

Clinical Features of Hepatitis D

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Abstract

Hepatitis D is caused by infection with hepatitis D virus (HDV), a defective RNA virus that requires the obligatory helper function of hepatitis B virus (HBV) for its in vivo transmission. Thus, HDV is acquired only by coinfection with HBV or by superinfection of an HBV carrier. The clinical outcome of hepatitis D differs according to the modality of infection. Whereas coinfection evolves to chronicity in only 2% of the cases, superinfection results in chronic infection in over 90% of the cases. HDV is a highly pathogenic virus that causes acute, often fulminant hepatitis, as well as a rapidly progressive form of chronic viral hepatitis, leading to cirrhosis in 70 to 80% of the cases. The clinical picture of HDV disease is evolving as a consequence of a significant change in the epidemiology of HDV infection, which has led to a significant decline in incidence in Western countries, mainly as a result of universal HBV vaccination programs. However, in the face of a declining prevalence in areas of old endemicity like Europe, immigration poses a threat of HDV resurgence. The interaction of HDV with other hepatitis viruses or human immunodeficiency virus 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. Hepatitis D is not a vanishing disease, and continuous efforts should be made to improve its prevention and treatment.

Keywords

- ▶ hepatitis D virus
- ▶ acute hepatitis D
- ▶ chronic hepatitis D
- ▶ cirrhosis
- ▶ hepatocellular carcinoma
- ▶ clinical features
- ▶ liver pathology
- ▶ viral interaction

Introduction

Hepatitis D is caused by infection with one of the most interesting and unusual human pathogens, hepatitis D virus (HDV), a defective RNA virus that requires the obligatory helper function of hepatitis B virus (HBV) for its in vivo transmission.^{1,2} HDV is a hepatotropic virus and appears to replicate exclusively in the liver. Because of its vital association with HBV, HDV can be transmitted only in the presence of concomitant HBV infection as one of two patterns depending on the prior hepatitis B surface antigen (HBsAg) status of the infected individual: simultaneous infection of a susceptible individual with HBV and HDV (coinfection pattern) or HDV superinfection of an individual chronically infected with HBV (superinfection pattern).³ Individuals who are immune to HBV (anti-HBsAg positive) are not susceptible to HDV infec-

tion. The clinical expression and outcome of acute hepatitis D is different according to the modality of HDV acquisition. Since the early studies, HDV turned out to be a highly pathogenic virus that causes the most severe forms of acute hepatitis, including fulminant hepatitis, and of chronic liver disease in HBsAg-positive individuals. In this review, we discuss the clinical features of acute and chronic hepatitis D, how the changing epidemiology has affected the clinical scenario of hepatitis D, and the interactions of HDV with other viral infections.

Coinfection Pattern

Simultaneous infection of a susceptible individual with HBV and HDV results in both acute hepatitis B and acute hepatitis D.⁴

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As a defective virus depending on HBsAg synthesis, HDV infection starts only after HBV has infected hepatocytes; its expression relies on and is limited by the virulence of the concomitant HBV infection. A restricted expression of HBsAg may result in abortive HDV infection whereas a florid expression provides a fertile ground for the full expression of HDV and its pathogenicity. As a result of the complex interplay between the two viruses, the clinical expression of HBV and HDV coinfection varies from mild to severe or even fulminant hepatitis. The incubation period of hepatitis D is dependent on the titer of the coinfecting HBV inoculum, which determines the incubation time of hepatitis B.⁵ The acute hepatitis can present either with a single peak (monophasic) or with two distinct peaks (biphasic) depending on the relative titers of HBV and HDV. The first peak of hepatitis is caused by HBV and the second by HDV, even though an inverse pattern has been occasionally observed in the chimpanzee model.⁶ Coinfection usually leads to an acute self-limited hepatitis that cannot be distinguished clinically from ordinary hepatitis B. Because the HBs antigenemia required to support HDV replication is transient, in most cases the outcome of acute hepatitis D is complete recovery, as typical of acute hepatitis B, and in only 2% of cases it may progress to chronicity.⁷ Coinfection, however, is a cause of severe or fulminant hepatitis.⁸ The diagnosis of coinfection is based on the simultaneous presence of serologic markers of primary HBV and HDV infection.⁹

