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**Conflict of Interest:** There is no conflict of interest.

LITERATURE REVIEW

**RESULTS OF THE STUDY ON THE PREVALENCE OF HEPATITIS D VIRUS GENOTYPING IN THE REPUBLIC OF KAZAKHSTAN**

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**National Scientific Center of Surgery named after A.N. Syzganov1**

**Background** Hepatitis B virus (HBV) infection rates remain high in Kazakhstan, affecting approximately 8% of the population. According to the Republican Center for Reproductive Health, as of december 2017, 2922 patients with chronic HBV and delta agent coinfection have been registered. HBV-HDV coinfection remains the leading cause of chronic liver disease (CLD) in Kazakhstan.**Objective**to investigate the prevalence of chronic hepatitis D genotyping.

**Materials and Methods** Blood samples from patients were analyzed for HDV genotypes using polymerase chain reaction (PCR) techniques. HDV RNA extraction was performed using the GeneJETViral DNA and RNA PurificationKit (ThermoFisherScientific, USA) according to the manufacturer’s instructions. 200 μL of whole venous blood with EDTA was used for extraction.PCR was conducted using specific primers. Purified PCR products were sequenced bidirectionally using forward and reverse primers.

**Results** Phylogenetic analysis offers a novel perspective on the epidemiology of HDV infection and lays the groundwork for pharmacological research. New molecules for the treatment of CHB+D show promising results compared to approved antiviral therapy (AAT) while simultaneously raising questions regarding the development of pharmacogenetic predictors. Among patients with chronic hepatitis D, the highest frequency of occurrence was observed for subgenotypes D1 (61.5%), D2 (10.6%), and D3 (9.6%). In the Republic of Kazakhstan, chronic hepatitis D is associated with genotype 1.

**Conclusion**

HDV is the most severe form of chronic viral hepatitis, posing a life-threatening risk to patients. It is characterized by a predominantly rapid progression leading to cirrhosis much faster compared to other viral hepatitis types, higher rates of hepatocellular carcinoma development, liver transplantation, and mortality. Most HDV patients exhibit persistently elevated transaminase activity in laboratory tests. Patients often do not survive long enough to develop hepatocellular carcinoma and perish from various complications of cirrhosis, predominantly liver failure. The progression of HDV in the Republic of Kazakhstan is associated with genotype 1.

**Key words:** hepatitis B, virus, subgenotypes, hepatitis D, liver cirrhosis, genotypes

**Introduction**

Hepatitis D virus (HDV) was discovered in 1977 by M. Rizzetto and colleagues during histologic examination of liver tissue obtained from patients with chronic hepatitis B virus (HBV) infection. Immunofluorescence analysis of hepatocytes revealed the presence of a specific antigen, delta antigen (HDAg). Simultaneously, specific antibodies against this antigen (HDAb) were detected in the serum of these patients [1-3].

Hepatitis B virus (HBV) infection is a major cause of liver disease progression, including chronic hepatitis B (CHB), cirrhosis, and hepatocellular carcinoma (HCC) worldwide. Although prophylactic vaccines against HBV have been available for decades, the global prevalence of chronic infection remains high, exceeding 240 million individuals [1]. Chronic HBV infection continues to be a significant global public health concern [2].

Hepatitis D virus (HDV) infection constitutes a separate group of individuals co-infected with hepatitis B virus (HBV), characterized by severe chronic liver disease. HDV is a defective RNA virus that requires the presence of HBV for its life cycle [3]. Chronic liver disease associated with HDV (chronic hepatitis D) is characterized by liver necrosis and ongoing fibrosis formation, which can progress to cirrhosis [3]..

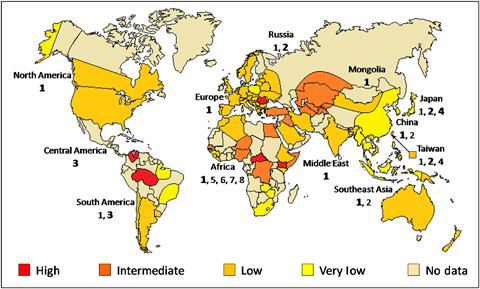
HDV has a single-stranded, circular RNA genome. The virion consists of an envelope provided by the HBV helper, surrounding the RNA genome and the HDV antigen (HDAg). Viral replication occurs in the nucleus of hepatocytes using cellular polymerases. HDV infection can be diagnosed by the presence of antibodies against HDAg (anti-HD) and HDV RNA in serum. Treatment involves the administration of pegylated interferon-α, which is effective in only approximately 25% of patients. In cases of liver failure, liver transplantation is indicated.

