Hepatitis delta virus (HDV): Some Details and features

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ABSTRACT

The hepatitis D virus causes liver disease. It affects all ages. Some call it "delta hepatitis" (HDV). Hepatitis D patients have previously had hepatitis B, which is why they have this illness. Hepatitis D is spread when contaminated blood or bodily fluids come into contact with an uninfected person's body. Hepatitis D can be an acute infection or a chronic illness, depending on the person. Hepatitis D can produce severe symptoms, liver damage that lasts a lifetime, and even death. Hepatitis B and D viruses can infect people at the same time (coinfection) or they might develop hepatitis D after getting hepatitis B (reverse coinfection) (a condition known as "superinfection"). Hepatitis D is not prevented by immunisation. Hepatitis B vaccination, on the other hand, protects against hepatitis D infection.

Keywords: HDV, hepatitis D virus, delta hepatitis, coinfection

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INTRODUCTION

Because of the severity of the problems associated with HDV and HBV co-infection, this kind of viral hepatitis is regarded as the most dangerous type of viral hepatitis. Chronic infections, on the other hand, have a higher chance of causing liver failure and the faster development of liver cirrhosis. Additionally, there is a greater chance of developing liver cancer. Hepatitis D has the greatest fatality rate of any hepatitis infection, at 20 %, when infected with hepatitis B virus. The virus has infected 48 million individuals as of 2020, according to the most recent estimates. [3].

Definition:

HDV: Hepatitis delta virus, is the most common form of hepatitis in the United States [5,6]. Hepatitis D virus (HDV) is one of the five known hepatitis viruses. A subviral agent, HDV can only replicate if it is present in the presence of the hepatitis B virus (HBV), and hence is classified as a satellite virus. Concurrent HBV infection or being superimposed on chronic hepatitis B or a hepatitis B carrier status are two

ways that HDV might be transmitted (superimposed transmission: superinfection).

History

The presence of a nuclear antigen for hepatitis D virus in individuals with severe liver disease who were infected with HBV was originally described in 1977 [8]. As a hepatitis B antigen, this nuclear antigen was then referred to as the Delta Antigen. Structure of an infectious agent that requires HBV infection in order to form a whole viral particle in the chimpanzees has been demonstrated to be HDAg, hepatitis delta antigen. All of the genes in the human body were discovered after cloning and sequencing the whole genome in 1986. Later, the virus was renamed Deltavirus. [10,11].

Virus Structure

HDV has a diameter of around 36 nm. RNA molecules with an internal delta antigen that surrounds the viral genome and an envelope

made from HBV surface proteins are circular, negative-sense RNA molecules. [12, 13,14,15].

Approximately 1700 nucleotides make up HDV's genomic RNA, which is bundled with roughly 200 molecules of HDAg to create a single viral particle. The genome appears as a rod-like shape double-stranded because of substantial base-pairing in the RNA molecule (plant pathogens). In contrast to the 200-400 nucleotides in a viroid RNA, the HDV genome has more nucleotides. Viroids lack the capacity to encode proteins, whereas HDV encodes itself and relies on HBV for proliferation [12,17].

Hepatitis B surface antigen (S-HBsAg), medium and large hepatitis B surface antigen (H-HBsAg) are all included within the envelope. The HDV genome has a ribozyme domain that is between 80 and 100 nucleotides long. Because of its high GC nucleotide content and circle-rolling replication method, HDV appears to be a unique animal virus. Currently, the virus is classified as a distinct genus, deltavirus, and awaiting an order and family classification [18,19,20].

Although most RNA viruses encode their RNA-dependant or own replicase DNA polymerase, HDV does not. As an alternative, it employs DNA-dependent RNA polymerases that are found in cells. HDV genome replication requires the production of three unique types of RNA: circular genomic RNA, circular complementary anti-genomic RNA, and linear anti-genomic RNA, all of which are formed through the process of circle-rolling. The circular rolling process uses cellular RNA polymerases to produce numerous copies of a circular genome through unidirectional replication of nucleic acids. Anti-genomic RNA that has been linearly polyadenylated acts as the messenger RNA (mRNA) for HDAg production [21].

It is forced to rely on the host cellular proteins (cellular machinery) in order to carry out the operations that are required for its replivative cycle, such as transcription, replication, post-transcriptional modifications, and translational modifications because it only has one HDAg and two isoforms encoded by the virus [19,22].

In the genus Deltavirus, there are eight species of negative-sense, single-stranded RNA viruses as well as virus-like particles that are

grouped collectively as the hepatitis delta viruses [23]. Hepatitis B surface antigens (the three proteins that make up the HDV virion's viral envelope) coexist with host phospholipids in the viral envelope, making the HDV virion an enveloped particle with a diameter of 36 nm.

Hepatitis D antigen (HDAg) molecules surround an inner ribonucleoprotein (RNP) particle, which includes the genome surrounded by roughly 200 molecules for each genome. Evidence suggests that HDAg's core region is capable of binding RNA [24]. HDAg's N terminus has a coiled-coil domain that mediates many interactions [25,26].

As the smallest virus known to infect mammals, HDV has a closed circular DNA genome, negative-sense single-stranded, roughly 1700 nucleotides. HDV may have sprung from a type of plant infections known as viroids, which are considerably smaller than viruses, according to some theories. GC nucleotide richness makes its genome one of a kind among animal viruses [27,28].

Due to the fact that the nucleotide sequence is 70% self-complementary, the genome can create a partly double-stranded, rod-like structure composed of partially complementary nucleic acids.[29]. By assembling partially complementary nucleic acids [28]. Different strains of HDV have been fused together and sequences have been posted in public databases using different starting points for the circular viral DNA involved in these fusions. As a result, this virus's molecular categorization was in a state of flux until recently when a suggested reference genome and an unified classification scheme were put in place [30].

Nucleic acid Structure

In addition to providing confirmation that HDV genomic RNA was circular in shape, it also predicted that this RNA might fold back on itself, resulting in what has come to be described as "an unbranched rod-like structure" (31). Assumedly, the genome has a base-pair rate of 74% and an 805 kcal negative free energy. Electron microscopy has been used to detect the rod-like structure in previous studies (33).

