Seroprevalence and Epidemiological Characters of Hepatitis Delta Virus among CHB Patients: Review Article

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Abstract:
Hepatitis delta virus (HDV) is a single-stranded circular RNA satellite virus. HDV requires the hepatitis B virus (HBV) envelope proteins for the dissemination of virus particles. Thus, hepatitis delta infection occur only in hepatitis B surface antigen (HBsAg)-positive individuals.

HDV is divided into 8 major genotypes: genotype I, distributed worldwide including the Middle East; genotype II, mainly in Asia; genotype III, in South America; genotype IV in Taiwan and the Okinawa islands; and genotypes V to VIII, in west and central Africa.

Patients who have HBV-HDV co-infection may be more prone to severe acute disease, fulminant hepatitis, accelerated progression to cirrhosis and hepatocellular carcinoma (HCC) than those infected by HBV alone.

Currently, it is believed that 15 million to 20 million people are infected with HDV; however, this estimation may have limited accuracy given the lack of systematic screening, the inability to identify HDV in immunocompromised patients, and the lack of HDV RNA testing, also, due to an accelerated progression to cirrhosis, resulting in a lower prevalence of the disease than might otherwise be expected.

The epidemiology of HDV infection worldwide was obscure, the prevalence of infection remained uncertain and geographic information are incomplete because many countries do not report the prevalence of HDV. Mapping the epidemiology of the infection is highly required.

In this review, we tried to provide the Seroprevalence and epidemiological Characters of Hepatitis Delta Virus among CHB Patients worldwide.

Key words: HBV, HDV epidemiology & prevalence

INTRODUCTION

Rizzetto and colleagues defined a new antigen, named delta, in the liver of hepatitis B patients with liver damage that was first supposed to be a hepatitis B antigen [1]. In subsequent
chimpanzee experiments the delta antigen was identified as a structural component of a distinct pathogen that required HBV during its life cycle [2, 3].

Later, the most serious form of viral hepatitis was due to hepatitis D (HDV) and it was reported that during eighties that the severe courses of acute infections and higher prevalence of advanced cirrhosis in patients coinfected with HBV and HDV than do those with HBV only [4].

Currently, it is believed that 15 million to 20 million people are infected with HDV; however, this estimation may have limited accuracy given the lack of systematic screening, the inability to identify HDV in immunocompromised patients, and the lack of HDV RNA testing, also, due to an accelerated progression to cirrhosis, more patients will likely die of HDV infection, resulting in a lower prevalence of the disease than might otherwise be expected [5].

EPIDEMIOLOGY

In the region of Central Africa, the Horn of Africa, the Amazons, eastern and Mediterranean Europe, the Middle East and parts of Asia, there are high rates of HDV carriage and the virus is endemic [6].

Genotype 1 of HDV is common globally, whereas in Japan, Taiwan, and the Russian Yakutia region, genotype 2 (previously called the genotype 2a) is the predominant [7]. Genotype 3 is the most divergent genotype that is widespread in the Amazon [8], while in Japan and Taiwan genotype 4 (previously 2b) is found [9]. HDV genotypes 5 to 8 develop in people of African origin, including migrants to northern Europe [10].

Two systematic reviews were recently published [11, 12] screened a wide range of studies showed that the number of people who were potentially affected by HDV was surprisingly high; Chen and colleagues suggested that up to 70 million people worldwide may be infectable with HDV [11] Miao et al. reported a prevalence of HDV of about 0.8% in the population and 13% in the total HBV carriers, equivalent to 48–60 million case worldwide [12].

Table (1): Prevalence of HDV worldwide.