The first publication describing the delta agent, initially believed to be a hepatitis B antigen, appeared in 1977 [4]. The key to the discovery of hepatitis D virus (HDV) was the identification of the delta agent and associated antibodies in carriers of the hepatitis B surface antigen (HBsAg) in Turin, Italy, during the mid-1970s. Initially, the new antigen was thought to be a marker of the HBV virus. Given its complex structure, it might have been dismissed as another HBV subtype, similar to many others described in the 1970s. Fortunately, a collaborative research effort between the Turin group and the National Institutes of Health and Georgetown University in the United States commenced in 1978. This collaboration, fueled by American scientists, led to an unexpected and astonishing chapter in virology by 1979. Experiments conducted on chimpanzees demonstrated that the delta antigen was not part of the HBV particle but rather a separate, defective virus requiring HBsAg for infection [5]. To align with the hepatitis virus nomenclature, it was designated hepatitis D virus. The virus is primarily transmitted through superinfection with HDV in chronic HBsAg carriers.

The delta agent was officially recognized as a distinct virus in 1983, receiving the formal name hepatitis delta virus. Currently, the term hepatitis D virus is preferred, although “delta” is still used. The unique nature of this virus was confirmed in 1986 after the cloning and sequencing of its genome [6].

***Epidemiology of the Virus***

Hepatitis D virus (HDV) does not discriminate based on age groups. Current estimates of prevalence suggest that 15-20 million individuals worldwide are infected with HDV. However, it’s important to note that these estimates are imprecise and difficult to assess accurately, as screening for HDV in individuals with HBV infection is not routinely performed, especially if their liver function tests are normal [7]. Despite the fact that HDV requires HBV for its life cycle, the epidemiology of each virus differs. In the Pacific Islands, 90% of HBV carriers are co-infected with both viruses (HBV+HDV), while rates are 8% in Italy and 5% in Japan [8]. Based on current analyses, 15-20 million individuals are infected with HDV. Furthermore, in immunocompromised patients, anti-HDV may be absent, and seroconversion can occur after recovery from the disease, making it impossible to diagnose past infections. The main areas of distribution include Mediterranean countries, the Middle East, Central and Northern Asia, Western and Central Africa, Venezuela, Colombia, and some Pacific Islands. The Far East is less affected, although HDV is present in Taiwan, China, and India (Figure 1) [8].