Furthermore, when the HDV RNA is separated by electrophoresis under nondenaturing conditions, it acts as if it were double-stranded.. Because of the effect of RNA-

editing, which will be discussed in further detail later, it appears that at least some of the antigenomic HDV RNA can fold into a rod-like shape, which is consistent with previous findings (34).

Another piece of circumstantial evidence stems from the fact that circular RNA cannot be recleaved after it has been generated, as previously stated. Forced rod-like folding may have rendered the ribozyme domain inactive, according to one theory. Among spite of the overwhelming evidence that this form is possible, we still don't know for sure if it is the most common in living organisms.

A single rod-like shape is a common assumption, however we must stress that many configurations are not only feasible but may be necessary for HDV RNAs. Elegant findings support the idea of metastable RNA structures in the case of plant viroids. There is also a predicted hairpin shape that is absent from the rod-like folding of potato spindle tuber viroid (PSTVd). For PSTVd replication to take place, this hairpin must be able to form, according to strong genetic evidence (35).

HDV RNAs, on the other hand, also require several structures. Ribozyme domains on the genome and antigenome, for example, are not folded in the same way as the rod-like structure. For HDV RNAs, there is little doubt that further examples of metastable states will be discovered. The full RNA sequence of HDV has now been disclosed in a number of different ways. The majority of DNA sequences are 1,679 nucleotides (nt) long (30,31).

The genome, antigenome, and mRNA are the three types of HDV RNA that receive the greatest attention. The genome is defined as the RNA species that is organised into viral particles. It is a single-stranded RNA molecule with a circular shape. The antigenome, the genome's exact complement, is present in cells where this genome is replicating at levels that are generally 5-20 times lower. The antigenome shares the same polarity as the third RNA type. Polyadenylated at the 3' end, it is linear. Since it covers the open reading frame for Ag and is around 800 nt in length, it is thought to be the mRNA for the gene itself. There are several types of post-transcriptional RNA processing that all three of these RNAs have through, as

will be discussed more in the following paragraphs (36,37).

During the replication of HDV RNA, minor amounts of other processed RNAs are present in the resulting RNA molecule. For both genomic and antigenomic polarity, there are only a few number of dimers and even trimers of the unit-length molecule available. The bulk of the RNA in both the multimers and the monomers is in a circular shape (38).

Primer extension experiments were first used to map the mRNA's 5' terminus at position 1631. It was eventually determined to be located at 1630 utilising 5'-RACE techniques. This is the most common 5'-end, however there appear to be a number of less common and less particular places. Because mRNA quantity was so low compared to antigenomic RNA in early research, there is some degree of uncertainty (39).

Viral antigen

Several open reading frames have been discovered in the HDV genome (ORFs). It is yet uncertain what the other orphan reading frames do, as only one of them appears to be actively transcribed and encodes an antigen (HDAg). HDAg comes in two sizes: small (S-HDAg) at 24 kDa and big (HDAg 27 kDa), both of which include 195 amino acids (L-HDAg). To make S-HDAg, the open reading frame is transcribed by host cell RNA polymerase II into an mRNA. Adaminase-1 (ADAR 1), an enzyme in the cell, substitutes the stop codon (UAG at position 196) on the mRNA with a tryptophan (codon UGG), resulting in an extra 19 amino acids being added to the reading frame [40].

L-HDAg has functional characteristics that are distinct from S-HDAg because of the addition of nineteen amino acids to the carboxyl terminus. There are two distinct types of HDAg: one that is necessary for viral genome replication, the other that functions as a primary inhibitor of replication and is critical for virion particle assembly. It is not only HDV genome replication that L-HDAg controls, but also its own production by blocking viral replication, which precludes the editing of the amber/W site essential for L-HDAg expression [37].

The HDAg has a variety of functional domains, including the RNA-binding domain, the Coiled-coil sequence, and the Nuclear

Localization Sequence (NLS). Additionally, the L-HDAg comprises domains for viral assembly (VAS) and nuclear export signal (NES). The L-VAS HDAg's makes it mandatory for virion assembly. By binding to RNA, HDAg may directly stimulate viral genome transcription.

Repressor binding to RNA polymerase II may be replaced by HDAg to aid in transcription elongation [41]. A lack of HBsAg causes nuclear localization of both S and L-HDAg, as they both carry nuclear localization signals. In order for L-HDAg to be translocated into the nucleus, HBsAg is required since only L-HDAg has a nuclear export signal for its proven involvement in virion formation [42].

The Delta (HDAg) antigen, a phosphoprotein, is the only protein encoded by the HDV genome. A short version, known as HDAg-S, and a long form, known as HDAg-L, are both present with molecular weights of 24 kilodaltons (195 amino acids) and 27 kilodaltons (214 amino acids), respectively [43]. High-density lipoprotein (HDAg) S has been shown to stimulate RNA replication, whereas high-density lipoprotein (HDAg) L has been shown to promote HDV RNA enveloping, which is required for virion assembly [44, 45, 46, 47, 48].

HDV is distinct from viroids in that it produces a single protein, HDAg, whereas viroids generate no proteins. There are two sizes of HDAg available: a 27kDa large-HDAg and a 24kDa small-HDAg. The N-terminal sequences of the two forms are identical, however the C-terminal sequences of the giant HDAg differ by 19 amino acids from their smaller counterparts. UAG stop codon 196, which ordinarily yields only the small-HDAg, is present in the same reading frame that produces both isoforms. To make large-HDAg, the stop codon must be changed to UGG by the cellular enzyme adenosine deaminase-1 [49,50].

In spite of their almost similar DNA sequences, these two proteins have quite different roles during an infection. Supports viral replication by entering the nucleus in the early stages of an infection. HDAg-S At this latter stage of an infection, the production of HDAg-L, which is essential for the assembly of viral particles as well as an inhibitor of viral replication, takes place. Cellular enzyme RNA editing is therefore crucial to the viral

replicative cycle because it manages the equilibrium between viral replication and virion assembly [51,52,53].

Surface proteins of the HBV bind to the HDV envelope protein, which contains three of them. The S region of the genome is the most often expressed area when it comes to the formation of subviral particles. Even though it is feasible to make viral-like particles that look and behave like mature HDV, these particles are not contagious because the HDV antigen proteins and the viral genome combine to form a ribonucleoprotein (RNP). The N-terminal pre-S1 domain of the big protein was shown to be the determinant of HDV infectivity, according to previous research (L). It was discovered to play a role in cellular receptor binding.