<table>
<thead>
<tr>
<th>Area</th>
<th>Tested population</th>
<th>No. of HBs Ag +ve</th>
<th>HDVAb %</th>
<th>RNA %</th>
<th>Genotype</th>
<th>Cirrhosis</th>
<th>HCC</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>Randomly collected samples</td>
<td>234</td>
<td>2.1</td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
<td>[13]</td>
</tr>
<tr>
<td>Algeria</td>
<td>HBV chronic carriers</td>
<td>112</td>
<td>5.3</td>
<td>0.8</td>
<td>1</td>
<td></td>
<td></td>
<td>[14]</td>
</tr>
<tr>
<td>Australia; queensland</td>
<td>Individuals tested for HDV between 1997 and 2016</td>
<td>4407</td>
<td>4.1</td>
<td>30.7</td>
<td>7.8</td>
<td></td>
<td></td>
<td>[15]</td>
</tr>
<tr>
<td>Brazil; West amazon</td>
<td>HBsAg positive individuals</td>
<td>224</td>
<td>29.4</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Brazil</td>
<td>HBV chronic</td>
<td>409</td>
<td>23.9</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Area</td>
<td>Tested population</td>
<td>No. of HBs Ag +ve</td>
<td>HDVAb %</td>
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<td>Genotype</td>
<td>Cirrhosis</td>
<td>HCC</td>
<td>Reference</td>
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</tr>
<tr>
<td>Brazil</td>
<td>HBV chronic carriers</td>
<td>498</td>
<td>6.2</td>
<td>1</td>
<td>16.1</td>
<td></td>
<td></td>
<td>[18]</td>
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<tr>
<td>Burkina Faso</td>
<td>Different cohorts (blood donors, pregnant women, outpatients)</td>
<td>117</td>
<td>3.4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>Cameroon</td>
<td>Treatment-naive HBV-infected patients</td>
<td>128</td>
<td>22.6</td>
<td>7.8</td>
<td>N/A</td>
<td>25</td>
<td></td>
<td>[20]</td>
</tr>
<tr>
<td>Cameroon</td>
<td>HBsAg-positive cases</td>
<td>1928</td>
<td>46.7</td>
<td>34.2</td>
<td>1 6 7 8</td>
<td></td>
<td></td>
<td>[21]</td>
</tr>
<tr>
<td>Cameroon</td>
<td>HBV chronic carriers</td>
<td>426</td>
<td>6.5-27.3</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td>[22]</td>
</tr>
<tr>
<td>Cote D Ivoire</td>
<td>HBsAg carriers</td>
<td>87</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[23]</td>
</tr>
<tr>
<td>Egypt, Cairo</td>
<td>Chronic hepatitis B virus genotype D</td>
<td>121</td>
<td>8.3</td>
<td>9.9</td>
<td>2b</td>
<td></td>
<td></td>
<td>[24]</td>
</tr>
<tr>
<td>Egypt, Ismailia</td>
<td>Patients with elevated liver enzymes</td>
<td>129</td>
<td>0</td>
<td></td>
<td>0</td>
<td>-Ve</td>
<td></td>
<td>[25]</td>
</tr>
<tr>
<td>Egypt, Ismailia</td>
<td>HBsAg positive population</td>
<td>170</td>
<td>4.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[26]</td>
</tr>
<tr>
<td>Egypt, Upper Egypt</td>
<td>Chronic HBV carriers</td>
<td>216</td>
<td>14.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[27]</td>
</tr>
<tr>
<td>Egypt, Upper Egypt</td>
<td>HBsAg positive population</td>
<td>186</td>
<td>43</td>
<td>31.3</td>
<td>43.8</td>
<td>8.8</td>
<td></td>
<td>[28]</td>
</tr>
<tr>
<td>Gabon</td>
<td>Random rural inhabitants</td>
<td>303</td>
<td>27.7</td>
<td></td>
<td>1 7 8</td>
<td></td>
<td></td>
<td>[29]</td>
</tr>
<tr>
<td>Ghana</td>
<td>Hepatitis B-related liver diseases</td>
<td>53</td>
<td>11.3</td>
<td>N/A</td>
<td>N/A</td>
<td>1.9</td>
<td>1.9</td>
<td>[30]</td>
</tr>
<tr>
<td>Iran</td>
<td>HBV chronic carriers</td>
<td>25</td>
<td>100</td>
<td>48</td>
<td>1 2</td>
<td></td>
<td></td>
<td>[31]</td>
</tr>
<tr>
<td>Iran</td>
<td>HBs-Ag-positive patients</td>
<td>582</td>
<td>8.2</td>
<td>6.4</td>
<td>1 2 3</td>
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<td></td>
<td>[32]</td>
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<tr>
<td>Lebanon</td>
<td>HBsAg-positive cases</td>
<td>63</td>
<td>19</td>
<td></td>
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<td>[33]</td>
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<tr>
<td>Lebanon</td>
<td>HBsAg-</td>
<td>258</td>
<td>1.2</td>
<td>0.6</td>
<td>1</td>
<td></td>
<td></td>
<td>[34]</td>
</tr>
</tbody>
</table>
### Area Tested population No. of HBs Ag +ve HDVAb % RNA % Genotype Cirrhosis HCC Reference

