EPIDEMIOLOGY OF HEPATITIS DELTA VIRUS INFECTION IN LESS DEVELOPED COUNTRIES

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INTRODUCTION

The epidemiology of hepatitis delta virus (HDV) infection in less developed countries is marked by great contrasts. HDV may cause devastating outbreaks of fulminant and chronic hepatitis in the poorest countries in northern South America and Africa, yet is virtually absent in parts of Asia with similar or higher hepatitis B virus (HBV) endemicity. Several broad patterns of endemicity can be defined, yet explanations for the worldwide variations in endemicity and for the unusual severity seen in HDV infections in the tropics have so far escaped us. This article will review patterns of HDV infection in less developed countries, focusing on our studies of severe HDV infection in northern South America.

BACKGROUND

HDV is dependent on HBV and can only cause infection by coinfection with HBV or as HDV superinfection of an HBV carrier. For this reason, the epidemiology of HDV generally parallels that of HBV (Rizzetto, 1983). The pathways of HDV transmission are similar to those of HBV, and include direct or indirect parenteral exposure to blood or infective body fluids, perinatal transmission from mother to infant, and sexual transmission by either heterosexual or homosexual contact. Nevertheless, important differences in the relative efficiencies of HBV and HDV transmission are evident (Hadler and Fields, 1990). Perinatal HDV transmission is of minor importance, primarily because most
HDV-infected HBV carrier mothers are not highly infective for HBV (i.e. are anti-HBe positive), and rarely transmit HBV to their infants. Sexual transmission of HDV appears less efficient than for HBV, as evidenced by relatively low frequency of HDV among homosexual men worldwide. HDV is transmitted efficiently by direct blood contact, through contaminated needles, or indirectly through open skin wounds or environmental contamination. In less developed countries, transmission by direct or indirect blood contact and by heterosexual contact appears to be of greatest importance.

Based on its dependence on HBV, HDV frequency would be expected to correlate closely with that of HBV. Worldwide, HBV prevalence can be grouped into three levels - high (>5% HBV carriers), moderate (1-5% HBV carriers) and low (<1% HBV carriers) - and is relatively uniform within countries and within broad regions of the world. The highest HBV endemic areas, in Africa, Asia, and the Amazon basin of South America, would be expected to have the highest HDV prevalences.

Estimating HDV prevalence is problematic, however, because HDV increases the severity of chronic liver disease, and HDV infection prevalences are higher in persons with chronic HBV liver disease than in asymptomatic HBV carriers. To estimate HDV prevalence in any population it is best to compare prevalence in both HBV carriers and in persons with chronic HBV liver disease (Hadler and Fields, 1990). Based on these, four levels of endemicity and possible patterns of spread can be defined (Table 1).

**TABLE 1. Patterns of HDV Infection in Less Developed Countries**

<table>
<thead>
<tr>
<th>HDV Endemicity</th>
<th>HDV Prevalence in:</th>
<th>Age Groups Affected (yrs)</th>
<th>Outbreaks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic HBV Carriers</td>
<td>Chronic Liver Disease</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>&gt; 20 %</td>
<td>&gt; 60 %</td>
<td>5-40</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-19 %</td>
<td>30-60 %</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Emerging (Low)</td>
<td>3-9 %</td>
<td>10-25 %</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Very Low</td>
<td>&lt; 3 %</td>
<td>&lt; 10 %</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>
In highest endemicity areas, HDV superinfection in HBV carriers is a major cause of chronic liver disease, and may cause devastating outbreaks of fulminant hepatitis. In these areas, disease commonly affects both children and young adults age 5-24 years. Highest endemicity occurs in the poorest countries or populations in northern South America and Africa (Central African Republic); in addition, Romania has also reported high prevalences similar to these less developed areas (Ponzetto et al., 1985) (Fig. 1). Intermediate HDV endemicity is observed in disparate areas including parts of the Middle East, Africa and certain Pacific Islands and in the Asian Soviet Union (Ponzetto et al., 1985; Dimitrikakis et al., 1986). In such areas, HDV is an important cause of chronic liver disease, but infection occurs primarily among adults. Outbreaks are uncommon at present but may have occurred in the past.

Low (or emerging) HDV endemicity, in which HDV is a moderately important cause of chronic liver disease, is the pattern most often seen in developed countries, and in these areas is marked by high frequency in parenteral drug abusers and their sexual contacts (Rizzetto, 1983; Ponzetto et al., 1985). This pattern occurs in some less developed countries in Africa and Asia, and has been most carefully studied in Taiwan, where the rapid emergence of HDV among drug abusers and prostitutes may be signs of an emerging HDV problem for this region. Finally, HDV infection is essentially absent in many less developed countries in Asia and among native Americans and Eskimos; the reasons for absence are not apparent, but these populations are clearly fortunate in the failure of HDV to penetrate these regions.