Superinfection Pattern

The clinical expression and outcome of hepatitis D differ when HDV infects individuals who are chronically infected by HBV (superinfection pattern). In this setting, the preexisting HBsAg status provides a perfect biologic background for the rapid expression of the defective delta virus, which immediately establishes infection using the HBsAg from the preexisting HBV infection, not the one provided by the HBV present in the infectious inoculum.³ The clinical outcome of superinfection is variable, although it generally causes a severe acute hepatitis with a relatively short incubation period. Clinically, it may present with an exacerbation of the preexisting chronic hepatitis B leading to liver decompensation,¹⁰ or as a new hepatitis in a previously asymptomatic HBsAg carrier. If the HBsAg status is unknown, the acute hepatitis may be misdiagnosed as a classical acute hepatitis B.¹¹ The correct diagnosis is suggested by a negative test for IgM anti-HBc and confirmed by positive HDV serology. Superinfection with HDV may result in fulminant hepatitis. Since the HBsAg status provides the biologic terrain for the maintenance of HDV replication, chronic HBsAg carriers superinfected by HDV develop progressive chronic hepatitis D in over 90% of the cases.³ Interestingly, however, a minority of HBsAg-superinfected carriers experience a self-limited hepatitis and clear HBV.^{12,13} The correct diagnosis of HDV superinfection is suggested by a negative (or very low titered) IgM anti-HBc and confirmed by the detection of HDV markers.¹¹

The liver transplantation setting has provided evidence for the existence of a third form of HDV infection defined *latent*

infection.¹⁴ It is characterized by the presence of markers of HDV infection associated with very low levels of HBV replication,¹⁵ which initially went undetected due to the low sensitivity of the tests used.¹⁴ Thus, this pattern cannot be considered a form of bona fide viral latency and reiterates the strict dependence of HDV upon HBV for its replication.

Acute Hepatitis D

Symptoms and Course

The clinical symptoms of acute hepatitis D are indistinguishable from those reported in other forms of viral hepatitis, although they tend to be more severe. After an incubation period of 3 to 7 weeks, characterized by active HDV replication, nonspecific clinical symptoms such as fatigue, anorexia, lethargy, and nausea begin along with biochemical evidence of hepatitis, as shown by a dramatic rise in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, concomitant with a decrease in viral replication.⁵ This phase may be followed by an icteric phase with the appearance of frank jaundice and persistence of nausea and fatigue in parallel to an increase in serum bilirubin levels, dark urine, and clay-colored stools. In patients with acute self-limited hepatitis, the convalescence phase begins with disappearance of the clinical symptoms, starting from anorexia and nausea and subsequently lethargy and fatigue. Because of the complex interplay between HBV and HDV, the acute disease tends to be more severe in the superinfection pattern. Superinfection with HDV may be associated with fulminant hepatitis, also named acute liver failure (ALF),¹⁶ which is a dramatic clinical syndrome characterized by the sudden loss of hepatocytes leading to multiorgan failure in a subject with no prior liver disease.¹⁷ ALF is a rare sequela of acute viral hepatitis, albeit more frequent in acute hepatitis D than in the other forms of viral hepatitis. More than half the cases of ALF in HBsAg-positive subjects are due to HDV rather than HBV alone.^{8,18} Clinically, it may begin with malaise and nausea, followed by jaundice, coagulopathy, and hepatic encephalopathy, which is manifested initially by confusion, changes in personality, and then somnolence and coma.⁵ The onset of encephalopathy may also precede the appearance of jaundice. Serum ALT and AST may be high or low at presentation because they decrease as massive liver necrosis leaves only few viable hepatocytes, along with a marked decrease in the level of HDV replication. The clinical course is often so rapid that the patient goes from a healthy status to near death within 2 to 10 days. Before the advent of orthotopic liver transplantation (OLT) the mortality rate of ALF was very high, ~80%.¹⁶