<table>
<thead>
<tr>
<th>Area</th>
<th>Tested population</th>
<th>No. of HBs Ag +ve</th>
<th>HDVAb %</th>
<th>RNA %</th>
<th>Genotype</th>
<th>Cirrhosis</th>
<th>HCC</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mali</td>
<td>Blood donors</td>
<td>300</td>
<td>2.7</td>
<td>0.3</td>
<td>1</td>
<td></td>
<td></td>
<td>[35]</td>
</tr>
<tr>
<td>Mauritania; Nouakchott</td>
<td>Blood donors</td>
<td>447</td>
<td>20</td>
<td>12.5</td>
<td>1</td>
<td>5</td>
<td></td>
<td>[36]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>-HBV/human immunodeficiency virus (HIV)</td>
<td>306</td>
<td>4.9</td>
<td>3.2</td>
<td>1</td>
<td></td>
<td></td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>coinfect ed individuals -HBsAg+ve, HIV-negative blood donors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>HBV chronic carriers</td>
<td>2761</td>
<td>23</td>
<td>16.4</td>
<td>43</td>
<td></td>
<td></td>
<td>[38]</td>
</tr>
<tr>
<td>USA. Northern California</td>
<td>Chronic HBV carriers</td>
<td>499</td>
<td>8.4</td>
<td>N/A</td>
<td>73</td>
<td></td>
<td></td>
<td>[39]</td>
</tr>
</tbody>
</table>

### VIRAL GENOTYPES

Eight different genotypes of HDV are currently known, with 2 to 4 subtypes per genotype distinguished by a similarity of > 90 percent over the whole genome sequence. [40]. Over time, the distribution of the HDV genotypes has modified, owing to human migration patterns. Genotype 1 is actually the most prevalent globally and the predominant one in the north of America and Europe [41].

Genotype 2 was previously limited to Asia, but has now appeared in regions in the Middle East like Iran [31] and Egypt [25]. Genotype 3 can be found in South America primarily in the Amazon and is the most different of all genotypes with 40% nucleic acid divergence [42]. Genotype 4 is mainly found in Taiwan, China and Japan [6].

Genotypes 5, 6, 7 and 8 have been identified historically in Africa alone; however, recent studies identify migration genotypes 5, 6 and 7 to different parts of Europe. [43-45]. Central Africa, with the presence of genotypes 1, 5, 6, 7 and 8 is considered as the principal location for HDV diversification [46].

Different HDV genotypes are well known for affecting clinical outcomes. The most pathogenic of all HDV genotypes tends to be HDV genotype 3 [47]. Patients with HDV genotype 1 have lower recovery rates, more aggressiveness and worse outcomes than patients with the HDV genotype 2. [40].

For instance, Su et al. reported significantly lower rates of recovery in HDV genotype 1 than HDV genotype 2 (15.2% vs 40.2%, P = 0.007) and more adverse effects (cirrhosis, hepatocellular carcinoma [HCC] or death) (52.2% vs 25.0%, P = 0.005) [48]. That is because HDV genotype 1
is a more efficient than genotype 2 as regard virion assembly, RNA editing and more virus particles are secreted [49, 50].

**IMMUNOLOGY**

The CD8+ T cells of the virus are considered to play a vital role in HDV / HBV infection outcomes [51]. These cells detect HDV epitopes presented by multiple HLA molecules. The activated HDV-specific CD8+ T cells target conserved epitopes and potentially lead to the progress of disease. The memory-like HDV-specific CD8+ T cells are functional however, because of escape variants they are not able to remove HDV [52].

Other authors have stated that, in HDV patients, there is an active, functionally disabled and significantly reduced subgroup of innate-like T cells called the mucosa-associated invariant T cells (or MAIT cells) which are normally plentiful in peripheral blood and the liver [53].

**CLINICAL FEATURES AND NATURAL HISTORY**

Acute HDV infection can arise via either coinfection or superinfection. Acute coinfection occurs when an individual is simultaneously infected with HDV and HBV during the same exposure. The clinical course is similar to that of an acute HBV infection; however, and may be associated with increased risk of acute liver failure [54].

