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Clinical Practice, and Diagnosis and Treatment Strategies of Chronic Hepatitis D Virus (HDV)

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Abstract

Hepatitis is the liver inflammatory disease that gradually damages the liver. Hepatitis D/delta hepatitis is a liver infection caused by the hepatitis D virus (HDV). The HDV is a blood-borne pathogen and only occurs as either a co-infection with hepatitis B virus (HBV) or as a super-infection of persons with chronic HBV. It can be an acute for short-term infection or become a long-term chronic infection. In chronic infection HDV can cause serious liver damage (cirrhosis) and death at the end stage. The HDV infection is more common in Eastern Europe, South America, Africa, Central Asia, and the Middle East. At present no vaccine is available to prevent HDV. Vaccination against HBV provides the best prophylaxis against hepatitis D. The pegylated interferon alpha (Peg-IFNα) is the only therapy available to treat HDV infection that is associated with significant side-effects. Recently new medication bulevirtide, an HDV entry inhibitor, is approved to treat it. In this study, I have tried to discuss the virology, transmission, diagnosis, and treatment of the HDV infection.

Keywords: chronic hepatitis, cirrhosis, diagnostics, hepatocellular carcinoma, HDV, treatment

1. Introduction

Hepatitis D virus (HDV) is a dependent virus that depends on hepatitis B virus (HBV) to survive, transmission, replication, and synthesize genomes in human body. Therefore, hepatitis D is always associated with a co-existent hepatitis B infection (Muhammad et al., 2021). The HDV is the most aggressive form that can transform the disease rapidly to cirrhosis, hepatocellular carcinoma (HCC), and ultimately to death. In the absence of vaccination most exposed neonates and young children will be infected and become lifelong carriers (Gow & Mutimer, 2001). The HDV is discovered in 1977 by Italian virologist Mario Rizzetto and then he thought it to be an unrecognized new HBV antigen and is characterized it as the hepatitis delta virus (Rizzetto et al., 1977). However, later it was found to have a unique structural component of infectious pathogens and associated with HBV surface antigen (HBsAg) in experimentation with chimpanzees (Rizzetto et al., 1980). It is the smallest virus capable of infecting humans. It is a single stranded circular ribonucleic acid (RNA) virus that has 1678 nucleotide and contains two viral proteins that are p24 and p27 that lead to significantly higher risk of liver-related complications (Wang et al., 1986).

Hepatitis D is a neglected disease and primarily affects developing countries. The HDV uses the same receptor as HBV to infect liver cells. Once HDV becomes self-defendant and can replicate in the absence of HBV inside the liver cell. The HDV is too small to encode the viral proteins responsible for an autonomous replication (Scarponi et al., 2018). Severe acute disease and higher risk of fulminant hepatitis with HBV-HDV co-infection, HDV usually becomes dominant that is a main source of potential liver damage. Super-infection is usually developed for chronic HDV infection that is a high risk of severe chronic liver disease (Caredda et al., 1985).

Global HDV prevalence rates were 48-60 million and 62-72 million people in 2018 and 2019, respectively, and a

total 12 million reduced in 2020 (Stockdale et al., 2020). In 2020, about 5% of the HBV carriers (about 15-20 million) are estimated worldwide to be infected with HDV that is responsible for the major liver infection (Gaeta et al., 2000). At present about 74 million of HBV surface antigen (HBsAg) positive patients worldwide are also co-infected with HDV (Chen et al., 2021). Most prevalence regions are the Mediterranean, Middle East, Pakistan, Central and Northern Asia, Japan, Taiwan, Greenland, East Africa, the Amazon Basin, and certain areas of the pacific (Niro et al., 2012). Hepatitis D is very uncommon form hepatitis that appears in conjunction with Hepatitis B and could not replicate without HBV presence in blood. That is why it is considered an additional infection for people with hepatitis B (Gish et al., 2013).

The HDV infection is more common among parenteral drug abusers, persons with hemophilia, and persons emigrating from endemic areas. Management of hepatitis B and D co-infection can be more complicated than living with hepatitis B alone (Rifai et al., 2007). Treatment option for HDV has limited success. Liver transplantation is the only option for patients due to HDV and HBV with end-stage liver disease, such as liver cirrhosis, HCC, fulminant liver failure when the disease does not respond with medications or therapies (Muhammad et al., 2021).