Chronic Hepatitis D

Symptoms and Course

Chronic hepatitis D is a very common sequela of acute hepatitis D acquired through the superinfection pattern, occurring in over 90% of cases. It is the least common, but the most severe and rapidly progressive form of chronic viral hepatitis at all ages, leading to cirrhosis in ~70% of the cases

within 5 to 10 years and at younger age.¹⁹ In ~15% of patients, cirrhosis develops within 1 to 2 years from the onset of acute hepatitis D.²⁰ The risk of developing cirrhosis is three times higher in HDV-infected patients compared with those with HBV alone.²¹ Once established, HDV cirrhosis can be a stable disease for many years, although a high proportion of patients eventually die of liver failure or hepatocellular carcinoma (HCC) unless they receive OLT.²² The association of HDV with HCC has been demonstrated, but the data on the risk of HCC in patients with chronic hepatitis D are controversial. Whereas in some studies HDV appeared to be a promotion factor of HCC^{23–25} with a threefold increased risk compared with patients with HBV cirrhosis alone,²¹ in other studies HDV did not appear to significantly increase the risk.^{26,27} Although cirrhosis represents the major risk factor for the development of HCC, it remains to be determined whether HDV has inherent oncogenic properties. The defective nature of HDV, the rapid progression of HDV disease to end-stage liver disease, and the lack of large prospective studies in chronic hepatitis D make it extremely difficult to define the role of HDV in the pathogenesis of HCC.

In about half the patients, chronic hepatitis D is initiated by a clinically manifest acute hepatitis, which most likely represents the time of HDV superinfection.³ The clinical presentation is highly variable because chronic hepatitis D may be symptom free and discovered incidentally, or it may be associated with symptoms such as fatigue, malaise, and anorexia.⁵ Once cirrhosis develops, the disease may be stable and asymptomatic or it may present complications related to advanced cirrhosis leading to liver failure. A high proportion of patients die of end-stage liver disease if they do not receive OLT. Symptoms may vary from marked fatigue to right upper quadrant discomfort, ascites, muscle weakness and wasting, jaundice, and dark urine. Patients may also present with major complications of advanced cirrhosis such as portal hypertension, ascites, and encephalopathy. The majority of patients with chronic hepatitis D have elevated serum ALT and AST values and exhibit splenomegaly, which is a distinct clinical feature of this disease; patients with chronic hepatitis D show high levels of HDV viremia,²⁸ even though the viral load does not seem to correlate with the severity of the disease,²⁹ along with high titers of IgG and IgM antibodies to HDAg, and usually antibodies to anti-HBeAg (anti-HBe positive) with little or null levels of HBV replication.²⁸ In addition to its diagnostic value, IgM anti-HD correlates with disease activity³⁰ and may predict the outcome of hepatitis D because an impending resolution, either spontaneous or induced by therapy with IFN, correlates with a significant decrease or loss of IgM anti-HD.³¹ Chronic hepatitis D can be associated with several autoimmune manifestations, including the presence of autoantibodies against nuclear lamin C and thymic cells, and heteroantibodies to the basal cell layer of the rat forestomach.³ Nearly 15% of patients with chronic hepatitis D are positive for an autoantibody that is reactive against the microsomal membranes of the liver and kidney (LKM3).³² LKM3 reacts with a 55-kd microsomal band that corresponds to UDP glucuronyltransferase (UGT1). It is not known

whether LKM3 has any biologic effect on UGT1, and the autoantigen exhibits no sequence homologies with HDV.³³ In experimental models, the titer of anti-LKM3 increases as a secondary immunologic phenomenon in the course of chronic hepatitis D.³⁴ In addition, liver kidney microsomal antibodies have been reported in one out of four HDV patients with severe hepatitis while on full dose of interferon.³⁵ At the present time, however, the data are still limited to support the use of autoantibodies to monitor antiviral treatment or to predict HDV disease outcome.

