CTMI (2006) 307:173–186

Functional and Clinical Significance of Hepatitis D Virus Genotype II Infection

J.-C. Wu (✉)

Department of Medical Research and Education, Institute of Clinical Medicine, Taipei Veterans General Hospital, National Yang-Ming University, 201 Shih-Pai Road, Sec. 2, 112 Taipei, Taiwan
jcwu@vghtpe.gov.tw

Abstract Hepatitis D virus (HDV) infection is one of the important etiologies of fulminant hepatitis and may aggravate the clinical course of chronic HBV infection to cirrhosis and liver failure. HDV was classified into three genotypes. Recent molecular phylogenetic analysis of HDV suggests at least seven major clades. The genotype I HDV is widely spread, genotype II is found in East Asia and genotype III HDV is prevalent in South America. The genomic size is 1682–1685 nucleotides (nt) for genotype II, and 1676 nt for genotype IV (IIb). The divergence in HDV nucleic acid sequences between genotype II and other genotypes varies from 13.8% to 35.3%. The divergences in the HDAg-coding region may range from 17.8% to 29.8% between genotype II and other genotypes. There is no genotypic or size restriction on the interactions of either the small or the large hepatitis delta antigens (HDAgs) between genotypes I and II, and there is also no genotypic incompatibility during co-package of HDAgs

of different genotypes into virus like particles. There appears no apparent universal genotypic restriction of the transactivation of genotype I HDV RNA replication by small HDAg of genotype II. In contrast, there appears more genotypic restriction for genotype I small HDAgs to transactivate genotype II HDV RNA replication. Of the functional domains of HDAg, the 19 amino acids at the carboxyl-end of the large HDAg show the greatest divergences (70%–80%) between genotypes I and II. The viral packaging efficiencies of genotype I HDV isolates are usually higher than those of genotype II. The 19 amino acids at the carboxyl-end seem to be the most important determinant for viral packaging efficiencies. The editing efficiencies of the genotype I HDV are also higher than those of the genotype II. Genotype II HDV infection is relatively less frequently associated with fulminant hepatitis at the acute stage and less unfavorable outcomes [cirrhosis or hepatocellular carcinoma (HCC)] at the chronic stage as compared to genotype I. It appears that the clinical manifestations and outcomes of patients with genotype IV (IIb) HDV infection are more like those of patients with genotype II HDV infection. Persistent replication of HBV or HDV was associated with higher adverse outcomes (cirrhosis, HCC or mortality) compared to those who cleared both viruses from the sera. HBV of the genotype C is also a significant factor associated with adverse outcomes (cirrhosis, HCC or mortality) in patients with chronic hepatitis D in addition to genotype I HDV and age. However, most patients with chronic HDV infection have low or undetectable hepatitis B virus DNA levels. During longitudinal follow-up, genotype I HDV is the most important determinant associated with survival.

1 Introduction

The hepatitis D virus (HDV) is composed of an envelope of hepatitis B surface antigen (HBsAg), a genome of 1.7 kb and the only encoded protein, hepatitis delta antigen (HDAg) [1–4]. HDV is of negative polarity and the HDAg is encoded by the antigenomic strand of the virus. There are two molecular weight forms of HDAg. The large HDAg (L-HDAg) that has an additional 19-amino acid (aa) extension at the C terminus after editing of the antigenomic HDV RNA plays a key role in the assembly of HDV virions [2–4]. However; it inhibits HDV replication in a transdominant negative manner. The small HDAg (S-HDAg) transactivates the replication of HDV RNA [2, 3]. The HDV is a defective virus. It can replicate by itself, through a double-rolling circle mechanism, but it needs the supply of HBsAg from its helper hepatitis B virus (HBV) to complete the assembly of HDV particles and the subsequent secretion and transmission [5, 6].

Although HDV infection is not a common cause of infection except in high risk groups and certain areas, it is one of the important etiologies of fulminant