HDV envelope proteins have an antigenic loop, which researchers Georges Abou Jaoudé and Camille Sureau analysed for a 2005 paper on the virus' infectivity. The antigenic loop, like the N-terminal pre-S1 domain of the big protein, is exposed on the virion's surface. According to a research by Jaoudé and Sureau, altering portions of the antigenic loop may help to reduce the infectivity of HDV in the host cells [54].

Mode of Transmission

Hepatitis D has the same transmission pathways as hepatitis B. Hepatitis B infection is most common among those who inject drugs and those who get clotting factor concentrates. More than 15 million people throughout the world have both HIV and hepatitis C. The use of intravenous drugs is a significant risk factor for HDV in most developed countries. However, in the sub-Saharan Africa, immediate Mediterranean region, the Middle East, and northern South America, HDV is far more frequent [55]. HDV may have infected as many as 20 million individuals worldwide [56].

Infection of hepatocytes by the hepatitis delta virus (HDV), which is distinct from the other viruses that cause hepatitis, necessitates the presence of HBV's helper function. According to the World Health Organization, more than 257 million individuals (or 3.5 percent of the world's population) were infected with HBV in 2015, representing a global epidemic. According to the World Health Organization, HDV has no reported prevalence or death rates

[57]. When an HBV-infected individual is concurrently infected with HDV, the chance of developing cirrhosis and hepatocellular carcinoma rises. People with HBV infection (about 13 million people globally) in high endemicity foci or among immigrants from high endemicity regions are estimated to have a 5-percent chance of contracting HDV coinfection. (58,59).

By 2030, the Global Health Sector Strategy (GHSS) on Viral Hepatitis [61] aims for the eradication of hepatitis (less than 65 % death and less than 90 % incidence). As part of the GHSS, HBV vaccination and blood and injection safety programmes are designed to prevent HDV and HBV infection infection. The GHSS, on the other hand, only offers a few options for diagnosing and treating HDV infection. Around 60 million people worldwide are infected with hepatitis B each year, according to two recent meta-analyses [62, 63].

Viral replication

Although the process by which HDV enters the hepatocytes is not fully known, it is widely accepted as comparable to that of HBV. Heparin Sulphate Proteoglycan (HSPG) is a proteoglycan on the surface of hepatocytes that binds to HDV. In order for HDV to enter hepatocytes, the N-terminal aminoacids of the pre-S1 domain of L-HBsAg must be included. Deletions/mutations of pre-S1 sequence and N-terminal amino acid acetylation or myristoylation have been shown to limit HDV entrance into the hepatocytes [65]. It has recently been discovered that HBV and HDV enter the liver through a potential receptor described by Yan et al. [66]. According to the study's authors, the pre-S1 domain of L-HBsAg may interact with sodium-taurocholate cotransporting polypeptide, an integral transmembrane glycoprotein implicated in the enterohepatic circulation, to promote deltavirus infection in the hepatobiliary tract.

HDV infects cells by infecting them with a coated viral particle that is then uncoated. The uncoated virus is then translocated into the nucleus by HDag, which then uses RNA polymerases I and II to copy and replicate the viral genome. However, whereas DNA polymerase I catalyses genome replication from an antigenome and transcription of mRNA in

the nucleus, DNA polymerase II catalyses genome replication from a nucleoplasmic antigenome as well as transcription of mRNA in the nucleoplasm [67].

The transcription of the antigenome using the viral genome, which is performed by a circle rolling mechanism that results in an antigenomic RNA that is larger than one unit in length, is the first step in the replication process. The antigenomic RNA is then cleaved by intrinsic ribozyme activity and ligated to form a circular antigenome, with the assistance of cellular ligases in the following phase. It is then used to synthesise genomic RNA in the nucleoplasm, which is then recycled back into the cell by a process known as reverse transcription.

HDag is created when the mRNA is transcribed using the same genomic transcript as the mRNA and then translated into the protein. Because of this, it is obvious that HBV does not participate in HDV replication and that the virus may reproduce even in the absence of the helper virus (HBV). Cell entry, virion assembly, and virion export are the only functions that it is capable of doing.

As part of its replication strategy, HDV makes use of a replication process known as the double-rolling circle, which is strikingly similar to the technique taken by virusoids, viroids, and viroid-like satellite RNAs [68]. Main notably, the use of a circular RNA strand as a template, which is translated by an RNA-dependent RNA polymerase of the host or a helper virus, is the most distinguishing characteristic of this kind of replication in general. Furthermore, it should be pointed out that HDV is the only human pathogen that makes use of the host enzyme [69, 70, 71].

The HDV virus, on the other hand, is deceiving, and when the host cell is a hepatocyte, and because to the absence of RNA-dependent RNA polymerase in eukaryotic cells, the virus takes advantage of the hepatocyte's own RNA polymerase during its reproduction. Following that, the new RNA strands are cleaved by ribozymes and, lastly, they are linked together by enzymes from the host cell [72, 73, 74].

Multiple studies [73, 74] have examined the processes of HBV replication, and it appears that the same mechanisms are involved in the early stages of hepatocyte infection as in the

later stages of infection. Surface proteins generated by the HBV envelope would first attach to proteoglycans made of the sugar heparan sulphate, which would prevent the virus from spreading (HSPG). Despite the fact that this connection has a low affinity [75], it is critical to the infectious process because it facilitates in the attachment of the virion to its cellular receptor, the Na⁺ taurocholate co-transporting polypeptide (NTCP) [76]. Only when this virion [77,78,79] binding phase with NTCP occurs, high affinity binding occurs, which initiates the viral particle entry process by endocytosis-mediated internalisation and initiates the viral particle entry process by endocytosis-mediated internalisation and initiation of the viral particle entry process [74, 80].

A nuclear localization site (NLS) in the cytoplasm of the infected cell is used by HDAg to transport HDV ribonucleoprotein to the cell nucleus during infection. Cellular importins are responsible for bringing the ribonucleoprotein into the cell once it has been synthesised [77,78,79].

