CHAPTER 7

Clinical Features of Hepatitis Delta Virus

Dimitrios Vassilopoulos* and Stephanos J. Hadziyannis

Introduction

In the early days following the discovery of the hepatitis delta virus (HDV) much emphasis was given on the severity of delta hepatitis and its rapid progression to cirrhosis and liver failure. However with time going on, evidence started to accumulate indicating that in several individuals, chronic HDV infection could run a benign course, with silent clinical and even biochemical features and that in such patients liver histology would be more consistent with the mild changes of chronic persistent hepatitis rather than with the severe necroinflammation and advanced fibrosis of chronic active hepatitis.[1-4] In particular the search for serological markers of HDV infection in the general population of several communities worldwide and among blood donors (Japan, Taiwan, Greece and Italy)[3,4] revealed that the actual spectrum of delta hepatitis is very wide and heterogeneous and that similarly to the infection with the other known hepatitis viruses it can range from a very mild, clinically latent disease to florid active hepatitis and decompensated cirrhosis. With time going on and with the accumulation of new data from long-term follow-up studies[4,5] it also became obvious that the natural course of acute and chronic HDV infection is extremely variable and includes all possibilities from complete cure and burning out to slow progression, rapid progression, development of cirrhosis and liver failure and development of hepatocellular carcinoma (HCC). Furthermore with the application of refined serological, virological and other laboratory techniques, the clinical aspects of HDV infection could be associated and linked meaningfully with numerous viral, host and other variables.

In this article an attempt is made to describe the evolution over the years of our concepts on the clinical correlates and syndromes developing in acute and chronic HDV infection and on their natural course. In this context it is important to stress that hepatitis delta represents infection not with one but with two viruses (the HDV and the HBV) that are transmitted to the host either concomitantly (coinfection) or in the case of HDV superinfection in a host with preexisting chronic HBV infection. Moreover, due to epidemiological reasons and common risk factors coinfection or superinfection with the hepatitis C virus (HCV) and with the human immunodeficiency virus (HIV) is also encountered in clinical practice. Complex clinical features may thus arise while interactions between the coinfecting viruses may have significant impact on their replicative activity, on immune and pathogenetic mechanisms and consequently on the severity, course and outcome of the nosological syndromes resulting from each of them.

*Corresponding Author: Dimitrios Vassilopoulos—Athens University School of Medicine, Hippokration General Hospital, Academic Department of Medicine, 114 Vass. Sophias Ave., 115 27 Athens, Greece. Email: dvassilop@med.uoa.gr

Hepatitis Delta Virus, edited by Hiroshi Handa and Yuki Yamaguchi.
©2006 Landes Bioscience and Springer Science+Business Media.

Acute Hepatitis Delta

Infection with the hepatitis D virus of susceptible individuals results in acute hepatitis provided that the HDV gets the necessary helper function from the surface proteins of the HBV particularly the preS1 in order to achieve entry into hepatocytes and replicate. This condition is met either (a) by concomitant transmission of the two viruses to susceptible individuals lacking anti-HBV immunity (coinfection) or (b) by transmission of HDV to individuals with preexisting chronic HBV infection (HDV superinfection). Individuals with natural or vaccination-acquired immunity against HBV, harboring antibodies to the hepatitis B surface protein (anti-HBs), are protected from HDV infection.

Depending on the type of HDV infection (superinfection or coinfection) and on several host and viral factors like age, sex, immune status of the host, size of the viral inoculum, HBeAg/anti-HBe status of the infecting and infected individuals (in case of superinfection) and probably on the HDV and HBV genotypes, the acute HBV infection may attain mild, severe or even fulminant course, may resolve or may progress to chronicity.

Acute Hepatitis Due to Coinfection with HDV and HBV

The clinical features of acute hepatitis D due to coinfection are not much different from those of HDV superinfection. However in both conditions severe and even fulminant forms of hepatitis appear to occur more frequently compared with ordinary acute hepatitis B.[4,6] On the other hand, acute hepatitis D is indistinguishable from ordinary hepatitis B on clinical and histological grounds. The differential diagnosis is possible only on the basis of serological assays showing the presence of markers of HDV infection together with markers of primary HBV infection (high titers of IgM anti-HBc). The clinical expression may be biphasic with two episodes of acute hepatitis occurring a few weeks apart. The first is linked to peak HBV replication and the second to HDV replication. The HDV may suppress the replication of HBV and milder forms of acute hepatitis may, thus, occur in coinfection. Early suppression of HBV has been observed in Italy to inhibit the synthesis of HBsAg resulting in non detectability of this marker in serum.[7] In a recent study, a transient decrease in the levels of HBV DNA was observed in HBV/HDV acutely coinfected patients compared to patients with acute hepatitis B.[8]

Coinfections with HDV and HBV contrary to HDV superinfections of chronic HBsAg carriers also are known to be self limited in their vast majority.[9] This difference is attributed to the duration of infection with the helper hepatitis B virus which, being transient in coinfection, does not permit the HDV to outlive the episode of acute hepatitis. Why HBV infection is transient in coinfection can be explained better now by the fact that most coinfections have been identified among adults in whom, unlike the pattern observed in children, acute hepatitis B is self limited in more than 95% of its cases.[6] Moreover in most cases of coinfection the transmitted HBV strain is HBeAg-negative (usually precore mutant) and, as known, acute infection with HBeAg-negative HBV strains may cause severe acute and even fulminant hepatitis but rarely if ever chronic hepatitis B, irrespective of the age of patients.[3] In communities with endemic HBV infection self-limited coinfections with HBV and HDV appear to be quite frequent. A significant number of individuals who are positive for serological markers of past HBV infection (anti-HBc and anti-HBs positive) are also positive for serum anti-HDV of IgG class, a marker of past HDV infection.[10]

HDV RNA can be detected in serum in 93% to 100% of coinfected individuals.[11] At the same time, HBV is expressed in a lower percentage of patients and becomes undetectable with time. With resolution of HBV/HDV coinfection HDV RNA becomes undetectable, serum HBsAg is cleared and markers of past HBV and HDV infection develop.