**Figure 1.** Geographic distribution of HDV in the world [8].

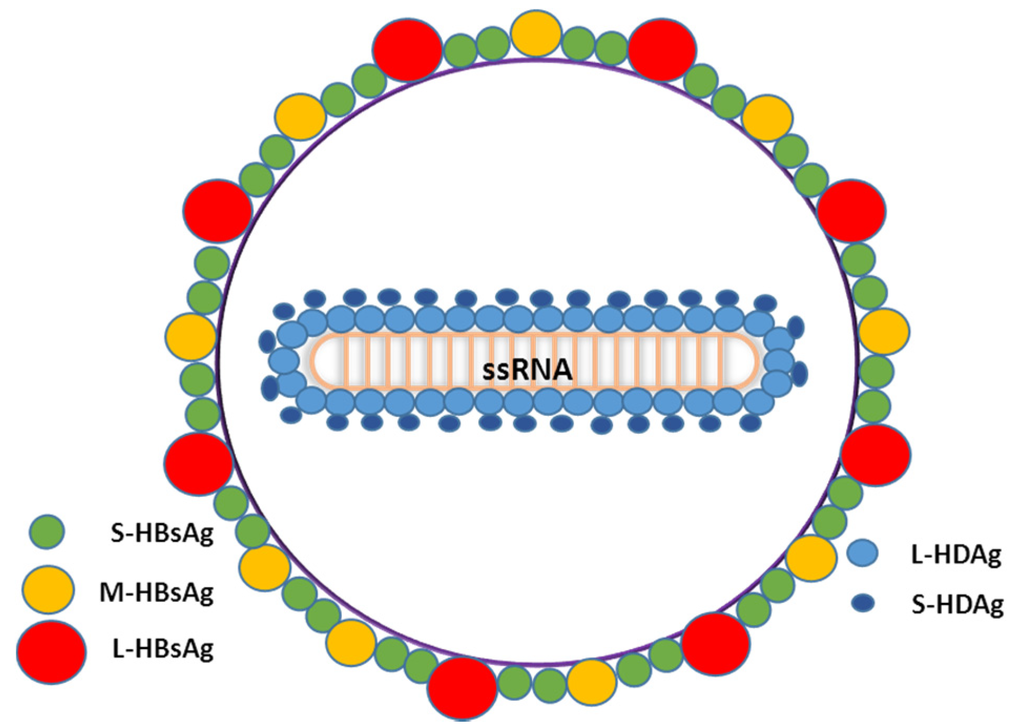
***Prevalence and Trends***

The prevalence of HDV infection has significantly declined in some regions of the world, such as Italy [9, 10], Spain [11], Taiwan [12], and Turkey [13]. This decrease is attributed to the implementation of HBV vaccination programs, systematic blood screening, prenatal screening, blood-borne safety measures among healthcare workers, the transition to single-use syringes, and increased public awareness of sexually transmitted infections [14].

Despite the decline in some areas, HDV prevalence remained stable in the 1990s in certain European countries, such as England [7], Hannover (Germany) [15], and Italy [14], and appears to be increasing in France [16]. This resurgence in developed countries is largely attributed to an increase in immigrants from Eastern Europe, Africa, the Middle East, Turkey, and the former Soviet Union. Immigration from endemic regions is not the sole contributor to the spread of the virus. Intravenous drug use, sexual practices, and body cosmetic procedures also play a significant role. Furthermore, in the 1990s, HDV emerged in new regions such as Russia [17], Northern India, Southern Albania, and China.

***Structure of HDV***

HDV is the smallest known RNA virus. It is a defective virus, requiring HBsAg for virion assembly, release, and transmission. While ribonucleoprotein formation in infected cells is independent of HBV, HDV cannot exit the cell and infect other hepatocytes without the HBsAg coating. The HDV virion is a spherical particle approximately 36 nm in diameter, containing an HBsAg envelope and a nucleocapsid encompassing the RNA genome in association with HDAg [18, 19]. Its viral envelope contains host phospholipids as well as three proteins derived from the hepatitis B virus – the large, middle, and small HBV surface antigens. The HDV RNA genome is approximately 1.7 kb long and consists of a single-stranded, circular RNA of negative polarity with a high degree of intramolecular base pairing, which allows it to fold into an unbranched rod-like structure under native conditions [20, 21]. The virus consists of the HDV RNA genome and around 200 molecules of hepatitis delta antigen, enclosed by the hepatitis B surface antigen (HBsAg) and a host lipid membrane. The HBsAg envelope protects the viral genome from the extracellular environment and determines the entry of HDV into hepatocytes.



**Figure 2.** Schematic representation of HDV virions describing all components of the viral particle. L-HDAg: HDV large antigen; S-HDAg: HDV short antigen; S-HBsAg: HBV small surface antigen; M-HBsAg: HBV medium surface antigen; L-HBsAg: HBV large surface antigen; ssRNA: single-stranded RNA [22].

***HBV Dependence and Viral Replication***

HBV is solely required by HDV for the acquisition of the HBsAg capsid, which facilitates attachment to liver cells and the propagation of infection [23]. Inside cells, HDV-RNA associates with multiple copies of HDV proteins, forming a ribonucleoprotein complex that is exported through the HBV envelope via incorporation into the lumen of the pre-Golgi compartment before being secreted [23]. Although HBsAg itself can encapsidate the HDV ribonucleoprotein and assemble into virions [24].

***HDV Genotypes***

The genotype of HDV is a factor that can influence the course of the disease. Currently, this virus is divided into eight major genotypes, differing by as much as 40% in nucleotide sequence [25].

Genotype I is the most prevalent worldwide and exhibits varying pathogenicity. In a study conducted in Taiwan, HDV genotype I-infected individuals had a lower remission rate and worse outcomes [26] compared to those with genotype II. Genotypes II and IV have been found in East Asia, causing relatively mild disease [27]. Genotype III has been linked to HBV genotype F and fulminant hepatitis in South America [28]. While the HBV genotype does not appear to influence the interaction of HBsAg with HDV, the HDV genotype may influence the efficiency of HBsAgvirion assembly. The deeper interaction between HDV genotype I and HBV may play a role in the widespread distribution and pathogenesis of HDV I globally [29].