HDag-S is synthesised in the nucleus by RNA polymerase II, which is found in the nucleoplasm of the nucleus and is subsequently exported to the cytoplasm, where it is translated into genomic DNA (needed for HDV RNA replication) [89, 90]. RNA polymerase I [82] transcribes genomic RNA in the nucleus, especially in the nucleosome, using an antigenomic RNA template that is complementary to the genomic RNA. RNA polymerase II transcribes antigenomic RNA into new genomic RNA in the nucleoplasm [81].

An modified antigenomic transcript serves as the template for the edited genomic transcript, which in turn produces HDag-L [91]. Study results have indicated that HDV genetic variability can be caused by mistakes in the addition of polymerase and ADAR1-catalyzed amber/W editing, as well as RNA recombination. Recombination is not uncommon, according to certain studies [85]. An analysis of HDV genome sequences by Sy et al. (2015) has shown that recombination can occur upstream of HDV's ribozyme activity and polyadenylation signal sequence, which is situated at nt908 in the HDV genome. This

recombination may contribute to HDV genotype variation.

Upon arrival in the nucleus, the two HDag isoforms bind to the new, unedited genomic RNA, which is then exported into the cytoplasm [78]. HDV RNA replication and the formation of HDV RNPs in hepatocytes were convincingly confirmed without the aid of HBV [87]. Even though HDag-L and HBV are required for a successful infection, it is not necessary for the virion to be formed, as HDag-L and HBsAg interact in ER to form a viral particle that may infect additional cells. HDV infection is therefore dependent on the presence of HBV [78,88].

HDV, like hepatitis B, enters liver cells by the bile transporter NTCP [92]. It is the big hepatitis B surface antigen, HBsAg, which has the N-terminal domain that HDV utilises to identify its receptor [93]. The receptor-binding site is formed by the amino acid residues 9–15, according to mutagenesis mapping of this domain [94]. When the virus enters the hepatocyte, it is uncoated, and the nucleocapsid is translocated to the nucleus owing to the presence of a signal in the HDag protein. [95].

RNA polymerases from host cells are used by HDV since the HDV genome does not code for its own RNA polymerase. After years of speculation that HDV replication relied solely on RNA polymerase II [96,97] it has recently been established that RNA polymerases I and III are also necessary for HDV replication [98]. A DNA template is often used by RNA polymerase II in order to create messenger RNA. As a result, HDV would be the first known animal disease that may use an RNA-dependent polymerase as a DNA-dependent polymerase if it does really use RNA polymerase II during replication.

RNA polymerases recognise the folded rod-like structure of the RNA genome and treat it as if it were double-stranded DNA. There are three forms of RNA that are produced: circular genomic RNA, circular complementary antigenomic RNA, and a linear polyadenylated antigenomic RNA that includes the open reading frame for the HDag. There is antigenomic and genomic RNA production in the nucleolus and nucleoplasm, respectively, facilitated by RNA polymerase I and RNA polymerase II [100]. This RNA is initially

generated in linear form, which has multiple copies of the HDV genome in it. The hepatitis delta virus ribozyme, a sequence of 85 nucleotides, operates as a ribozyme, cleaving the linear RNA into monomers, in both the genomic and antigenomic RNA. Circular RNA is formed by ligating these monomers together [101,102].

The existence of a rolling-circle process for HDV replication has been largely accepted as a model for the virus' reproduction; nevertheless, crucial features such as the host cell components involved have yet to be validated and/or defined. [102].

Unlike retroviruses, A DNA intermediate has not yet been identified in HDV, as has been shown in retroviruses [102], and the lone HDV protein, the delta antigen, is far too small in size to operate as a polymerase. HDV RNA must in some way direct host DNA-dependent RNA polymerases to use HDV RNAs as templates in order for this to be accomplished. It has been widely explored how this is performed and which host polymerase (s) is (are) involved, albeit the results have remained a source of debate.

The presence of the host RNA polymerase II appears to be required for the virus to initiate transcription of genomic HDV RNA (pol II). Researchers have discovered that inhibiting pol II with low doses of the specific inhibitor -amanitin reduces HDV RNA synthesis on both the genomic and antigenomic strands of an endogenous HDV RNA template [103, 104]. This has been demonstrated in nuclear run-on experiments using an endogenous HDV RNA template. According to one theory, the rod-like shape of HDV RNAs may deceive pol II into believing the RNA is a double-stranded DNA template, resulting in the transmission of the virus. It has been demonstrated through the use of immunoprecipitation assays that pol II interacts with the terminal stem loop areas of the HDV genome. [104].

Pol II is also capable of elongating multimeric RNA species after attaching to the stem-loop, which allows it to carry out transcription [105] after binding to the stem-loop. It was discovered that a partial antigenomic RNA stem loop had grown longer, resulting in the formation of a hybrid molecule including freshly produced transcript that was

covalently attached to the 5' end of the template. As a result, it is unclear if such elongation is of biological significance.

However, It has been hypothesised [106, 107] In spite of the fact that it has been demonstrated that pol II interacts with genomic HDV RNA, it has been hypothesised that a separate host polymerase is responsible for the synthesis of antigenomic HDV transcripts. Using transfected cells, it was demonstrated that the synthesis of fresh HDV antigenomic RNA was not blocked by doses of -amanitin that would have lowered the activity of pol II, leading to the conclusion that at least two separate host polymerases are involved in the HDV replication cycle. [108].

Pol I, it has been proposed, copies genomic HDV RNA in order to create antigenomic RNA [108]. Previous nuclear run-on tests, which indicated that both genomic and antigenomic RNA syntheses are sensitive to low doses of -amanitin, consistent with pol II involvement, are in direct conflict with the findings of the current research, which contradicts their findings [66] . It should be noted that HDV RNA has been discovered in the nucleoplasm of cultivated cells that have been excluded from the nucleus. According to this evidence, it is pol III and not the host polymerase II that is engaged in RNA replication, rather than the host polymerase II. Pol III is more resistant to high doses of -amanitin than pol I [109].

It has been discovered that sections of the HDV RNA genome interact with pol II, as well as with pol I and III in vitro research have demonstrated that. Additionally, this adds another layer of intricacy to the current investigation. The fact that such in vitro interactions do not result in RNA-directed transcription, however, raises the possibility that they are of little biological consequence. (110).

