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Unmet Needs of HDV: Addressing Challenges in Diagnosis and Treatment

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Abstract

Hepatitis D virus (HDV) is a defective RNA viroid that requires HBsAg for transmission. HDV infection occurs in individuals positive for HBsAg, leading to severe hepatitis, fibrosis progression, hepatic decompensation, and hepatocellular carcinoma. Treatment success rates remain low, presenting unmet needs. About 13 million individuals are chronically infected with HDV, accounting for 5% of chronic HBV infection cases. Transmission has shifted to immigration and sexual transmission in recent years.

HDV occurs in people with Hepatitis B, causes liver damage, and has no specific treatment. The study aims to identify barriers, potential improvements, and unmet needs in HDV diagnosis and treatment, including better access to treatment options and improved support for patients.

HDV infection continues to pose significant challenges worldwide, particularly in individuals co-infected with HBV. The declining trend in HDV infection due to HBV vaccination is encouraging, but treatment success rates remain suboptimal. Addressing the unmet needs of HDV requires a multifaceted approach encompassing improved diagnostics, targeted therapies, increased awareness, and accessible healthcare services. By focusing on these aspects, we can strive to improve outcomes and reduce the burden of HDV infection on affected individuals and global health systems.

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INTRODUCTION

In 1977, Mario Rizzetto and his colleagues described an antigen in the hepatocytes of patients infected with HBV (1). In particular, patients with a severe course of HBV infection were found to have antibodies against the so-called 'delta antigen' (2). Therefore, the hepatitis D virus (HDV) was identified as the infectious agent that causes hepatitis in the presence of HBV infection (3). Thus, hepatitis D occurs only in individuals who are infected with HBV, as HDV uses the surface antigen of the hepatitis B virus (HBsAg) as its envelope protein, which is essential for viral transmission. Therefore, HDV infection can occur either as a superinfection of a chronic HBV infection or as a simultaneous acute co-infection of HBV and HDV.

The discovery of HDV opened up a new field for further research in three main directions:

- The evaluation of the epidemiological and medical impact.
- Understanding the mechanisms of HDV replication and infection.
- Researching a therapy for Chronic Hepatitis D.

Currently, there is no effective treatment available for HDV infections, and the only therapy option is interferon alpha (IFNα), which has shown poor efficacy. Even the addition of antivirals, like Adefovir (ADV), Entecavir (ETV), and Tenofovir (TDF), against the HBV partner does not help (4). In the Hep-Net International Delta Hepatitis Intervention Trial (HIDIT-1), the largest trial for CHD, using Pegylated (Peg)-IFN in monotherapy or in combination with ADV resulted in a cumulative rate of sustained viral response of only 28% (5), with frequent post-therapy relapses (6).

Therefore, there is an urgent need for new therapies against hepatitis D, but it is a daunting challenge. HDV, with an RNA genome of only about 1700 nucleotides, does not code for proteins like viral polymerases and proteases of HBV and HCV, and therefore cannot be targeted by conventional antivirals (7). HDV depends on the helper HBV and host replicative machinery for dissemination and replication. Hence, emerging treatment approaches aim to target host factors critical to virus replication and disrupt the viral life cycle by depriving the HDV of critical biological functions provided by the liver cell.

In our country, which is considered endemic for hepatitis B and Delta, we have very little data on the latter. Hepatitis D represents a burden on health in some areas of the world, as well as in our country. In Western countries, the immigrant population has a high prevalence of HDV infection. Diagnosis is a challenge in itself and requires an understanding of the complex dominance relationships between different types of hepatitis viruses. Treatment alternatives are limited, as so far only IFN-α has been proven to have an antiviral effect against HDV and provides good results over the long term. Further research is necessary to better understand the pathophysiology of HDV infection and to develop new treatment alternatives for this

disease, which represents the most severe form of viral hepatitis.