HIGH ENDEMICITY REGIONS

Populations in northern South America serve as the prototype for high endemicity HDV infection. Investigation in western Venezuela in 1981 showed HDV superinfection of HBV carriers to be the cause of severe outbreaks of fulminant hepatitis among the Yucpa Indians (Hadler et al., 1984). The commonalities of this outbreak and two historic entities of severe acute hepatitis in Colombia (Santa Marta hepatitis) and the Amazon basin of Brasil (Labrea hepatitis) were rapidly recognized. The unique histopathology of such cases, including microvesicular fatty infiltration and eosinophilic necrosis of hepatocytes was described by Dr. Hans Papper at earlier symposia on HDV
infection (Popper et al., 1983).

Historical studies of yellow fever in Colombia led to the examination of viscerotomic specimens of liver from 1936 to present. The typical histopathology described above was identified in four distinct areas of Colombia (Buitrago et al., 1986). Illness occurred in a mixed race population (mestizo), primarily in males (63%) and was equally common in young children (age < 10 years), older children (age 10-19 years) and adults. Popper, reviewing 100 liver specimens from the Santa Marta region, found 70% to be positive for HDV by immunoperoxidase staining and demonstrated delta antigen in nuclei of morula cells. During the last 10 years, HDV outbreaks have been identified in several villages in the Santa Marta region, as well as in the Uruba region in northwestern Colombia and in the Amazon territories of Colombia.

High endemicity of HDV infection has been identified throughout the central and western Amazon Basin of Brasil (Bensabath et al., 1987; Fonseca et al., 1988). Studies in the Boca do Acre region show several characteristic features. First, prevalence of HDV infection is highest in persons with chronic hepatitis B (100%) and fulminant hepatitis B (72%), and lower in persons with benign forms of disease, including chronic HBV carriers (23%) and acute non-fulminant hepatitis B (28%). These greatly exceed prevalences in similar groups in developed countries. Prevalence among HBV carriers averaged 23%, but was relatively low in children < 10 years old (<5%), rising rapidly to 26% in 10-14 year olds and >40% in those over age 14. Prevalence also varied greatly among villages, from 0% in some small villages to 20-60% in other nearby towns.

This problem has been most intensively studied in Venezuela, where prospective studies have examined how the disease spreads and its clinical consequences. Following investigation of the initial outbreaks in 1981-1982, an HB vaccination program provided an impetus to screen all Yucpa Indians in 1983, and to identify all HBV carriers for prospective followup. HBV carriers were followed clinically by physical exam, and with serum specimens drawn for testing of alanine transaminase (ALT) and HBV and HDV serologic markers on a 6 monthly basis for 5 years.
Initial HDV prevalence was 34% among 216 known HBV carriers. During the next 5 years, 36 new infections, including 6 cases of fulminant hepatitis, were identified for a 10% annual attack rate among susceptible persons. HDV prevalence was initially highest in young adults 20-24 years of age (67%), and was also relatively high in children age 5-19 years (35-47%) (Fig. 2). New infections occurred most commonly in younger children (1-9 years) and young adults (15-19 years). Prevalence and incidence did not vary significantly with sex.

Disease distribution varied greatly by village location, with both prevalence and incidence highest in 6 villages in the South mountain base region, where 50% of 125 HBV carriers were infected at the start of the study and 80% by the end. Attack rates were moderate in the 6 South mountain villages, but disease prevalence and incidence were extremely low (<5% each) in the 5 Northern villages, despite presence of large numbers of HBV carriers and living conditions identical to those in the affected Southern villages. A case-control study showed that the most important risk factor for disease acquisition was living in a household with an acute case of HDV.

![Graph showing risk of HDV infection by age](image)

Figure 2. Risk of HDV infection in Yucpa Indians by age.
superinfection; virtually all persons who were so exposed became infected. A lower, but still elevated risk was also found for persons who lived in the same village or household as an HDV carrier, when compared to persons who lived in villages with no HDV carriers. Neither tattoos, injections, acupuncture, dental work, or presence of skin disease could be directly linked to HDV infection.

These data imply that HDV spreads most easily among HBV carriers within households and to a lesser extent within the same village, but does not spread easily from one village to another. Acute cases are more likely to spread disease, perhaps due both to higher intensity of viremia and to intensive exposure in the household necessitated by caring for a person with severe illness. The age specific pattern of illness suggests sexual contact among young adults and contact through open skin lesions, which are present in more than 40% of children, as the predominant pathways of transmission.

The clinical consequences were contrasted among HBV carriers with and without HDV infection. HBV carriers without HDV infection uncommonly showed persistent ALT elevation (5%) or organomegaly (10% with enlarged liver). In contrast, 70% of persons with HDV infection showed persistent increased ALT > 1.5 times normal, and in 25% ALT levels were more than 4 times elevated. About half showed significant organomegaly, particularly enlarged spleens. Mortality also depended on HDV status (Table 2). Among HBV carriers with HDV infection at the start of the study, mortality averaged 7% per year; 17 of 19 deaths were due to end-stage chronic liver disease. Among HBV carriers with new HDV infection, annual mortality reached 9.2%, including 6 deaths due to fulminant hepatitis, and 5 additional deaths due to chronic liver disease between 1 and 3 years after HDV infection. Mortality among HBV carriers not known to have HDV infection was 1.4%, including 3 cases of fulminant hepatitis for which HDV testing was not done. Finally, among non-HBV carriers of similar age, mortality was 0.4% per year, with no deaths due to liver disease.