Liver Pathology

In hepatitis D, the pathologic changes are limited to the liver, the only organ in which HDV seems to replicate. The liver biopsy may contain only changes typical of acute hepatitis in the setting of HBV-HDV coinfection, elements of acute and chronic hepatitis if acute HDV infection is superimposed on established chronic hepatitis B (with preexisting liver damage), or histopathologic changes typical of chronic hepatitis if the individual is chronically infected by HBV and HDV. In acute hepatitis D, the histologic changes are characterized by hepatocellular necrosis and inflammation, with lymphocytes and Kupffer cells infiltrating both the parenchyma and the portal areas. Hepatocytes may be swollen and undergoing eosinophilic degeneration.³⁶ Although these histopathologic features are not specific for hepatitis D and can be seen in all the other forms of acute viral hepatitis, they tend to be more severe in HDV disease.⁵ The hepatocyte injury is typically focal, except in the most severe cases when confluent necrosis occurs, leading to submassive or massive necrosis accompanied by infiltration of inflammatory cells within the collapsed lobules and in the portal areas, as typically seen in fulminant hepatitis.³⁷ A characteristic histologic lesion observed in epidemics of fulminant hepatitis in Northern South America, especially in the Amazon Basin, is a microvesicular steatosis that leads to the formation of “morula cells,” which represent hepatocytes with small fat droplets and central pyknotic nuclei.³⁸ Similar cells, however, have been observed in severe hepatitis D elsewhere, including Africa and Italy.^{3,36} A subacute, rapidly progressive form of HDV superinfection has been seen in HBsAg carriers among the Yucpa Indians, an indigenous population of Venezuela.³⁸ These patients often died within 18 months from disease onset. The histopathologic changes of chronic hepatitis D consist of hepatocellular necrosis, portal and parenchymal inflammation associated with different degrees of liver fibrosis.³⁶ Periportal necrosis (interface hepatitis) is usually more prominent than in other forms of chronic viral hepatitis. Hepatic fibrosis starts from the portal areas, which expand and develop fibrous septae between portal areas and central veins. This progresses to bridging fibrosis leading to cirrhosis characterized by distortion of the liver architecture with fibrosis and regenerative nodules. In the early stages, the liver fibrosis may not be uniformly distributed and a needle biopsy of the liver may not reflect the extent of the fibrosis. Patients with chronic hepatitis D exhibit hepatitis D antigen (HDAg) expression in the liver. The amount of HDAg decreases along with the

progression of liver fibrosis, being minimal or undetectable in patients with end-stage liver disease.^{3,5}

HDV Genotypes and Pathogenicity

Genetic analysis of HDV collected worldwide has revealed the existence of eight distinct HDV genotypes.³⁹ Over the past decade, the relationship between the HDV genotypes and the clinical course of hepatitis D has represented an important area of investigation. Genotype-1, which is the most common worldwide, has been associated with a wide spectrum of disease severity.⁴⁰ By contrast, the other genotypes appear to be more geographically restricted and to be linked with different degrees of disease severity. Genotype-2 and 4, found predominantly in the Far East, have been associated with milder forms of liver disease,^{41,42} whereas genotype-3, found exclusively in South America, has been associated with outbreaks of severe and fulminant hepatitis in this geographic area.⁴³⁻⁴⁵ More recently, four additional genotypes (5 to 8) have been described and found exclusively in West and Central Africa.^{39,46} The extent of the pathogenicity associated with the African clades as well as their range of heterogeneity and geographic distribution remain to be established. Although evidence is accumulating to suggest a link between milder forms of HDV and genotypes-2 and 4, at variance with the higher pathogenicity associated with genotype-3, further studies are needed to elucidate the critical question of whether major biologic differences exist among the different HDV genotypes and whether genotypes play a different role in the pathogenesis and severity of hepatitis D.