Epidemiology

Viral Hepatitis Delta is distributed worldwide. It is estimated that there are more than 350 million individuals with chronic infection from HBV and 15-20 million of these individuals are believed to be coinfected with HDV (8). HDV infection has been highly endemic in Southern Europe. Various studies carried out in the 80s and 90s showed that the prevalence of HDV infection in individuals with positive HBsAg is >20% (9). However, the implementation of HBV vaccination programs in the 80s has significantly reduced the incidence by 5-10% (10).

There are many regional variations, with a higher rate of infection in some countries. This is true for the Mediterranean countries, Northern Africa, and the Middle East. For example, in Turkey, the prevalence of HDV infection in individuals with positive HBsAg ranges from 27% in southeast Turkey (11). Another country with a particularly high prevalence of HDV infections is Mongolia, where more than 1/3 of chronic hepatic infections are attributed to HDV (12). Excluding the decrease in the prevalence of hepatitis D in Southern Europe, the disease still constitutes a health cost in Central Europe, where its prevalence is mainly attributed to immigration from high-endemic areas (13,14). In a German reference center for liver disease, about 8-10% of patients with positive HBsAg test positive for anti-HDV antibodies. More than 3/4 of these patients with hepatitis D were not born in Germany. The geographic origin of HDV-infected patients in this center is said to have changed over the past decade.

Until the mid-1990s, the majority of HDV-positive patients were born in Turkey; however, the number of HDV-infected patients born in Eastern Europe and the former Soviet Union has increased significantly since the late 1990s.[13] Another German hepatology center has also reported an increase in the number of patients with hepatitis D born in Eastern Europe and Central Asia.[14] HDV infection has a significant increase in South London (15). Between 2000-2006, 82 (8.5%) out of approximately 1000 patients with chronic hepatitis B tested positive for anti-HDV at King's College Hospital in London (16). In that study, HDV-infected patients were mostly born in Africa or Eastern Europe. Like the German and English experience, the immigrant population in France also has a high prevalence of HBsAg-positive individuals who tested positive for anti-HDV antibodies. Despite these data, acute HDV infections can rarely occur in the non-immigrant population. The main risk factors for HDV infection in Italy are attributed to uncontrolled sexual activity, cosmetic treatments, and intravenous drug use (17).

Data on the epidemiology of hepatitis D in the USA is limited. Studies published between 1985 and 1993 reported a prevalence of 2% among homosexual males (18), around 20% among hemophiliacs (19), and female prostitutes (20),

and up to 30% in individuals with HBV infection (21). However, no epidemiological study with a significant number of patients has been published. Particularly in the USA, the increased prevalence of HDV infection is known in populations at high risk, such as intravenous drug users. Hepatitis D is also prevalent in HBsAg-positive populations in the western Amazonian regions of Brazil (22), mountainous regions of Venezuela, and the population of the Western Pacific (23). High frequencies of HDV infection and high rates of morbidity and mortality have been described in the western Amazonian regions of Brazil (22,24,25).

Albanian data:

Regarding our country, it is believed that before 1995 the prevalence of HBsAg in the unvaccinated Albanian population varied between 18% and 19%. In a 2009 article published by Resuli B. et al. in the World Journal of Gastroenterology, "Epidemiology of hepatitis B virus infection in Albania," we find important data on the spread of hepatitis B. This estimate was achieved through testing for HBsAg in a large population group: 410 students, 666 university students, 500 soldiers, 1,286 randomly selected blood donors, 378 voluntary blood donors, and 640 pregnant women - a total of 3,880 unvaccinated individuals from rural and metropolitan areas throughout Albania.

The study lasted for approximately 2 years (2004-2006) and provided us with the following data: HBsAg prevalence was 9.5%, and anti-HBs prevalence was 28.7%. The highest prevalence was found in the youngest age group - students (11.8%) and soldiers (10.6%). This reduction in prevalence by around 2 times is attributed to the beginning of population vaccination in 2004 as well as the prevention of perinatal transmission. Despite this positive change, Albania remains a country with a high endemicity for hepatitis B.