2. Literature Review

In any research, the literature review is an elementary section where research works of previous researchers are introduced briefly to make familiar with the new researchers in the research area (Polit & Hungler, 2013). It serves as an indicator of the subject that has been carried out previously (Creswell, 2007). Pietro Lampertico and his coauthors have found that chronic infection with hepatitis delta virus (HDV) affects between 12-20 million people worldwide that represents the most severe form of viral hepatitis, leading to accelerated liver disease progression, cirrhosis and its complications, such as end-stage-liver disease and hepatocellular carcinoma (Lampertico et al., 2023). Haris Muhammad and his coauthors have discussed the epidemiology, pathogenesis, clinical presentation, treatment options, and ultimately liver transplantation of HDV patients (Muhammad et al., 2021).

Christopher Dietz-Fricke and his coworker have confirmed on the safety and efficacy of bulevirtide monotherapy in a large real-world cohort of patients with hepatitis D treated in Germany. More studies are needed to explore the long-term benefits and optimal duration of bulevirtide treatment (Dietz-Fricke, 2023). Gian Paolo Caviglia and his coworkers have discussed the progress in the understanding of the biological life cycle of HDV, the striking achievements on its virology and evolution, the contemporary epidemiologic scenario of the infection in Italy and the current therapeutic perspectives of HDV (Caviglia et al., 2022). Theo Heller and his coauthors have observed that novel therapies have been developed that hold promise for real therapeutic benefit for most patients with HDV that will be allowed for optimal treatment of the correct patients at the correct time (Heller et al., 2023).

Prooksa Ananchuensook and her coworkers have aimed to update the prevalence of HDV infection among patients with HBV infection at hepatology. They have studied the demographic, biochemical characteristics, and liver-related complications, including cirrhosis and hepatocellular carcinoma (Ananchuensook et al., 2023). Lin-Yuan Chen and her coworkers have analyzed various factors influencing the estimation of HDV prevalence with the advantages and disadvantages of currently available HDV laboratory diagnostic methods for improving the detection of HDV (Chen et al., 2021). Patrizia Farci and Grazia Anna Niro have provided the interaction of HDV with other hepatitis viruses or human immunodeficiency virus (HIV) is complex and may lead to different patterns in terms of virologic expression and immunologic responses. Multiple viral infections are associated with rapid progression of liver fibrosis and eventually with the development of hepatocellular carcinoma (Farci & Niro, 2012).

3. Research Methodology of the Study

Research is a logical and systematic search for new useful information on a specific topic that investigates to find solutions of scientific and social problems through systematic analysis (Rajasekar et. al., 2013). Methodology is the systematic and theoretical analysis of the methods applied to a field of study (Patel & Patel, 2019). It reflects the ontological and epistemological standpoints of the researcher that shows the research design and analysis procedures (Hallberg, 2006). Therefore, research methodology is a strategy for planning, arranging, designing and conducting fruitful research confidently to obtain a successful result (Legesse, 2014). To prepare this article, I have used secondary data sources of HDV that are collected from published and unpublished data sources, such as books and papers of famous authors (Mohajan, 2017, 2018, 2020). I have tried our best to maintain the reliability and validity, and also have tried to cite references properly both in the text and reference list (Mohajan, 2024a-i).

4. Objective of the Study

Main objective of this article is to discuss the aspects of hepatitis D that can be an acute, short-term infection or

become a long-term, chronic infection. The HDV causes infection only in human with the HBV infection, which is characterized by symptoms of fever, tiredness, anorexia, loss of appetite, abdominal discomfort, nausea, vomiting, and sometimes arthralgia and rash that often progresses to jaundice (Stockdale et al., 2020). It affects about 72 million people worldwide with the more rapid progression to cirrhosis and then progresses to hepatocellular carcinoma (HCC) and liver failure. Ultimate there is option of liver transformation (Negro & Lok, 2023). Other minor objectives of the study are as follows:

1) to highlight on the complex virology of HDV,

2) to show the symptoms and transmission of HDV, and

3) to discuss the diagnosis and treatment of HDV.