Changes in the Epidemiologic and Clinical Scenario

The general improvement in socioeconomic conditions and life style, and especially the introduction of universal vaccination programs against HBV have determined a significant decline in the incidence of HDV infection over the past two decades, particularly in Southern Europe and in the Mediterranean area.⁴⁷ Control of HDV infection has not only resulted in a reduction of new cases, but has also changed the clinical picture of hepatitis D. In the early studies performed after the discovery of HDV in Europe, hepatitis D was described as a very serious and progressive liver disease leading to cirrhosis more rapidly than hepatitis B.¹⁹ However, as a consequence of the significant changes that have occurred in the epidemiology of HDV, the clinical picture of HDV disease has evolved dramatically. Although in the 1980s the majority of patients had chronic active hepatitis and less than 20% had inactive cirrhosis, by the end of 1990s the proportion of long-standing infections in patients who survived the initial florid phase during the HDV epidemic in the 1970s and 1980s, had increased significantly up to 70%.⁴⁸ As a consequence, in the 1990s patients presented either with advanced cirrhosis or with an indolent, nonprogressive course lasting for more than a decade.²² Over the past few years, however, new fresh and florid cases are emerging again in Western Europe as a consequence of the immigration influx from areas where

HDV is endemic.^{26,49} Thus, in the face of a declining prevalence in areas of old endemicity, immigration poses a threat of HDV resurgence in other countries, and hepatitis D should be considered in the differential diagnosis of HBsAg-positive liver disease. Moreover, recent studies have shown that after a dramatic decrease in the prevalence of HDV infection in Europe, the prevalence of anti-HD in Italy among carriers of HBsAg is again similar to that found in 1997 (9.7%).⁵⁰ The reservoir of HDV in Europe is sustained by a mixed population represented by the residual pool of individuals who survived the HDV epidemic in the 1970s and 1980s, and by the pool of younger individuals who immigrated from areas where HDV is endemic.^{48,51} The virus has remained endemic in the Middle East, Central Africa, Mongolia, Tajikistan, and northern parts of South America, whereas data are lacking from many areas where hepatitis B is highly prevalent.⁴⁸ In Southeast Turkey, HDV accounts for almost half of all cases of liver cirrhosis and HCC.⁵² According to the changing epidemiology and natural history of chronic HDV disease over the past two decades, the risk of HCC should be reconsidered. In Southern Europe the incidence of HCC is likely to be rising along with the increased survival of aging patients with long-standing disease who survived the HDV epidemics of the 1980s and 1990s.

Interaction of HDV with Other Hepatitis Viruses

The interaction of HDV with other hepatitis viruses is complex and may lead to different patterns of viral interference. Hepatitis D, B, and C (HCV) viruses share similar transmission routes, primarily via parenteral and sexual exposure, increasing the likelihood that multiple hepatitis viruses may infect, either simultaneously or sequentially, a proportion of patients.⁵³ Although the epidemiology, natural history, viral kinetics, and treatment strategies for each single infection have been extensively studied, less is known about the specific features of multiple hepatitis virus coinfections. Because clinical trials conducted in patients with viral hepatitis commonly exclude dual or triple infections, most of the data on multiple infections derive from retrospective studies conducted on a limited number of patients or from epidemiologic surveys.⁵⁴ Moreover, coinfecting patients represent a heterogeneous group, with various patterns of viral replication and immune responses.⁵⁵ The evidence hitherto accumulated indicates that multiple infections are frequently associated with progression of liver fibrosis and HCC⁵⁶; nevertheless, no standard recommendations exist for therapy. Treatments are often individualized based on the patient's specific clinical features, but the optimal strategy remains an important challenge for clinicians.

Clinical Scenarios

Multiple hepatitis viruses may be simultaneously transmitted and induce acute hepatitis. However, coinfecting patients often seek medical attention with evidence of multiple infections without a clear chronology of acquisition. In areas of high endemicity of HBV infection, mainly due to vertical

transmission, coinfection is most often due to HDV or HCV superinfection. In other geographic areas, however, the sequence of infection remains largely undefined.