Acute HBV and HDV coinfection is diagnosed by detection of acute HBV markers, HDV antigen, HDV immunoglobulin M, and HDV RNA (if available) in serum. During an acute HBV and HDV co-infection, majority of patients recover and less than 5 % suffer chronicity [55].

Acute HDV superinfection occurs when an individual is infected with HDV in the presence of an established HBV infection (HBsAg positive). In patients with known HBV infection, acute HDV infection may be mistaken for a hepatitis B flare. In those who are unaware of their viral hepatitis status, initial clinical investigations may be mistaken for an acute HBV infection if superinfection with HDV is not considered. The clinical progress during acute HDV superinfection may be more severe than that during HBV and HDV coinfection, and acute liver failure can occur [56].

Diagnosis of acute HDV superinfection is made with the existence of HBV markers suggesting an established infection along with detection of HDV antigen, HDV immunoglobulin M and/or HDV RNA (if available) in serum. Acute HDV superinfection results in chronicity in most cases. [57].

Chronic infection with HDV is known to result in more serious liver disease than chronic HBV monoinfection [58]. Studies have described an increased rate of fibrosis progression in HDV infection compared with monoinfection with HBV or hepatitis C virus (HCV), and progression to cirrhosis with chronic HDV infection can occur in 5 years to 10 years in up to 80% of cases [6, 59].
Hepatocellular carcinoma (HCC) may also develop as a complication of cirrhosis in HDV infection, with risks reported to be up to threefold higher compared with HBV monoinfection [60]. A recent systematic review has identified an increased HCC risk for anti-HDV-positive patients with a pooled odds ratio of 1.28 compared to the HBV single infection [61].

For HDV-related cirrhosis, hepatic decompensation is twice as high as in HBV mono-infected patients with cirrhosis. Chronic HDV infection usually results in death due to decompensation or HCC [62, 63]. It has been suggested that HDV genotype plays a role in the rate of adverse outcomes, with genotype 1 being more virulent than genotype although other factors are likely important [48].

**DIAGNOSIS**

As described in table 2; Hepatitis D should be taken into consideration in HBsAg positive individuals or those who have suffered from HBV infection recently. The diagnosis of hepatitis D infection is confirmed after serologic tests positive for the virus. The detection of HDV antibodies (IgG or IgM anti-HDV) in HBsAg-positive patients is typically the first step in the diagnosis of HDV; followed by confirmatory HDV RNA viral load.

**Table (2): Diagnostic tests for hepatitis delta virus infection [55].**

<table>
<thead>
<tr>
<th><strong>Diagnostic test</strong></th>
<th><strong>Mechanism of action</strong></th>
<th><strong>Result if positive</strong></th>
<th><strong>Comments</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HDV serum Antigen</td>
<td>Detects HDV antigen in serum</td>
<td>Indicates acute and chronic HDV infection</td>
<td>No FDA-approved assay, rarely performed</td>
</tr>
<tr>
<td>Anti-HDV IgM antibody</td>
<td>Detects IgM antibodies against HDV in serum</td>
<td>Indicates acute and ongoing active HDV infection</td>
<td>Used as a gauge of activity when HDV RNA is not available</td>
</tr>
<tr>
<td>Anti-HDV IgG antibody</td>
<td>Detects IgG antibodies against HDV in serum</td>
<td>Indicates previous or current infection with HDV</td>
<td></td>
</tr>
<tr>
<td>HDV RNA qualitative</td>
<td>Detects the presence of HDV RNA in serum</td>
<td>Indicates active HDV infection</td>
<td></td>
</tr>
<tr>
<td>HDV RNA quantitative</td>
<td>Detects and quantifies HDV RNA in serum</td>
<td>Indicates active HDV infection</td>
<td>No FDA-approved assay</td>
</tr>
<tr>
<td>HDV genotyping</td>
<td>Determines HDV genotype in serum</td>
<td>Indicates HDV genotypes 1-8</td>
<td>Requires HDV RNA for it to be performed</td>
</tr>
<tr>
<td>HDV antigen</td>
<td>Antibody to HDV antigen staining of liver structure</td>
<td>Indicates active HDV infection</td>
<td>Available in few centers</td>
</tr>
</tbody>
</table>

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**Author roles:**
RS drafted the paper. All authors revised and edited the manuscript. All authors approved the final version.
REFERENCES

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