DELTA VIRUS HEPATITIS

Mario Rizzetto
Divisione di Gastroenterologia
Molinette, Cs. Bramante 88, Torino, Italy

THE VIRUS

The Hepatitis Delta Virus (HVD) occupies a unique niche in human virology. At variance with conventional animal viruses, it cannot replicate autonomously but requires the presence of the Hepatitis B Virus (HBV) to initiate infection. It behaves like a defective interfering agent, in that it inhibits the synthesis of the competent HBV helper once its infection is established. This cooperation is reflected in the HD virion, a 36 nm spherical particle formed by an envelope of HBV-derived surface antigen (HBsAg), which encloses the genome and a specific delta antigen (HD-Ag) (1).

The HDV genome is a small circular single-stranded RNA molecule of which the entire sequence has been decoded (2, 3). The genome has a high prevalence of internal complementary base pairing that under native conditions drives the molecule to assume a rod-like configuration. Genomic and antigenomic RNA could potentially encode for five large polypeptides containing an amino terminal methionine but only a single antigenomic open reading frame (n. 5) appears to encode for polypeptides that possess the immunologic reactivities of HD-antigen; this suggests that HDV may be a negative strand virus (4).

HDV resembles two subgroups of encapsidated RNAs belonging to the microcosmo of the viroids of plants, presently recognized as the satellite viruses and satellites RNAs (5).

Same as HDV, the RNA satellites and the satellite viruses have small sizes, are encapsidated and capable of protein translation; they are not autonomous but depend for replication on the helper effect of a mature plant virus with which they do not share genomic homologies.

Like the viroids, whose genetic material has been localized primarily in the nuclei of infected cells, in situ hybridization studies have shown that HDV RNA is localized in the hepatocytic nuclei of HDV-infected chimpanzees and woodchucks. Most important, the decoding of the HDV genome has revealed sequences in its RNA that are analogous to short consensus sequences maintained in viroids throughout evolution (6).
The biological dependence of HDV on HBV is also analogous to the dependence of satellites on a concomitant mature plant virus; as HDV derives its capsid from HBV, the satellites obtain the capsid from the helper plant virus. Same as satellites modify the expression of symptoms caused by the helper virus in plants, HDC alters the natural history of HBV infection in man; satellites, however, most often attenuate the disease caused by the competent helper (7), whereas HDV seems to invariably aggravate the natural course of the underlying HBV infection in man.

Properties essential to the survival of HDV are the capacity of adaptation and a high infectious potential. The defective virus is able to exploit helper functions provided not only by HBV but also by the other Hepadnaviruses. It was successfully transmitted to the woodchuck (marmota monax); in this animal the HD virion became coated antigen derived from the woodchuck hepatitis virus (8). In the appropriate host (the carrier of HBV) HDV infections has developed after inoculation of serum diluted up to 10\(^{-1}\) fold (9); this is the highest infectious titre in transmission of etiologic agents.

The mode of HDV replication remains an enigma. No reverse transcriptase nor other replicases were found in the virion and the size of the RNA does not allow for coding of enzymatic functions. Replication and transcription are not mediated by a RNA dependent/RNA polymerase activity provided by the helper virus. Presently the hypothesis is that HDV subverts the normal replicative mechanism of the hepatocyte to its own advantage in a manner similar to that proposed for the viroids.

Possibly HDV replicates via the rolling-circle mechanism proposed for viroids (10). In this model, genomic and antigenomic RNA would be copied as multimeric plus and minus strands by repeated rounding over the respective input circular strand of opposite polarity. Subsequently, specific cleavage produces unit-length genomic molecules with characteristic end-groups, which are eventually circularized to yield progeny circles, a process reminiscent of RNA splicing. Indirectly evidence that this mechanism may be effective in HDV replication is the finding of circular forms of genomic and antigenomic RNA in livers of chimpanzees infected with HDV, some of which appeared to be twice the length of virion RNA or in form of a double stranded RNA complex (11).

**Epidemiology**

The HDV is a global health problem. The occurrence is highest in tropical and subtropical zones, with a prevalence gradient that diminishes in temperature zones in parallel with the decrease of HBV from the equator to the poles. In the Western World HDV is confined within groups that have overt factors predisposing to transmission. The epidemiology of HDV follows therefore two patterns, one of endemic infection in the general HBsAg population and one of sporadic infection with endemic or epidemic clusters within well defined HBsAg-subpopulations.

Inferential evidence implicates the HDV as the cause of outbreaks of fulminant hepatitis that have ravaged the South American Continent since the beginning of the century (12) and markers of HDV have been found in immunoglobulins prepared in the US in 1944 (13).

No predisposing modalities of transmission are detectable in endemic areas indicating that HDV is spread by the inapparent permucosal or percutaneous routes of HBV. Spreading occurs primarily within the household and is facilitated by promiscuity and overcrowding; the incidence is therefore highest in the poor population of the third world.