***Course of Hepatitis D***

An individual can acquire HDV infection simultaneously with HBV (HBV/HDV coinfection), leading to both acute HBV and acute HDV, or as a superinfection in a chronic HBsAg-positive individual (HDV superinfection) [30].

The diagnosis of acute coinfection is made when markers of acute HBV infection (HBsAg, anti-HBc IgM, and IgG) and acute HDV infection (anti-HDV IgM and IgG, and HDV RNA in serum/plasma) are present concurrently.The specific marker of HBV+HDV coinfection is the detection of anti-HDV IgM alongside elevated anti-HBc IgM [31].

HDV superinfection in an individual with chronic HBV infection very often leads to severe acute hepatitis, which in 90% of cases progresses to chronic hepatitis D [32].

It’s known that HDV superinfection can cause unexplained exacerbation of hepatitis in individuals with previously known chronic HBV infection. The absence or low levels of anti-HBc IgM can differentiate superinfection from HBV/HDV coinfection. In the case of coinfection, the disease course is characterized by high levels of anti-HBc IgM [33].

Chronic HDV infection is diagnosed by the detection of elevated anti-HDV IgG, often associated with anti-HDV IgM and the identification of HDV RNA in serum. Since the presence of active HBV infection is crucial to both the outcome of HDV infection and the course of the disease [34].

Patients with chronic HBV infection require accurate HBV infection diagnostics based on HBeAg and anti-HBe marker status, and quantitative assessment of HBV DNA levels in serum [30].

Dynamically, both HBeAg status and HBV DNA should be re-evaluated during follow-up (typically every 3-6 months), especially if there are significant changes in liver disease profiles, such as normalization of alanine aminotransferase (ALT) or HDV RNA [35].

Currently, the correlation between plasma HBsAg marker levels and their fluctuations over time with prognosis and clinical outcomes in HBV patients remains under investigation. Conversely, preliminary analyses have shown that quantitative monitoring of serum HBsAg levels has been helpful in identifying patients who respond to treatment with pegylated interferon-α (pegIFNα), as a decrease in HBsAg levels was a necessary criterion for determining the achievement of definitive HDV RNA clearance [36].

***Novel Therapies for Chronic HDV Infection***

HDV virions initially attach to heparan sulfate proteoglycans (HSPG) and then to the viral receptor NTCP for entry into the host cell. After membrane fusion, the ribonucleoprotein (RNP) is released and further transported to the nucleus to initiate RNA replication. The incoming genome (G) serves as a template for the first rolling circle amplification [37].

HDV G multimersare synthesized and further cleaved to form monomers. HDV Ag can be edited by the ADAR1 molecule, triggering the synthesis of the long chain hepatitis delta virus antigen (L-HDAg), part of which is subsequently prenylated. The short and long chain hepatitis delta virus antigens (S-HDAg and L-HDAg) (intact and prenylated) are transported to the nucleus to regulate viral replication or bind to HDV RNA to form RNP. G-containing RNP can be exported to the cytoplasm and encapsulated in the HBV envelope through an interaction between L-HDAg and S-HBsAg [38, 39, 40, 41]. HDV virionsare released through the ER-Golgi secretory pathway. In addition to de novo HBV-dependent, envelope-dependent infection, HDV can also spread through cell division by an HBV-independent mechanism.

Nucleic acid polymers (NAP) block the release of HBsAg from infected hepatocytes. These compounds have been shown to uniquely eliminate serum surface antigen in DHBV-infected Peking ducks and achieve multiple logarithmic reductions or loss of HBsAg in patients with chronic HBV infection and HBV/HDV coinfection. It has been shown in ducks and confirmed in clinical studies (in humans) that the blockade of HBsAg release by NAP occurs through selective targeting of the assembly and/or secretion of subviral particles (SVP) [42].

Currently, new molecules are undergoing Phase 2 and 3 clinical trials. Clinically developed therapeutic strategies for chronic hepatitis B virus with delta agent target cellular structures.

***Advanced Therapeutics for Chronic HDV Infection***

The most advanced drug for chronic HDV infection is bulevirtide (BLV), formerly known as Myrcludex B. This novel molecule, bulevirtide (BLV), blocks de novo infection by effectively binding to the viral receptor NTCP [43, 44]. BLV binds to NTCP, effectively blocking viral entry.