Acute Hepatitis

Five different patterns can occur when triple infection presents with an acute onset, depending on the various combinations of single- or double-virus superinfections in a patient with a preexisting chronic infection. Liaw⁵⁷ described the course of liver disease in 30 multiply-infected patients with acute hepatitis occurring in previously unrecognized chronic HBV carriers (HBsAg-positive but IgM anti-HBc-negative). Fifteen patients had acute HDV superinfection on a chronic HBsAg-carrier status with HCV markers; six had acute HCV superinfection on a chronic HBsAg-carrier status with HDV markers; and nine had acute HCV and HDV superinfection on a chronic HBsAg-carrier status. Risk factors were recognized as related to sexual contact and tattooing or acupuncture in the months preceding acute hepatitis. Hepatic decompensation and liver-related death were frequent (53% and 27%, respectively). Of note, the severity of liver disease tended to increase linearly from acute HDV superinfection in patients with HBV-HCV markers (decompensation 33%, mortality 7%), to acute HCV in preexisting HBV-HDV markers (decompensation 50%, mortality 33%), to HCV-HDV superimposed on chronic B infection (decompensation 89%, mortality 55%). Other studies also suggested that triple infection increases the risk of fulminant hepatic failure.⁵⁸ However, if the patients survived the catastrophic effects of acute superinfection, the clinical outcomes were relatively benign; nearly 50% ran a silent course whereas only 20% were slowly progressive. Moreover, spontaneous HBsAg clearance occurred in 19% of the patients with triple infection. At present, no data on multiple superinfections in patients with preexisting HCV infection have been reported.

Chronic Hepatitis

The clinical and virologic profile of triple infection is more often described in the setting of chronic rather than acute hepatitis.^{57,59-62} Coinfected patients are generally male, 40 to 45 years old, with low prevalence of HBe-Ag and a history of intravenous drug use. Each virus can affect the replication of the other viruses and can be responsible for the progression of liver disease.

Viral Interaction

In a study conducted in Taiwan, serum HCV RNA, assayed by nested polymerase chain reaction (PCR), was detected in 21 of 27 (78%) patients with chronic liver disease, whereas HBV DNA and HDV RNA, detected by slot-blot hybridization, were positive in 26% and 44%, respectively.⁵⁷ A higher prevalence of HCV (>70%), either alone or in combination with the other viruses, was also documented in another study, with persistent positivity throughout a 5-year follow-up course, whereas serum HDV RNA and HBV DNA remained detectable in only 22% and 12% of the patients, respectively.⁵⁷ This study suggested that HCV plays a dominant role in patients with triple infection, exerting a suppressive effect on HBV and

HDV.⁵⁷ However, other studies showed that in triple infections HDV is the dominant virus, with negative effects on HBV and HCV replication. The patients investigated had HDV viremia detectable by PCR, while HCV RNA ranged from 0 to 29% and HBV DNA from 12 to 27%.⁵⁹⁻⁶¹ In one study, the viruses were also defined with respect to their genotypes and HBV precore/basic core promoter (BCP) mutations.⁶¹ The prevalence of patients with precore mutations was lower in triple infection compared with single HBV infection, and no differences were observed in the overall percentage and distribution of HBV-BCP mutations. HCV genotype-3 was the most prevalent in triple coinfection. The overall distribution of HBV genotypes was not statistically different from that observed in chronic single HBV infection. Finally, the study of HDV genotypes documented the presence of genotype-1 in all cases.