Worldwide, high HDV endemicity and occurrence of severe outbreaks are not limited to South America. Outbreaks have been carefully studied in the Central African Republic and have recently been identified in Kashmir (Lesbourdes et al., 1986; Khuroo et al., 1988; Sarocco et al., 1988). The
TABLE 2. Mortality of HBV Carrier and Non-HBV Carrier Yucpa Indians During a Five Year Period.

<table>
<thead>
<tr>
<th>HBsAg Status</th>
<th>HDV Status</th>
<th>Number Studied</th>
<th>Died</th>
<th>Annual Mortality (%)</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>...</td>
<td>498</td>
<td>7</td>
<td>0.4</td>
<td>0 0 1 6</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>98</td>
<td>6</td>
<td>1.4</td>
<td>3 0 0 3</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>68</td>
<td>19</td>
<td>6.9</td>
<td>0 17 2 0</td>
</tr>
<tr>
<td>+</td>
<td>- +</td>
<td>36</td>
<td>11</td>
<td>9.2</td>
<td>6 5 0 0</td>
</tr>
</tbody>
</table>

AVH - Acute hepatitis; CLD - Chronic liver disease; Unk - Unknown

The focal nature of high HDV endemicity has also been described in careful studies in Kenya (Greenfield et al., 1986), in which wide variation of prevalence among different tribal groups and in different villages of the same tribe parallel observations in Brasil and Venezuela.

The unusually high mortality and unique histopathology of HDV infection in this region and in the Central African Republic contrast with those of HDV infection in developed countries and remain unexplained. Possible explanations include genetic or racial factors - which appear unlikely as severe HDV infection has now been described in black, Amerindian, and mestizo populations; nutritional factors or other cofactors unique to tropical climates, or differences in HDV strains. The latter may be supported by animal inoculation studies of the Venezuela and African strains, which have been reported in this symposium by Krawczynski et al and Faure et al. Inoculation of a gibbon and of woodchucks with these strains has caused severe illness and histologic findings similar to those in humans infected with these strains. Clearly, additional animal studies and sequencing of isolates from these regions will be necessary to conclusively answer this question.

MEDIUM AND LOW HDV ENDEMICITY

Moderate HDV endemicity is characterized by HDV prevalence...
of 10-19% among asymptomatic HBV carriers and 40-60% in chronic HBV liver disease. This pattern is seen in parts of Africa, the Middle East, the Asian Soviet Union, and certain Pacific Islands. Our direct experience is limited to American Samoa, where HBV-HDV screening was completed during an islandwide HB vaccination program in 1986. Among 1100 HBV carriers identified, 11% were HDV positive, a rate 1/3 that of the Yucpa Indians. Age specific prevalence was markedly different from that in the Yucpa, being extremely low in children and young adults under age 30 years (<5%) but reaching 20-33% in adults over age 40 years (Fig. 3).

Among HDV positive persons, fewer than 5% had a history of clinical hepatitis and only 7% had elevated transaminases, a proportion similar to that in HDV negative persons. Thus in American Samoa, HDV infection appears to be benign clinically; in addition prevalence may be declining as few children or young adults are becoming infected. This pattern could be the residuum of more widespread HDV infection in the past with the most severely affected having died due to chronic liver disease. Nevertheless, the infrequent history of clinical hepatitis and paucity of active liver disease both suggest important differences in disease severity compared to that in other developing areas.
A third pattern, of low but possibly increasing HDV endemicity, has been identified in Taiwan (Chen et al., 1988; Chung et al., 1989). Here, multiple studies have shown only 3% of asymptomatic HBV carriers and 10% of persons with chronic liver disease have HDV infection. Nevertheless, recent data has shown extremely high prevalence among parenteral drug abusers (>80%), moderately high prevalence in prostitutes (20%), and possible transmission from prostitutes into the general population. This pattern parallels HDV transmission observed in Europe and the United States, but is of greater concern because of the larger population of susceptible HBV carriers in Asian countries. Higher prevalence of HDV has also been seen in drug abusers in Thailand. Interestingly, clinical studies of HDV-infected drug abusers in Taiwan show little evidence of chronic liver disease, similar to our findings in American Samoa, and contrasting findings in South America.

CONCLUSIONS

Thus, HDV epidemiology in less developed countries is a complex tapestry of patterns, some of which are well defined and others which remain to be explained. The transmission patterns and severity in highest endemicity areas are well defined, and present a clear mandate for development of prevention programs by hepatitis B vaccine. In South America, recognition of epidemic HDV infection has been the major stimulus to begin vaccination programs in Venezuela, Colombia, and Brasil. The variable rate of spread in HBV endemic areas is well defined but not well explained; clearly, spread within families and villages is predictable, but movement from one village to another more haphazard. The worldwide distribution, particularly the relative low frequency in Asia, has not been explained. Finally, the relative severity in tropical Africa and South America, as contrasted with the mild nature of disease in the Pacific and Asia, remain unexplained; studies to define strain differences of HDV derived from these areas and to identify possible nutritional or genetic cofactors are of utmost importance in the near future.

REFERENCES