Another drug, lonafarnib (LNF), prevents the prenylation of L-HDAg by inhibiting farnesyltransferase, thereby disrupting HDV assembly and secretion [45]. LNF inactivates farnesyltransferase, thus preventing the engulfment of hepatocyte RNA by HBsAg [46]. This leads to direct inhibition of virion release through target interaction, influences serum HDV RNA levels through an indirect effect, namely, by reducing the pool of HDV-producing cells through cell turnover and through sustained suppression of de novo infection.

Based on these differences in mode of action, the kinetics and magnitude of drug-induced suppression of serum HDV RNA levels differ significantly.

A third drug currently under clinical development is nucleic acid polymers (NAP) [47, 48]. These molecules are associated with multiple mechanisms of action, including affecting HBsAg secretion, inhibiting virions through direct interaction with HDAg [49, 50]. Furthermore, NAP is thought to influence immunologic mechanisms, but these mechanisms are not yet fully understood [50].

**Materialsand methods**

The study included 256 patients with positive HDV PCR from 13 regions of the Republic of Kazakhstan. Patients were recruited from regional hepatological centers in Kyzylorda, Turkestan, Mangystau, Atyrau, East Kazakhstan, West Kazakhstan, Pavlodar, Akmola, Karaganda, Aktobe regions, Shymkent, Astana, and Almaty.

Patient blood samples were analyzed for HBV and HDV genotypes and subgenotypes by PCR. HBV DNA extraction was performed using the GeneJET Viral DNA Purification Kit, ThermoScientific. PCR was conducted using specific primers. Purified PCR products were sequenced bidirectionally using forward and reverse primers.

**Results**

A total of 256 blood samples, positive for both hepatitis B surface antigen (HBsAg) and anti-hepatitis delta antigen (anti-HDVAg) as determined by ELISA, were collected from thirteen regions across Kazakhstan. These regions included Kyzylorda, Turkestan, Mangystau, Atyrau, East Kazakhstan, West Kazakhstan, Pavlodar, Akmola, Karaganda, Aktobe, as well as the cities of Shymkent, Astana, and Almaty.

All 256 samples tested positive for HDV by polymerase chain reaction (PCR) and were subsequently genotyped. Phylogenetic analysis and sequence comparison of the HDV PCR products revealed that all isolates belonged to genotype 1. This finding aligns with existing global data on the predominant spread of HDV genotype 1 worldwide.

However, despite belonging to the same genotype, the nucleotide sequences of these isolates exhibited a degree of variation, with pairwise identity ranging from 79.1% to 99.7%. This genetic diversity within HDV genotype 1 suggests ongoing evolution and potential for differences in virulence and response to treatment within the Kazakh population.

**Discussion**

The prevalence of HDV genotype 1 in Kazakhstan aligns with trends observed in other regions of the world. This genotype is known to be associated with higher viral replication rates and more aggressive disease progression, emphasizing the need for early diagnosis and effective treatment strategies. The observed genetic diversity within the HDV genotype 1 isolates, ranging from 79.1% to 99.7% identity, highlights the ongoing evolution of the virus and the potential for variations in virulence and treatment response.

The findings of this study have important implications for public health policy in Kazakhstan. The high prevalence of HDV genotype 1 warrants a focus on preventative measures, including vaccination against hepatitis B, screening programs for high-risk populations, and education about safe practices to reduce transmission. The study also underscores the need for ongoing research into the pathogenesis of HDV genotype 1 and the development of novel therapeutic approaches, particularly for patients with advanced liver disease.

This study, focusing on the influence of HDV genotypes on the course of chronic HBV infection with delta agent in the Kazakh population, contributes to a broader understanding of the complex interplay between these viruses. The results provide valuable insights for healthcare providers in Kazakhstan, enabling them to better understand the specific characteristics of HDV infection in this population and develop appropriate clinical management and public health strategies. Further research into the genetic and molecular mechanisms driving the distinct characteristics of HDV genotype 1 in Kazakhstan is needed to develop more targeted and effective treatments and improve the overall health outcomes for individuals affected by these viruses.

**Research Transparency:** The study had no sponsorship. The authors do not bear full responsibility for providing the final version of the manuscript in printed form.

**Acknowledgment:** We would like to express our gratitude to the staff of the A.N. Syzganov Novosibirsk Scientific Center of Surgery and the entire research group.

**Authors' Contributions B.S.Abzhaparova** conceptualization, validation, **G. Muratkyzy, Ch. Aitbayev** formal analysis, **S.T. Doskojayeva** writing original / draft preparation, writing review and editing, visualization, supervision.

**Funding** The study was funded by the A.N. Syzganov National Scientific Center of Surgery

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