In these circumstances, it can be said that hepatitis D has a broad base for superimposition or co-infection. As for the prevalence of anti-HDV in our country, we have very little data. In a paper accepted as an abstract at the World Congress of Gastroenterology in 2005 (Resuli.B et al.), a prevalence of hepatitis D of around 11% (in chronic B hepatopathy) is reported.

In 2012, we concluded a 5-year study at the University's Gastroenterology/Hepatology and Internal Medicine Services. The study consisted of 405 individuals with chronic hepatitis B (HBsAg positive), with the majority having chronic hepatitis B (323), while the others presented with B cirrhosis (72) or hepatocellular carcinoma (9). All patients were diagnosed and treated at the University Gastroenterology/Hepatology and Internal Medicine Services during the 2007-2011 period.

Based on our study and the goals we had set, we obtained the following results: The prevalence of Hepatitis Delta virus in our country was found to be 9.13%. The prevalence of Hepatitis Delta virus by gender was found to be 2.22% for females and 6.91% for males. The average age was found to be 35.67 years, with the youngest patient being

18 years old and the oldest being 62 years old. The incidence of Hepatitis Delta virus for the four-year period (2007-2011) was 1.16/100,000. The annual average indicating the number of new cases in a year was 0.29/100,000. In the group of patients with Hepatitis Delta, 5.4% were in the compensated cirrhosis stage, 13.51% were in the decompensated cirrhosis stage, and 81.08% were in the chronic Hepatitis Delta stage. All patients infected with the Hepatitis Delta virus were HBeAg negative and anti-HBeAg positive, indicating they carried the mutant B virus.

Over the course of another 10-year study involving 1523 patients, all of whom tested positive for anti HBe and negative for HBe Ag, it was found that the prevalence of the condition was 11%, with an incidence rate of 3%. The sex ratio was found to be 2:1 in favor of males, and the mean age at diagnosis was 38 years (ranging from 20 to 66 years). The condition was found to be transmitted through various means, including blood transfusion, hemodialysis, drug use, sexual contact, surgery, and perinatal transmission (although the latter was rare). Upon diagnosis, 73% of patients were diagnosed with chronic hepatitis, 23% with compensated cirrhosis, and 4% with decompensated cirrhosis. Furthermore, it was found that a 96-week course of peg INF alfa treatment was more effective than a 48-week course in decreasing HDV RNA levels.

HDV

When a person is infected with both HBV and HDV, they may experience acute hepatitis with symptoms that are similar to other viral infections. Typically, patients make a complete recovery, and severe complications are rare. However, when HDV infects someone who already has chronic HBV, the disease can progress more rapidly and become more severe. In fact, 70-90% of patients with chronic HBV and HDV co-infection experience a faster progression to cirrhosis compared to those with only HBV. In addition, HDV superinfection can cause cirrhosis a decade earlier than HBV alone. Patients who develop cirrhosis due to HDV infection are also at an increased risk of developing hepatocellular carcinoma (HCC) (26).

Chronic hepatitis D (CHD) is known to be associated with the most severe form of viral hepatitis caused by hepatotropic viruses. The course of CHD can be influenced by various factors including those related to the host and virus itself. CHD is known to be an immune-mediated disease, suggesting that the severity of the condition may be dependent on the individual's immune response. When considering viral factors, both the genotype of hepatitis delta virus (HDV) and hepatitis B virus (HBV) can have an impact. In particular, the genotype of HDV and HBV is known to be a significant determinant of the course and outcome of CHD. HBV has 8 different genotypes, each with distinct genetic characteristics that can influence the progression of CHD. Similarly, HDV has multiple genotypes that can contribute to the severity of CHD (27).

According to EASL guidelines, it is recommended to conduct anti-HDV testing on all individuals who test positive for HBsAg. However, it is still common for HDV infection to be undetected. Therefore, it is crucial to properly diagnose HDV to guide treatment and monitor the disease's progression (28).