In the HDV mRNA, a 5'-cap structure and a 3'-poly(A) tail are typical of a pol II transcript that is processed into an mRNA. However, the involvement of pol II in viral mRNA transcription is well established [111, 112].

The debate over the transcription process is thus restricted to the question of whether pol II or another polymerase, either pol I or pol II, is used to transcribe genomic RNA. Different polymerases, as well as additional components,

are required if these procedures are to be carried out [114].

An essential RNA-editing event occurs in addition to posttranscriptional processing to generate the three viral RNAs listed above. Antigenomes are altered by a host adenosine deaminase throughout the viral replication cycle (ADAR1). The adenosine in the amber codon is converted to inosine as a result of this mutation. Following this, guanosine is synthesised in the absence of inosine via RNA-directed RNA synthesis. So the UGG tryptophan code for the UAG stop codon is substituted for the UAG stop codon. A total of 19 amino acids are added to the delta antigen ORF by this method. The particular folding of the HDV antigenomic RNA influences the editing site's specificity [116].

PATHOGENESIS

Infectious HDV virion is an encapsulated, about 36 nm in diameter, spherically-shaped particle [44]. There are around 200 HDAg molecules in each genome of a virion, which is surrounded by a lipid coat including host lipids and HDAGs [117]. There's a common misconception that because HDV and HBV have the same envelope proteins, attachment and cell penetration must proceed in a comparable fashion.

Research has focused on the HBsAg areas that are critical to the entrance of HDV and HBV. The N-terminus of L-preS1 HBsAg's region is myristoylated. For HBV and HDV to enter hepatocytes, this posttranslational alteration and roughly 48 neighbouring amino acids are required. It has been shown that synthetic peptides that resemble this area are extremely effective in blocking viral entrance (118).

Host receptors for HBV have been sought out in a number of investigations (and maybe HDV) [119]. There have been a lot of applicants, but none have been verified. Activation of purinergic receptors has been shown to be necessary for HDV entrance in primary human hepatocytes when drugs that prevent the activation of these receptors are used [120]. This is contrary to the findings of another study, which found that blocking chemicals interfere with HDV and HBV infection because of their charge, not because receptors are directly engaged in the process [121].

HDV infection was suppressed just as effectively when one of the blocking chemicals, ivermectin, was introduced after infection as when it was added before infection. These findings reveal an HDV replication cycle phase other than receptor binding that Ivermectin focuses on. Glycosaminoglycan side chains of the heparin proteoglycan side chains of the hepatocytes were shown to be critical for HDV cell entrance, as has been reported for HBV infection [121].

A new work by Yan and colleagues shows that the sodium taurocholate cotransporting polypeptide is a required and sufficient receptor for HBV and HDV [122]. Multiple transmembrane transporters, such as this one, are found in the liver and are expressed there. Small interfering RNAs (siRNAs) reduced HBV and HDV infection in primary hepatocytes by suppressing the production of this protein. Cell lines of human liver that expressed this protein were more sensitive to HBV and HDV infection. For the first time, in vitro studies of these viruses may be conducted using known cell lines of human liver, which are more practical and repeatable than primary hepatocyte cultures.

Hepatocytes are the only cells where HDV may thrive. As a result, the liver is the organ most commonly affected by the cellular damage caused by human deltavirus infection. HDV infection is expected to cause immune-mediated liver damage [123]. It has been shown that HDV can have a direct influence on hepatocytes, particularly in the early stages of the disease [124,125].

As a result of acute HDV infection, it is hypothesised that infected hepatocytes suffer degenerative changes that are characterised by shrinkage of the nuclei and eosinophilic cytoplasm in the liver parenchyma, which is consistent with cytopathic damage to the liver cells. These findings are supported by studies conducted in vitro (in a cell culture system) and in humans. The large delta antigen, on the other hand, is non-cytotoxic and helps HDV survive longer periods of time (chronicity), it also makes hepatocytes vulnerable to immune-mediated harm [128].

Woodchuck model experiments have been extremely beneficial in understanding HDV aetiology and chronicity associated with HDV superinfection because of the striking parallels

between the course of disease in woodchuck animals and the course of disease in humans. [131,132]. This model may be used to investigate the effectiveness and protective function of novel HDV treatment options, including vaccines. It has been found that both protein and DNA immunizations for HDV are ineffective in protecting against re-infection, highlighting the need for various techniques to produce an HDV vaccine [133,134].

Because of the differences in immune-mediated responses between acute and chronic HDV infection, it is possible that the persistence and chronicity of HDV superinfection can be explained. [135]. By eliminating HDV-infected cells, cytotoxic T lymphocytes remove the virus. It has been suggested that the inability to eliminate the infection and the emergence of a chronic infection are linked to a delayed and inadequate immune response. One percent of HBV/HDV co-infected individuals and five percent of viral superinfected patients have had fulminant liver failure. Massive necrosis and liver destruction in fulminant liver failure may be caused by an overactive immunological response, particularly one that is cell-mediated [136,137].

HBV-HDV interaction is also considered to impact HDV pathogenesis, however this has yet to be fully understood by researching bodies. Co-infection with HDV or superinfection with HDV are the two most common ways in which HDV infection occurs. Co-infection with HDV/HBV generally results in the eradication of both organisms and the restoration of complete health, but superinfection frequently results in the development of chronic hepatitis D infection [139]. Patients with chronic hepatitis B who are concurrently infected with hepatitis D might develop ascites and hepatic encephalopathy, which can be fatal. This can lead to abrupt liver failure and ascites.

Various forms of reciprocal inhibition of viral replication are related with HBV coinfection with other hepatitis viruses. HBV replication has been commonly suppressed by HDV [140]. Myxovirus resistance is boosted by L-HDAg. Transcription is an interferon-inducible antiviral response mediator that is engaged in the decrease of HBV replication and is responsible for the reduction of HBV replication. Because of this, it has been

proposed that HBV/HDV superinfection is a cause of chronic liver disease. The combined effects of chronic HBV /HDV infection are far more severe than the effects of HBV monoinfection alone. This results in much earlier cirrhosis, decompensation, and hepatocellular carcinoma (HCC) and a much poorer 5-year survival rate. [141].