Almost all of the studies conducted thus far on viral interaction during triple infection have been cross sectional. In one longitudinal study, the virologic profile was evaluated in coinfecting patients every 2 months for 12 months.⁶² Fifteen of the 30 patients examined showed persistently inactive HBV and HCV infections, while 15 had active HBV (nine cases) or HCV (five cases) infections or both (one case). Over time, both HBV and HCV showed wide fluctuations of viremia levels. Serum HDV RNA also showed some fluctuations, underlying the importance of a longitudinal approach in this setting.⁶²

Histopathology in Multiple Hepatitis Virus Coinfections

In general, the severity of the histologic pattern characteristic of each viral infection is maintained when more than one hepatitis virus is involved. Lymphoid follicle formation was detected in a high proportion of patients expressing high levels of HBcAg or HDAg in liver tissue.⁶³ Multiple infections aggravate liver injury, particularly with regard to fibrosis. The fibrosis score was shown to be significantly higher in patients with triple infection than in matched single HCV-infected patients,⁶⁰ and the percentage of cirrhosis was greater than 50%.^{60,63} Patients with triple infection usually present at a relatively late stage of chronic HBV infection, as reflected by a mean age higher than 45 years and a very low prevalence of HBeAg as compared with patients with single HBV infection.⁵⁷ However, the long-term clinical outcome in these patients is still largely undefined. When HCV plays a dominant role and exerts a suppressive effect on HBV and HDV, a relatively benign but slowly progressive course has been described.⁵⁷ The annual incidence of cirrhosis was estimated at 3%, and the outcome of patients with triple infection, followed for a mean period of 4 years, was characterized as stable in 44% of the patients, with clinical remission in 36% and a progressive course in 20%.

Multiple hepatitis virus coinfections have been shown to correlate with an increased risk of developing HCC. In Italy, HBV-HCV and HBV-HDV coinfections increase the risk of HCC by two- to sixfold, relative to each infection alone, as seen with alcohol abuse.⁶⁴ In Mongolia, coinfecting patients, despite their younger age, have a significantly higher frequency

of HCC compared with those with single HCV infection.^{65,66} In addition, there is evidence that specific HBV genomic mutations may increase this risk of HCC, in particular a high incidence of T1762/A1764 double mutations in the basal core promoter (BCP) region of HBV.⁶⁷

In conclusion, controversies persist concerning the reciprocal effects of each virus in multiple infections. In Western countries, the dominant virus seems to be HDV,^{59-61,68} a finding consistent with the documented inhibition of the host DNA-dependent RNA polymerase II, which is involved in HBV replication, by the large delta antigen.⁶⁹ Moreover, clearance of HCV has been shown to occur when patients are superinfected with HBV and HDV.⁷⁰ On the other side, HCV was identified as the dominant virus by Liaw et al in Taiwan,⁵⁷ while a fluctuating virologic profile was documented by Raimondo et al in Italy.⁶² Several reasons could explain these discrepant results. The patient populations studied were from different geographic areas, had acquired infection at different times (perinatally, during infancy, or as an adult) and had a different host immune status. Routes of transmission, genotypes, viral strains, sequence of infection could all play a role in the variable evolution and dynamics of multiple infection. Triple infections are generally associated with advanced liver disease and HCC, but long-term, prospective studies are presently lacking.

Multiple Coinfections with Hepatitis Viruses and Human Immunodeficiency Virus (HIV)

HIV coinfection is recognized as a determinant of accelerated liver fibrosis progression in patients with chronic viral hepatitis.^{71,72} Although this may seem counterintuitive because liver damage is generally believed to be mediated by hepatitis virus-specific T cell responses, which are progressively impaired in the course of HIV disease, it underscores the fundamental differences in the pathogenesis of acute hepatitis versus chronic liver disease and fibrogenesis. The prevalence of multiple hepatitis viruses is markedly higher in intravenous drug users, who are often coinfecting with HIV, compared with patients who acquire hepatitis virus infections through other routes.⁷³

Viral Markers

At presentation, the pattern of past/nonreplicative hepatitis D (positive total anti-HD, negative anti-HD IgM), or chronic/replicative hepatitis D (repeatedly positive anti-HD IgM) is common.⁹ Patients with anti-HDV antibodies are frequently serum HDAg negative and serum HBeAg negative, anti-HBeAg positive.⁷⁴

