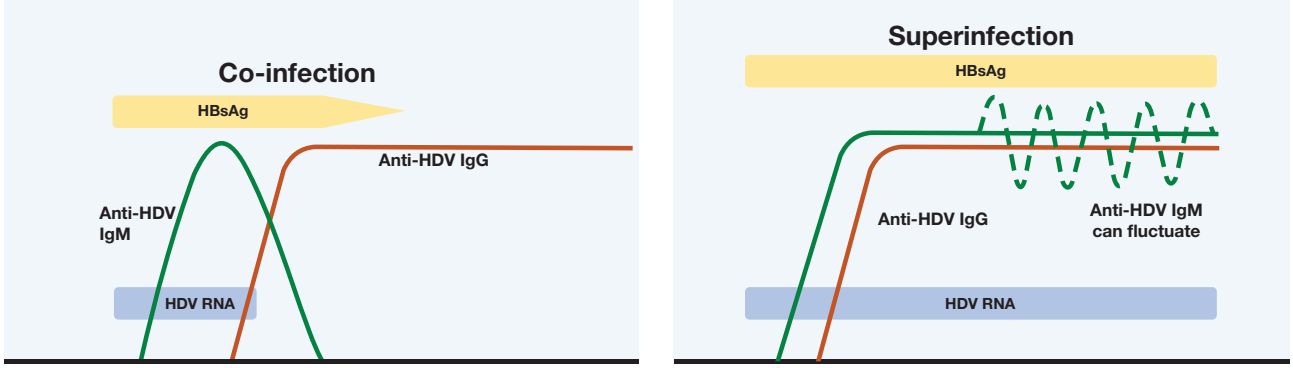

Figure 1. Serological patterns of HDV infection. (Adapted from reference 7)

Patients with chronic HBV/HDV co-infection have a three-fold increased risk of developing cirrhosis (usually within 5 – 10 years) and hepatocellular carcinoma compared to HBV mono-infected patients.[5,6] Three patterns of viral replication have been described in HBV/HDV co-infected patients:[5]

- HDV RNA replication with suppression of HBV DNA replication (55% of patients)
- HBV DNA replication dominates with lower-level HDV RNA replication (30% of patients)
- HBV DNA & HDV RNA replication occur in equal amounts (15% of patients)

Diagnosis

- **Serology**
  Anti-HDV IgM antibodies appear within 2 – 3 weeks after onset of symptoms and remain detectable for 2 months, and up to 9 months in cases of HDV superinfection. However, IgM antibodies are also detectable during disease flares in patients with chronic HDV infection. Thus, anti-HDV IgM antibodies cannot definitively distinguish between acute and chronic infection. Anti-HDV IgG antibodies become positive a few weeks after IgM antibodies and remain positive in patients with both resolved and chronic infection.[7] In clinical practice, detection of total (IgG and IgM) anti-HDV antibodies is used for screening of blood samples.

  Lancet Laboratories now offers total anti-HDV antibody testing performed on a serum (SST) sample.

- **Molecular testing**
  Because anti-HDV antibodies cannot distinguish between active and resolved infection, positive serology results should be followed up with molecular testing to confirm active infection with detection of HDV RNA. Despite the release of the First WHO International Standard for HDV RNA in 2012, significantly different results can be obtained using commercial kits and in-house developed quantitative real-time PCR assays. Reasons for this include variations in kit components, technical difficulties in detecting different HDV genotypes and the secondary structure of the HDV genome.[7]

  At present, the NHLS laboratory at the University of Cape Town is the only South African laboratory performing molecular tests for HDV. The presence of HDV RNA is confirmed qualitatively (positive/ negative) and the specific genotype is determined by nested RT-PCR followed by Sanger sequencing.

Current hepatitis treatment guidelines differ in their HDV testing recommendations. The World Health Organization (WHO), the European Association for the Study of Liver Diseases (EASL), and the Asian Pacific Association for the Study of the Liver (APASL) recommend testing of all patients with chronic hepatitis B (CHB) as part of the initial assessment for co-morbidities.[8-10] The American Association for the Study of the Liver (AASLD) currently only recommend testing in CHB patients with risk factors for HDV, including people from countries with high HDV endemicity.[11] The South African Department of Health recommends testing in CHB patients who come from African countries north of the equator, or those with hepatic deterioration despite low or undetectable HBV DNA.[12]

Unfortunately, HDV testing rates in the real world are low despite these recommendations. In a recently published study from Spain, implementing reflex anti-HDV testing in all HBsAg-positive individuals resulted in a five-fold increase in the number of people diagnosed with HDV. Of note was that 60% of the newly diagnosed individuals had no known risk factors for HDV.[13]

Treatment

At present, pegylated interferon alpha (pegIFNα) is the only fully approved medication for the treatment of hepatitis D infection worldwide. Both EASL and AASLD guidelines recommend treatment for at least 12 months in patients with compensated liver disease.[9,11] Patients should also be prescribed a nucleos(t)ide analogue (NA) if they have elevated HBV DNA levels, but neither these drugs nor ribavirin are effective against hepatitis D. Unfortunately, less than 50% of patients achieve HDV RNA suppression on treatment, and less than a third of these patients maintain HDV RNA suppression 24 weeks after stopping treatment, possibly due to persistence of HDV in the liver even at very low HBsAg levels.[9,14] Due to the poor response to pegIFNα with or without the additional of a NA, new therapies are currently being evaluated in clinical trials.

The entry inhibitor, bulevirtide, was conditionally approved by the European Medicines Agency (EMA) in July 2020 for patients with compensated liver disease due to chronic HDV. Bulevirtide is a small peptide able to block the entry of HBV and HDV into uninfected hepatocytes. In an Italian single-centre study, bulevirtide monotherapy, given at the EMA approved dose (2 mg/day) to patients with compensated cirrhosis and clinically significant portal hypertension for 48 weeks was found to be safe and effective. ALT normalisation occurred in 83% of patients, 78% of patients achieved > 2 log decline in HDV RNA level, and in 23% of patients the HDV RNA level became undetectable. Although an asymptomatic increase in bile salts was noted, none of the patients discontinued treatment.[15] Several unanswered questions remain regarding the use of bulevirtide. They include optimal dose and duration of therapy, its use as monotherapy or combination therapy, and efficacy in patients with decompensated cirrhosis.

Other experimental drugs that are currently being investigated include lonafarnib, a farnesyltransferase inhibitor, pegylated interferon lambda, nucleic acid polymers, and RNA interference compounds.

Prevention

Prevention of HBV transmission through HBV immunisation, providing safe blood and blood products, safe injection practices, and providing other harm reduction services to injection drug users are effective in preventing HDV transmission.[4]

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