As the viral response fluctuates over time, the suppression of HBV replication by HDV is not long-term [142]. About half of the individuals were found to have considerable HBV replication in a study [143]. In total, there are three stages of chronic hepatitis D:

There are three distinct phases in the progression of cirrhosis and hepatocellular carcinoma: Early active phase characterised by active HDV replication and suppression of HBV; moderately active phase characterised by lowering HDV and reactivating HBV; and late active phase characterised by remission as a result of a significant reduction in the levels of both viruses in the bloodstream (remission). [144].

At least eight HDV genotypes have been identified (1 to 8). Geographic variation in viral genotypic diversity is observed. The clinical effects of various HDV genotypes vary. Genotype 1 is the most frequent and has a wide variety of outcomes. Genotype 2 is the least common. Genes of genotype 1 are found in high abundance in Europe, North America, South and Central Asia, the eastern Mediterranean, and the Middle East, but those of genotypes 2 and 3 are extremely rare. It was found that, Genotype 1 be the most prevalent in Africa, accounting for 88 percent of the total population. Those living in the Yakutia region of Russia, the Japan of China, and Taiwan province are the most likely to have genotype 2. [156].

A common genotype 2 prototype may be responsible for this variation. A larger remission rate can be found for genotype 2 patients compared to genotype 1 patients. Most HDV infected persons 90 % are of genotype 3, which has been linked to more severe illness, an earlier start of HCC, and deadly acute liver failure [158].

Genes of genotype 4 have been found in the Far East, where they frequently cause only minor liver disease. However, the Miyako Islands in Japan have a variation of genotype 4

that is more likely to proceed to cirrhosis than the Taiwan Province in China [159]. In Africa and in African migrants to Europe, genotypes 5–8 have been recorded [160,161], although the natural history has not been thoroughly documented [162, 163].

In the United States [164, 165], the United Kingdom [166], and Iran, researchers found a link between the prevalence of HDV infection and injectable drug usage. Because of the high incidence of anti-HDV among PWIDs, it's safe to assume that injecting drugs increases the chance of HDV super-infection. The incidence of anti-HDV in sex workers, particularly those who inject drugs, is greater [167]. Migrants from countries with a high HDV infection frequency have an impact on the host country's epidemiology, which explains why the prevalence of HDV infection is growing in France, Greece, Italy, Spain, and the United Kingdom]. 55 to 95 % of HDV infections have been documented in Western European nations among more afflicted populations, including PWID and immigrants from highly endemic locations [166].

HEPATOCELLULAR CIRRHOSIS AND CARCINOMA

The presence or absence of superinfection or co-infection, HDAg variations [173] and HDV [174], and HBV genotypes have all been found to have an influence on the course of liver disease in HDV infection. Chronic HBV infection is associated with a more severe form of liver disease, possibly as a result of the worsening of pre-existing HBV damage produced by HDV infection. Instead of directly impacting liver illness, HBV genotypes govern HDV viral levels, which have a negative impact on disease outcomes [177].

In light of the fact that HDV infection leads to cirrhosis of the liver and fulminant hepatitis, L-HDAg has been demonstrated to enhance the TGF- and c-Jun-induced signalling cascades, which in turn may trigger the epithelial-mesenchymal transition and fibrogenesis [177,178]. By increasing TGF- expression, chronic HDV may lead to liver disease. Farnesylation (isoprenylation) of L-HDAg is the specific means by which this is achieved. Even though they are still in the early stages of research, isoprenylation inhibitors have the

potential to play a significant role in reducing the negative consequences of HDV infection [179].

Gene expression and cellular responses appear to be changed in HDV-infected cells, as evidenced by an increase in the expression of pro-inflammatory, growth, and anti-apoptotic proteins. HDV-infected individuals may develop HCC as a result of significant liver damage and enhanced hepatic cell survival.

NF-kappa B (NF- κ B) dysfunction has long been linked to inflammation and cancer. There is evidence that L-HDAg can generate oxidative stress by activating the enzyme NICOTinamide adenine denucleotide hydrophosphoric acid oxidase-4 (NADH). Because of this, L-HDAg has the potential to activate the signal transducer and activator of transcription-3 and nuclear factor-B (NF-B) through the oxidative stress pathway. [181].

As a result of TNF—induced NF-B activation, a protein called TRAF2: TNF receptor-associated factor 2 may also activate L-HDAg-induced NF-B. These findings suggest that HDV infection and the subsequent development to HCC may have an underlying cause of significant necroinflammation. The necroinflammation and cirrhosis of HDV infection may potentially play a role in the development of HCC. Compared to the HBV mono-infection group, those with HDV HCC had a significantly smaller liver compared to those with normal or increasing liver size. Endoscopy revealed smaller varices and decreased platelets in HDV patients [183].

Epidemiology

Estimates put the number of HDV infections globally at 12 million. HDV infection occurs in a wide variety of places across the world. For those who have been infected with the HBV, Those most at risk for HDV infection are in Central Asia (including Mongolia and Pakistan), Central and West Africa, Japan and Taiwan, the Pacific Islands (including Kiribati and Nauru), Eastern Europe, the Middle East, and Greenland.

According to a 2017 comprehensive research, the prevalence of HDV antibodies (anti-HDV) among HBV-infected patients ranged from 26 percent in Central Africa to 7 percent in West Africa and 0.05 % in Southern

and Eastern Africa, with the highest incidence in Central Africa. Geographically concentrated areas of high HBV prevalence were reported in Gabon 45 %, the Democratic Republic of Congo 26 %, Mauritania 19 %, Cameroon 14–35 %, and Nigeria 5 %. In Guinea-Bissau 25 %, Cameroon 12 % and Nigeria 7 %, the prevalence of HIV-HBV co-infection was highest.

Indigenous populations in the Americas are the primary victims of HBV. Anti-HDV prevalence was 29 % among HBV-infected people in the Amazon area of North Brazil between 2003 and 2009 [185,186]. In indigenous communities with HBV infection, anti-HDV prevalence was 39 % in Peru, 13 % in Brazil, 8 % in Colombia, and 4–6 % in Venezuela [187]. Between 2012 and 2016, the anti-HDV prevalence among HBV-infected people in the United States was about 3 % [188]. In the western Amazon Basin of Brazil, advanced fibrosis was related with a high viral load [189]. There were 2.2 deaths per million people in the North compared to 0.28 deaths per million in the rest of the country between 2008 and 2014 [185].