Viral Replication

According to the majority of the studies, HDV exerts suppressive effects on HBV and HCV replication.^{74,75} Peaks and rebound from undetectable hepatitis B-C and/or D viremia are influenced by HIV disease and antiretroviral treatment. In more advanced HIV disease, HDAg was detected in serum in 33% of the cases and HBV DNA in 25%.⁷⁶ In the presence of low CD4⁺ T cell counts, replication of all viruses (HBV, HCV, HDV)

may dominate at all time points or intermittently.⁷⁷ The inhibitory effect of HDV on HBV replication does not seem to occur in patients infected with HBV genotype D.⁷⁸

Liver Histopathology

An independent association was documented between HIV-induced CD4⁺ T-lymphocyte depletion and increased rate of fibrous septa formation in patients with chronic hepatitis C.⁷² Advanced fibrosis (F3-F4) is significantly associated with triple infection.⁷³ Two hypotheses have been proposed to explain this correlation: First, low CD4⁺ T cell counts predispose to elevated HCV RNA levels, which in turn may accelerate fibrosis; second, CD4⁺ T-lymphocyte depletion may be associated with an alteration of cytokine patterns leading to accelerated fibrogenesis.

Clinical Features

Two-thirds of HIV-infected patients with triple infection are cirrhotic.⁷⁹ Clinical episodes of liver decompensation occur in 30%, with at least one episode of ascites in 23%, varices of any grade in 59%, and encephalopathy in 12%. Splenomegaly is recognized in 61% and signs of portal hypertension on ultrasonography in 14% of the cases.⁷⁹ Moreover, in patients with HIV infection and hepatitis, the incidence of HCC is higher than in patients with HIV without hepatitis.⁷³ Overall, hepatitis D, which is not associated with progression to acquired immunodeficiency syndrome (AIDS), is the agent that induces a more rapid progression of liver fibrosis and cirrhosis, and increases the risk of liver-related death in HIV-infected patients.

Summary

HDV is a highly pathogenic virus that causes severe acute hepatitis, which may run a fulminant course, and the most progressive form of chronic viral hepatitis leading to cirrhosis in up to 70% of the cases. HDV is a unique agent because of its defective nature that allows it to survive and replicate only in association with HBV. Over the past two decades, the implementation of universal HBV vaccination programs in many countries has led to a dramatic decline in the prevalence of HDV infection, particularly in the industrialized world. This dramatic decline has changed the clinical picture of HDV in these countries, with a preponderance of long-standing infections compared with the typical florid and progressive form typically seen during the HDV epidemics in the 1970s and 1980s. However, globalization has resulted in increasing immigration fluxes from areas where HDV is endemic restoring an HDV reservoir among young immigrants with fresh, new cases of HDV infections that resemble the florid forms seen in the 1980s. Moreover, HDV remains a major public health problem in underdeveloped areas of the world where HBV is not under control. Considering the high pathogenicity of HDV, the fact that chronic hepatitis D is a difficult target for antiviral therapy, and the lack of an effective vaccine specific for HDV, which would be the only means to eliminate the risk of HDV superinfection for the 350,000 million HBsAg carriers infected worldwide, HDV should still be regarded as a major

public health concern. Hepatitis D is often forgotten, but is not gone.⁸⁰ Continuous research on HDV, one of the most unusual and interesting human pathogens, remains a high priority to better understand the pathogenesis of hepatitis D as well as to devise new preventive and treatment strategies to avoid the dire outcomes for those infected by this virus, which still represent 15 million people worldwide.

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Abbreviations

ALF	acute liver failure
ALT	alanine aminotransferase blood test
Anti-HBc	antibody to hepatitis B core
Anti-HDV	antibody to hepatitis delta virus
AST	aspartate aminotransferase blood test
BCP	basic core promoter
HBe-Ag	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HD-Ag	hepatitis D antigen
HDV	hepatitis D virus
HIV	human immunodeficiency virus
IgG anti HDV	IgG antibody to hepatitis D virus
IgM anti HDV	IgM antibody to hepatitis D virus
OLT	orthotopic liver transplantation

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