5. Virology of HDV

The HDV genome is a 1,700 nucleotides defective, single-stranded circular minus RNA virus that requires the presence of HBV in order to replicate (Miao et al., 2020). It is a negative-strand incomplete RNA virus that requires HBsAg (HDV virion) for its viral envelope and transmission. It is the only member of the genus Deltavirus, is from the Deltaviridae family (Kiesslich et al., 2009). It can encode two forms of hepatitis D antigen (HDAg), namely the small HDAg (S-HDAg) and the large HDAg (L-HDAg). The HDV-RNA folds into an unbranched rod-like structure in which the 70% of the nucleotides are paired (Chen et al., 2021). The virion is a 35-37nm particle, with the delta antigen and the RNA genome within a coat made by the HBsAg, with no nucleocapsid structure (Figure 1). The hepatitis D virus (HDV) utilizes HBsAg as its envelope protein (Rizzetto & Verme, 1985).

The HDV only occurs as a co-infection or super-infection with acute HBV (parenterally), which may then progress to severe fulminant infection and may cause acute hepatitis occurs immediately. Super infection is clinically manifested by exacerbation and rapid progression of the disease up to the development of liver cirrhosis (Ni et al., 2014).

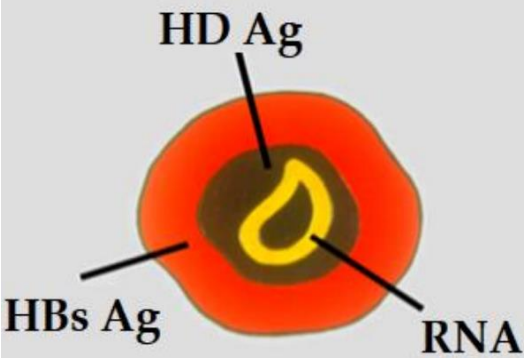

Figure 1. The HDV dependent on the HBsAg-positive

Source: Caviglia et al. (2022).

There are eight different HDV genotypes (GTs), with different geographic distribution. Classically, there are three main HDV genotypes (GTs): 1, 2, and 3; their lengths are restricted to a range of 1672 to 1697 nucleotides (Le Gal et al., 2017). The GT1 is global, and has been associated with hepatitis of varying severity. But it is predominant in North America and Italy (Miao et al., 2020). GT2 have been identified in Japan and Taiwan, and causes relatively mild hepatitis; GT3 isolates are associated exclusively with countries from Northern South America (Columbia, Venezuela, and Peru) and is associated with fulminant hepatitis (Casey et al., 1993). So far, GT3 only has been correlated to disease severity that tends to cause severe acute hepatitis, which can progress to liver failure (Niro et al., 1997).

The helper virus HBV does not share either sequence homologies or functional similarities with HDV in their mechanisms of genome replication. On the other hand, HDV shares some functional and structural similarities with viroids and virusoids (Wedemeyer & Manns, 2010). At present the worldwide prevalence of HDV is about to be 72 million that was about 48-70 million as previously. Top three countries with HDV prevalence are Mongolia (36.9%), Guinea-Bissau (23.9%), and Gabon (22%) (Stockdale et al., 2020).

5.1 Symptoms of HDV

Symptoms typically appear three-seven weeks after the initial infection. The symptoms of HDV infection are

indistinguishable from those of HBV infection. The majority of the patients are asymptomatic (Caredda et al., 1985). The symptoms of HDV infection are fever, fatigue, tiredness, loss of appetite, malaise, anorexia, nausea and vomiting, joint pain, confusion, bruising, abdominal pain, dark urine, clay-colored bowel movements and jaundice (yellowing of the skin and eyes) (Kamal et al., 2020).

The incubation period for co-infection is 45-160 days with an average 90 days. The incubation period of super-infection is 2-8 weeks after exposure (Miao et al., 2020). The case of co-infection is more likely to result in fulminant hepatitis or severe liver failure than that of only infected person with HBV. The disease is self-limiting and most patients recover completely, only 2% leading to chronic infection (Caredda et al., 1985). About 80-90% of patients progress to chronic hepatitis, such as coagulopathy, encephalopathy, and coma (Fattovich et al., 2000).

5.2 Transmission of HDV

The HDV mainly spreads among persons through the contact with blood or body fluids (parenterally) (horizontal transmission), such as saliva, blood, semen, vaginal secretions; sex with an infected partner (Liaw et al., 1990). The HDV may also be transmitted through various sexual activities, such as oral sex, vaginal sex, and annul sex. It only occurs primarily in drug addicts and persons with hemophilia (Urban et al., 2021). Vertical transmission, such as mother to infant through the birth to an infected mother may happen, but it is rare (Sellier et al., 2018). The highest prevalence of HDV is seen in individuals with intravenous drug use followed by commercial sex workers, men who have sex with men, hemodialysis recipients, HIV positive individuals, injection drug users, HCV-positive individuals, infants born to infected mothers, and patients with cirrhosis (Stockdale et al., 2020).