People with HBV infection who have anti-HDV antibodies are 15 % more likely to have the disease than those who do not, according to a 2010 comprehensive review. The prevalence of anti-HDV antibodies among people with HBV infection was estimated to be 15% in 2010. The rural Sindh province of Pakistan has a high prevalence belt [190]. There was one research that found 0.9 % in Lebanon , 2 % in Jordan, , 17 % in Somalia and 29 % in Afghanistan.

Some European countries, such as Romania 23 % [191], Eastern Turkey 15 % [192], which is higher than the Western Turkey 3 % [27], Yakutia 18–20 % [193], Siberia (1996), and Greenland 6 % [196] among Inuits, have significant anti-HBV prevalence. HDV is not widespread in Austria, Bulgaria, Belgium, the Czech Republic, France, Croatia, Greece, Switzerland, Poland, and Ireland, but it is common in the rest of the world. [197].

In 2003, 22% of HBV-infected people in Bangladesh tested positive for anti-HDV antibodies [198]. Anti-HBV prevalence among HBV-infected people was found to be 11% in New Delhi, India, in 2005 [199]. HDV is rare in

Indonesia [200] and Thailand [201] while HBV incidence is high [24].

Among HCV-infected Mongolians, anti-HDV prevalence was 45 % in 2013 (60 percent in 2017 when utilising a revolutionary quantitative microarray antibody capture test) [202] (HCC is the most frequent malignancy in Mongolia, with an annual incidence of 54.1 cases per 100,000 persons). In Xinjiang, Inner Mongolia and Tibet, where ethnic minorities reside, 4 % of those with HBV infection were anti-HDV positive [204]. Following vaccination, the prevalence of HDV and HBV infection reduced in Taiwan, China. According to the study, anti-HDV sentiment was far more prevalent in the south than in the north (6 % versus 2 %. One of the Miyako Islands, in Japan, has a high prevalence of HDV (24 % in 1997) [207]. Anti-HDV has been reported in Nauru, Western Samoa , Kiribati, and Niue, but it is missing or extremely low in other Pacific Islands [209, 210].

Patients who tested positive for HBsAg also tested positive for HDV-RNA in Viet Nam between 2000 and 2009, according to data collected between 2000 and 2009. According to the World Health Organization, HDV is uncommon in the total HBV-infected population in Australia, Malaysia, the Republic of Korea and the Philippines, [211].

On the basis of their estimates, the International Agency for Research on Cancer projected that about 430,000 56 % of new HCC cases were caused by HBV in 2012. According to the World Health Organization, about 380,000 individuals died of liver cancer caused by HBV in 2015, while 490,000 people died of cirrhosis caused by HBV [214]. While HDV coinfection has been shown to affect the outcomes of patients who have been infected with HBV, only a few studies have attempted to determine the fraction of HBV fatalities that are also related to HDV [212, 213].

It is essential for the molecular biology of the HDV RNAs, as well as their replication mechanism, to produce two closely similar virus-encoded proteins, the large and small versions of the delta antigen (Ag), which are referred to as Ag-S and Ag-L, respectively, in order for them to function properly, and which are related to each other. This chapter examines the features of these crucial proteins in further

detail. The RNAs of HDV will be the primary emphasis of this chapter, with consideration given to such characteristics as structure, transcription, post-transcriptional processing, and stability of the RNAs of HDV. Earlier reviews of these issues may also be of interest to the reader in this case [215,216,217].

When HDAg-S is replicated, an enzyme called Adenosine Deaminase (ADAR1), which is found in the host protein, modifies the antigenome post-transcriptionally, replacing an inosine with an adenine, resulting in the Amber/W site, which is responsible for producing HDAg-L, which has an additional 19 amino acids [218,219,220].

HDAg-L has an extra 19 amino acids in the C-terminal region compared to HDAg-S. Each of the two HDAg isoforms has several functional domains in common, including a coiled coil domain (CCD), the RBD, the NLS, and a C-terminal tract rich in proline and glycine. Variable and specific viral assembly signal (VAS) sequences may be found in HDAg-extra L's 19 amino acids. It acts as a binding site for HBsAg/membrane in viral assembly [221,222]. So far, eight different genotypes of HDV have been found, ranging from HDV-1 to HDV-8, based on the geographic origin of the isolates [223,224,225,226].

According to the World Health Organization (WHO), Globally, there are an estimated 400 million chronic HBV carriers, with between 15 and 20 million of them having been exposed to HDV, according to the World Health Organization [228]. High rates of endemicity have traditionally been observed in Central and Northern Africa, the Amazon Basin, the Mediterranean, and eastern Europe some parts of Asia and the Middle East, [228]. HDV-1 is widespread and frequently isolated in the United States, Europe, and the Middle East, but it has also been isolated in Russia, Africa, Asia, and Brazil. HDV-1 is also prevalent and frequently isolated in the Middle East. [230,231,232]. [229] Japan, Taiwan, and Russia are hotspots for HDV-2, originally known as genotype IIa [233,234,235]. A new strain of HDV-3 has been discovered in the Amazon Basin (which includes parts of Peru, Brazil, Ecuador and Colombia [236,237,238].

Taiwan and Japan [234, 239] are both known to have HDV-4 (the old genotype IIb). [223, 225] Africa is home to the four genotypes HDV-5, HDV-6, and HDV-7. HDV-8 was found in two local persons in the rural of the state of Maranhão (Brazil) [240]. In northern South America, HDV-3 is the virus that causes epidemics of severe and common fulminant hepatitis A and B, respectively. According to study, the HDV-3 virus is common in the Brazilian Amazon region. It indicates that this genotype is associated with a more aggressive strain of the HDV. [77, 84, 85,88].

An anti-HDV IgM and IgG test is the initial step in determining whether or not a patient has HDV. The serum HDV RNA test is the next step for patients with the anti-HDV reagent. This test will determine if the presence of an antibody against HDAg implies the presence of a persistent active infection (HDV RNA +) or whether the presence of an antibody against HDAg just shows a fading serological scar (HDV RNA -). When HDV and HBsAg co-infect or super-infect the same patient with chronic HBsAg, the prognosis and treatment of the two kinds of infection are significantly different. [241, 242].

