CHAPTER 8

Diagnosis of Hepatitis D Virus Infection

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Introduction

Hepatitis D virus (HDV) is a small defective virus with a single stranded circular RNA of 1.7 kb in size.[1-3] Its hepatitis B surface antigen (HBsAg) envelope is provided by the helper hepatitis B virus (HBV) for successful package and transmission of HDV.[4,5] The antigenomic strand of HDV encodes a single protein, hepatitis delta antigen (HDAg) of two molecular weight forms. The large form HDAg with a 19-amino acid extension at the C-terminus plays a key role in the package of HDV and suppresses viral replication in a trans-dominant negative manner, while the small form plays an essential role in trans-activating the replication of HDV RNA.[2,3]

There are two kinds of HDV infection.[4] Coinfection results from acute simultaneous infection of both HBV and HDV. Few patients with coinfection progress to chronicity because of self-limited nature of acute HBV infection in adults. Superinfection indicates the occurrence of HDV infection in patients with underlying chronic hepatitis B.[4] The great majority of patients with HDV superinfection progress to chronicity.[6] The disease spectrum of HDV infection varies greatly from an important etiology of fulminant hepatitis and rapidly progressive hepatitis to a subclinical course.[6-13] Persistent replication of HDV associated with relapsing acute exacerbations and elevated ALT levels is a characteristic of chronic active hepatitis D.[6] HDV is classified into three genotypes.[14] The most common isolate, the genotype I, has been cloned from patients with fulminant or chronic active hepatitis in Italy, America, Taiwan, Nauru, France and Lebanon. Genotype II has only been isolated from Japan and Taiwan, and it is less often associated with fulminant hepatitis or rapid progression to cirrhosis or HCC as compared to genotype I.[15,16] Genotype III has been isolated from patients with severe acute hepatitis in Peru and Colombia.[14]

Several steps are needed for an accurate diagnosis of HDV infection. The first step is to differentiate HBV from HDV infection. Differential diagnosis is essential for understanding and proper management of the disease, because HDV infection is an important etiology of fulminant hepatitis and an aggravating factor for the progression of chronic hepatitis B to cirrhosis.[6-12] In the clinical setting of antiviral therapy, nucleoside analogues are effective in the treatment of chronic hepatitis B, but not effective for chronic hepatitis D. In the setting of liver transplantation, recurrent HBV infection is associated with inflammation and tissue damage of the graft and the mortality of recipients, whereas HDV infection in the host liver seems to

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Table 1. Serological and histological markers for the diagnosis of HDV infection

Markers	Methods	Comments
Serum		
Total anti-HDV	Immunoassay	Positive in coinfection and superinfection High titer in active infection
IgM anti-HDV	Immunoassay	Positive in acute and chronic infection High titer in active infection
HDV RNA	Northern blot	Active HDV replication
	RT-PCR	Most sensitive, 10-100 copies
HDAg	Immunoassay	Masked in immune complex in chronic infection
	Western blot	Active HDV replication, research use
HBsAg	Immunoassay	Usually positive
IgM anti-HBc	Immunoassay	Positive in coinfection
Liver		
HDV RNA	Northern blot	Active replication, research use
	In situ hybridization	Active replication, research use
HDAg	Western blot	Active replication, research use
	Immuno-staining	Active replication, classical standard

reduce the risk of significant HBV-induced liver damage in the allograft.[17] The survival rate of liver transplant recipients is better in patients with both HBV and HDV infections than that of patients with HBV infection alone.[17] The different outcomes may be due to suppressed HBV replication in patients with chronic hepatitis D. The second step is to distinguish between HDV coinfection and superinfection, because the former seldom progresses to chronicity and the great majority of the latter becomes chronic. The third step is the differentiation between acute and chronic hepatitis D. Finally, the determination of HDV genotypes is also of clinical and epidemiological importance.[14,16] The diagnosis of HDV infection is based on the detection of the components (HDAg or HDV RNA) of HDV or antibodies to HDAg that will be discussed in the following sections (Table 1).

Serological Diagnosis Based on Antibodies to HDAg (Anti-HDV)

Radio- or enzyme-immunoassays of serum anti-HDV are commercially available, and are most convenient for the first-line screening of HDV infection in a large number of patients in daily clinical practice or epidemiological surveys. Acute HDV infection is diagnosed by seroconversion or rising titers of anti-HDV.[18,19] At acute stage, some patients with acute HDV coinfection or superinfection are diagnosed by seroconversion of anti-HDV.[19,20] Therefore, follow-up assays of anti-HDV at one month interval are needed to determine if HDV infection is the etiology responsible for acute hepatitis attacks in patients, particularly in those with risk behaviors (intravenous drug abuse or prostitute contact). However, patients with fulminant hepatitis may expire before seroconversion of anti-HDV. In such cases, detection of HDV RNA by a sensitive reverse transcription polymerase chain reaction (RT-PCR) is of great value to determine the etiology of fulminant hepatitis.[9] Within 2 months of HDV infection, more than 90% of patients become serum anti-HDV positive. Of the patients whose initial serum samples are already positive for anti-HDV, the diagnosis of acute HDV infection may be supported by rising titers of anti-HDV. If only one serum sample is tested, titration of anti-HDV is of value in the differential diagnosis between acute and chronic hepatitis D. The highest dilution that gives positive result is defined as anti-HDV titer. A low anti-HDV titer less than