The 2017 guidelines by the European Association for the Study of the Liver (EASL) and the 2016 guidelines by the Asian-Pacific Association for the Study of the Liver (APASL) both suggest that anti-HDV testing should be conducted in all individuals who are HBsAg-positive. This recommendation is aimed at improving disease management and surveillance.

However, the 2018 guidelines by the American Association for the Study of Liver Diseases (AASLD) differ in that they recommend anti-HDV testing only in individuals who are HBsAg-positive and considered at risk.

Aims of treatment

The primary goals of treatment for HDV and HBV infections are either to eliminate the viruses completely or to achieve prolonged suppression of both viruses. The treatment goals for patients with HDV and HBV infections include eradicating or achieving long-term suppression of both viruses. The IDEAL treatment outcome involves HBsAg loss with anti-HBs seroconversion. Additionally, a decline of 2 log UI/ml of HDV RNA and normalization of ALT levels are accepted measures of initial treatment efficacy in clinical trials. During therapy, at the end of the treatment and off therapy (24 weeks after discontinuation), the HDV RNA levels should be below the limits of detection (PCR assay). It is also important to eliminate replicating HDV RNA from the liver in HBs Ag + patients, which can be determined through liver biopsies (29).

There is a promising outlook for patients with CHD, with the development of hepatocyte entry inhibitors, prenylation inhibitors, and NAPs. Bulevirtide is currently the only drug approved by EMA (not FDA yet) for the treatment of Delta hepatitis. Although NUCs are not effective against HDV replication, they should still be given to prevent HBV flares.

There are some critical issues that need to be addressed in the treatment of viral hepatitis, particularly in the aging population where patients often have other health concerns in addition to viral hepatitis. In addition, special populations such as HIV coinfected patients, children, pregnant women, immunosuppressed patients, and those undergoing chemotherapy and dialysis require special attention due to the potential for drug toxicity.

The approach to long-term nucleos(t)ide analog (NA) therapy is also an interesting topic, as there is no uniform approach to finite treatment. These issues highlight the need for ongoing research and development of more effective and safe treatments for viral hepatitis.

Current recommendations and future options:

The epidemiology of HDV in our country is changing and this is due to the successful work being done to control HBV. Education of the population, family physicians, and all other healthcare workers for this dual infection of HBV and HDV, as well as detection and vaccination for hepatitis B, should remain a priority.

If infection with the D virus occurs, our duty and responsibility are to detect the pathology as early as possible, to evaluate the situation, initiate therapy, and follow the course of the disease. In all known cases of chronic hepatitis B, in any case where the transaminase values are 2-3 times above the normal level, testing for an underlying infection from the D virus (testing the patient for Anti-HDV) should be sought.

If the pathology progresses towards chronicity:

- Most guidelines recommend treating chronic HDV infection with PEG-IFN-α for at least 1 year. Aggressive treatments should be considered if patients can tolerate the side effects of therapy, show a biochemical and virological response to treatment, and are at high risk of progressing to the clinical end-stage. Measuring the kinetics of HDV RNA during treatment may help identify patients who do not respond to treatment and individuals who may benefit from prolonged treatment (30).
- Treatment with HBV polymerase inhibitors is indicated only if treatment with IFN is not possible and if high levels of HBV replication are seen. Data on the effectiveness of combination therapy involving IFN and HBV polymerase inhibitors are insufficient; however, significant reductions in serum HBsAg levels have been observed during treatment with PEG-IFN-α2a plus adefovir dipivoxil (31).
- Studies are seeking to optimize the effectiveness of available therapeutic options, for example, long-term use of combined therapy of PEG-IFN-α2a plus tenofovir. In addition, other treatment alternatives should be explored (32). Among them, prenylation inhibitors may be promising. HDV replication depends on a prenylation process and prenylation inhibitors have already been developed for the treatment of malignant diseases.

Three new therapeutic approaches have been developed to combat hepatitis B and D virus infections. The first strategy involves blocking the binding of the hepatitis B surface antigen (HBsAg) to the Sodium Taurocholate Co-transporting Polypeptide (NTCP), which is located on the surface of liver cells (33). By preventing the entry of HBsAg into liver cells (34), drugs that interfere with this process could potentially prevent new infections from occurring. Myrcludex B (Myr) (35), a small peptide that inhibits the engagement of the HBsAg preS1 with the NTCP, is the first drug that has entered clinical trials for this purpose.