It can be spread through the sharing items, such as razors, toothbrushes, needles, syringes, or other drug-injection equipment, etc. of an infected person (Mohajan, 2024f). Sexual transmission of HDV may also occur but is less common than with hepatitis B. Perinatal infection of the virus is rare (Wedemeyer & Manns, 2010). It can be also spread when persons traveling from and to countries where the disease is prevalent. There are two major patterns of infection, such as co-infection of HBV with HDV and super-infection of HDV in chronic HBV-infected patients (Caredda et al., 1985).

The HDV is not spread through food or water, sharing eating utensils, and breast feeding. The HDV cannot be transmitted casually and cannot be spread through sneezing, coughing, hugging, eating a meal with someone, or eating food prepared by someone co-infected with HBV and HDV (Caredda et al., 1985).

5.3 Diagnosis of HDV

The HDV infection is diagnosed by high levels of anti-HDV immunoglobulin G (IgG) and immunoglobulin M (IgM), and confirmed by detection of HDV RNA in serum. Radioimmunoassay and liver enzyme immunoassay for anti-HDV antibody are available (Wranke et al., 2014). Super-infection HDV/HBV is usually confirmed by detection of anti-HDV IgM in patients HBsAg positive and anti-HBV IgM negative (Mederacke et al., 2012). The most commonly available test for hepatitis D is a total anti-HDV assay that usually becomes positive approximately four weeks after acute infection (Farci & Niro, 2012). The HDV ribonucleic acid (RNA) is identified through the diagnosis. The HDV RNA polymerase chain reaction (PCR) testing is increasingly available that may become positive sooner than total anti-HDV (Urban et al., 2021).

The HBV deoxyribonucleic acid (DNA) and HDV RNA tests are helpful in understanding how active hepatitis B and hepatitis D are in the body (Le Gal, 2017). The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) tests can be helpful in understanding the current liver damage (Caredda et al., 1985). Alpha-fetoprotein (AFP), liver ultrasounds, liver elastography (Fibroscan), and liver biopsy can provide a more accurate and detailed understanding of current liver health during fibrosis, cirrhosis, and liver cancer (Farci & Niro, 2012).

5.4 Treatment of HDV

No specific treatment is available for HDV infected people. There are no known treatments for acute HDV (Urban et al., 2021). The primary way to prevent HDV infection is immunization against HBV. Oral drugs effective against HBV are ineffective against HDV (Loureiro et al., 2021). The pegylated interferon alpha (Peg-IFNα) is the generally recommended treatment to suppress the HDV for some patients (De Ledinghen et al., 2021). But it has limited efficacy with huge side-effects (Abbas et al., 2011). In 2020, a new medication Bulevirtide is conditionally approved by the European Medicines Agency for the treatment of hepatitis D at a daily dose of 2 mg without additional interferon under the trade name Hepcludex (Dietz-Fricke, 2023).

At present there is no vaccine available for hepatitis D. But vaccination with the hepatitis B vaccine can protect people from HDV infections. The screening of the blood supply for HBV has altered the epidemiology of HDV (Farci & Niro, 2012). Liver transplant is the only option when the disease reaches in the final stage of the disease when the patient does not respond in any treatment and therapy (Rifai et al., 2007).

A healthy balanced diet of fruit, whole grains, fish and lean meats, carbohydrate, and lots of vegetables is necessary to maintain the health of a HDV infected patient. Cruciferous vegetables, such as cabbage, broccoli, cauliflower, etc. protect the liver against environmental chemicals (Alfaiate & Negro, 2019). Moderate exercise, well-balanced diet, and avoid of alcohol and illegal drugs are necessary for a HDV infected patient (Franciscus, 2017).

6. Conclusions

Recently, there has been a significant decline in HDV transmission as a result of the decrease of HBV infection due to improved socioeconomic conditions, increased awareness of infectious disease transmission, and improved HBV vaccination rates. To reduce the transmission of HDV, all people infected with HBV must be screened for HDV. The HDV presents a severe health burden at the end-stage liver disease, such as hepatocellular carcinoma (HCC), fulminant hepatitis, and liver failure. About 50 years passed from the discovery of HDV, its fatality still poses great challenges from a clinical and biological perspective.

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