People who have HBsAg and reside in locations where hepatitis Delta is prevalent (such as the western Amazon) should be tested for total anti-HBc and IgM in order to ascertain whether they have acute or chronic HBV infection. The presence of anti-HBc IgM in acute HBV infection is indicative of HDV co-infection, as is the presence of total anti-HDV IgM. The presence of total anti-HBc reagent with non-reactive anti-HBc IgM in chronic HBV infection is indicative of an HDV super-infection, as is the presence of anti-HBc IgG in chronic HBV infection [243, 244].

Molecular approaches such as polymerase chain reaction (PCR) are used to screen for HDV RNA in order to determine the genotype (conventional PCR, sequencing, restriction fragment length polymorphism - RFLP) in both an HDV co-infection and an HDV super-infection [247]. If the HDV RNA testing results in a negative result, it is necessary to repeat the PCR and/or use further diagnostic techniques such as immunohistology for a liver biopsy and biochemical tests such as the verification of ALT. Hepatitis C virus (HCV) can also be

discovered by the screening of anti-HCV and/or HCV RNA antibodies. [246].

More than 20% of people with cirrhosis who have no known aetiology can be diagnosed with a liver biopsy [248]. When hepatitis D is acute, inflammation and necrosis of the parenchyma and the portal area are seen, as well as lymphocytes and Kupffer cells invading the tissue. In spite of the fact that viral hepatitis is not unique to hepatitis D, the pattern described here tends to be more extreme in hepatitis D. However, in the most severe instances, confluent necrosis might be found in the hepatocytes [248].

Hepatocellular inflammation and necrosis in the liver parenchyma and portal region have been described as part of the histology of chronic hepatitis D, according to certain reports, which are linked with variable degrees of hepatic fibrosis [249]. When it comes to the various kinds of viral hepatitis [250], periportal necrosis is the most typical finding. The conclusive diagnosis of HDV is made by detecting HDAg in the liver biopsy of individuals who have the virus. The quantity of HDAg in the blood diminishes as fibrosis progresses, becoming nearly undetectable in the last stage of the disease [247].

The development of molecular methods has made it possible to detect HDV infection with great sensitivity. Polymerase chain reaction (PCR) detection of HDV RNA is the most accurate diagnostic approach currently available. An enzyme immunoassay or radioimmunoassay cannot detect HDAg in serum because of the sequestration of the antigen in immunological complexes with high-titered circulating antibodies. Acute and chronic hepatitis may be studied by analysing the molecular processes that take place in the early stages of infection, before antibody seroconversion.

An antiviral agent's effectiveness may be monitored via PCR, which is able to identify 10–100 copies of the viral genome in serum. Primers from the most conserved region of the HDAg gene, the C-terminal half, are most effective in clinical practise because of HDV's genetic variability [252,253]. RFLP analysis, sequencing, and immunohistochemistry labelling of liver samples using genotype-

specific anti-HD antibodies can all be used to detect the HDV genotype [254].

An indirect method of determining the presence of HDV infection is to look for antibodies to (anti-HD) HDAg in the blood. Throughout addition to its role as a sign of original HDV infection, anti-HD IgM testing is important because it serves as a clinical marker in HDV's natural history. It is common for people with chronic hepatitis D to have significant levels of anti-HD IgM and IgG antibodies, however the IgM antibodies are monomeric rather than pentameric, as they were in the first infection. [257]. Predicted remission of chronic HDV illness, either spontaneous or driven by interferon (IFN), is indicated by the decline and elimination of anti-HD IgM [257].

Treatment

For chronic hepatitis D, the disease's severity and distinctiveness make it a tough target for antiviral treatment [258]. Acyclovir, ribavirin, and famciclovir have all been demonstrated to be ineffective in the treatment of chronic hepatitis D, but alpha IFN has been shown to be useful. Lamivudine, a nucleoside derivative that effectively suppresses HBV replication, has demonstrated little effect on HDV replication or disease activity [262]. Lamivudine and IFN treatment is still in its infancy, but first results are not encouraging [263].

IFN-alpha has been demonstrated to improve chronic hepatitis D in pilot studies and in randomised controlled trials. However, the dosage and duration of treatment are key factors in determining its effectiveness. After four months of therapy with an initial dose of 5 (MU) per square inch (m²), followed by 8 further months of 3 MU per square inch (m²), ALT levels returned to normal in 25 % of patients, but only in one patient at the conclusion of the 12-month follow-up period [264]. As many as 71% of those who received 9 MU three times per week for up to one year saw an improvement in their liver enzyme levels, and nearly 50% saw an improvement after six months of follow-up. However, the improvement in liver histology was not accompanied by a decrease in HDV viremia as assessed by PCR. IFN has been shown to have little or minimal effect on HDV replication in various investigations [265].

Fewer than ten percent of treated individuals had their delta viral RNA cleared, which is linked to a drop in anti-HD IgM titer. Those who successfully remove HDV RNA may also lose HBsAg [266, 267]. Chronic hepatitis D has no consistent predictors of long-term benefit from IFN usage, while individuals with a short illness duration are the most likely to react [268]. This underscores the significance of early therapy, which is why IFN should be administered as soon as possible. In patients receiving a high dose of medication for a long period of time, side effects are more likely to occur, which need constant monitoring to discover serious mental and medical problems [269, 270].

For the most part, information on short-term outcomes has been used to assess IFN's effectiveness in chronic hepatitis D. Long-term studies of individuals who received high doses of IFN for a year have recently yielded critical information on the long-term effects of IFN. After 14 years of follow-up, half of the patients who had a biochemical response at the conclusion of therapy had normal ALT readings. In other individuals, biochemical responses and loss of IgM anti-virus were maintained, but liver fibrosis was completely reversed in two successive biopsies conducted at

the conclusion of therapy and one year later, all of whom had an initial diagnosis of active cirrhosis [271].

It has been shown that extensive liver fibrosis does not have to be permanent. Clinical and histological improvement was associated with a long-term decline in HDV replication, which finally led to the elimination of viral RNA and, in some cases, HBV infection. On the other hand, in another case report, an HDV-cirrhotic patient was able to completely eradicate both HBV and HDV after receiving continuous IFN treatment for up to 12 years [271].

CONCLUSION

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