The second approach targets the process of viral assembly, which requires the host to farnesylate

the large HD antigen of the virus. Inhibiting this process by using drugs that inhibit cellular farnesylation, such as Lonafarnib (LNF), can disrupt viral assembly and prevent the production of new viral particles (36).

The third strategy involves preventing the export of HDV virions from liver cells. This process requires the encapsidation of HDV in the HBsAg coat. Nucleic acid polymers (NAPs) can interfere with the synthesis of subviral HBsAg particles and hinder the release of HDV virions from cells. REP 2139 is the first NAP that has been used to block the release of HDV virions from cells (37).

DISCUSSION

It is clear that the following populations are at a higher risk of contracting HDV: newborns whose mothers have HDV infection; sexual partners of individuals with HDV infection; men who engage in sexual activities with other men; individuals who inject drugs; people who live in the same household as those with HDV infection; health care and public safety workers who may come into contact with blood or blood-contaminated body fluids.

The diagnosis of hepatitis D poses several challenges due to a variety of factors. First, testing for HDV is not widely available in all regions, which hinders the prompt diagnosis of the infection. Secondly, even when HDV antibody tests are conducted, the results may not always be conclusive. This could be due to a number of factors, including the timing of the test or other confounding factors. Additionally, there is a lack of routine screening for HDV in patients who are already known to be HBsAg positive, which means that many cases of HDV may go undetected. Instead, many guidelines suggest risk-based screening for HDV, rather than universal screening. Another challenge is the lack of standardization of HDV RNA tests, which can lead to variability in test results. However, newer assays are now available which may help to improve the accuracy and reliability of HDV RNA testing. Overall, these diagnostic challenges underscore the importance of continued research and development in the field of hepatitis D diagnosis and management.

One of the significant challenges in managing HDV infection is limited education for healthcare professionals. The lack of awareness and knowledge about HDV and its associated risks among healthcare providers can lead to delayed diagnosis and treatment, which can increase the risk of complications. Additionally, there is reduced motivation to screen patients for HDV due to the lack of approved treatment options, particularly in certain areas. However, the recent approval of drugs for the treatment of HDV has increased awareness and motivation to screen and manage HDV infection.

Non-invasive tests (NI tests) used to stage fibrosis and predict cirrhosis in liver disease have not been as extensively studied as in other liver diseases. The diagnostic performance of these tests remains uncertain, and there is a significant unmet need for further research in this area.

CONCULSION

It is likely that CHD will continue to be managed using IFN treatment. In conclusion we can say that, it is recommended to raise awareness for regular screening of Hepatitis B surface antigen (HBsAg) carriers and patients who have migrated from high prevalence areas. Additionally, patients receiving appropriate treatment for HBV infection and have elevated liver function tests should also undergo regular screening. HBsAg positive patients with abnormal alanine aminotransferase (ALT) and low HBV DNA levels should also be screened regularly. Moreover, patients who are not responding well to appropriate treatment, regardless of their HBV DNA levels, should also be screened regularly.

According to the prevailing theory, succeeding in the treatment of HBV and HDV infections requires a combination of two different strategies. The first strategy involves the development of novel antivirals that directly target multiple steps in the virus replication, which is made possible by a better understanding of the structure and life cycle of the virus. These antivirals work by preventing the synthesis of new cccDNA, thereby inhibiting the virus from replicating and spreading. The second strategy involves the use of immunomodulators to subvert the state of tolerance found in the chronic phase of the disease. These immunomodulators help to promote the death of infected hepatocytes and neutralization of circulating virions, which can further limit the spread of the virus and help to clear the infection. By combining these two strategies, it may be possible to achieve the goal of eradicating or achieving long-term suppression of both HBV and HDV infections.

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