AN OUTBREAK OF FULMINANT HEPATITIS DELTA IN THE WAORANI, AN INDIGENOUS PEOPLE OF THE AMAZON BASIN OF ECUADOR

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Abstract. An outbreak of delta hepatitis occurred during 1998 among the Waorani of the Amazon basin of Ecuador. Among 58 people identified with jaundice, 79% lived in four of 22 Waorani communities. Serum hepatitis B surface antigen (HBsAg) was found in the sera of 54% of the jaundiced persons, and 14% of asymptomatic persons. Ninety-five percent of 105 asymptomatic Waorani had hepatitis B core (HBc) IgG antibody, versus 98% of 51 with jaundice. These data confirm that hepatitis B virus (HBV) infection is highly endemic among the Waorani. Sixteen of 23 (70%) HBsAg carriers identified at the onset of the epidemic had serologic markers for hepatitis D virus (HDV) infection. All 16 were jaundiced, whereas only two of seven (29%) with negative HDV serology were jaundiced ($P = .0006$). The delta cases clustered in families, 69% were children and most involved superinfection of people chronically infected with HBV. The data suggest that HDV spread rapidly by a horizontal mode of transmission other than by the sexual route.

INTRODUCTION

Hepatitis B virus (HBV) is highly endemic among various indigenous groups of the Amazon basin of South America. Serologic markers for HBV infection have been found at rates of 25 to 83% among Amazonian peoples in Bolivia, Brazil, Peru, and Venezuela. A study of the Waorani, an indigenous people of the Amazon basin of Ecuador, reported antibodies to the Hepatitis B core (HBc) in 74% of people living in three villages, but none of those living in a fourth community. Infection with hepatitis D virus (HDV) can only occur in individuals who are also infected with HBV. Superinfection of HBV carriers with HDV, or simultaneous infection with HBV and HDV, has been found to cause fulminant and sometimes fatal hepatitis. Evidence of HDV infection has been found in various South American groups in which HBV infection is endemic and not in others. To our knowledge, HDV infection has never before been reported in Ecuador. We describe the investigation of an outbreak of fulminant hepatitis caused by HDV in the Waorani people of Ecuador, among whom we confirmed HBV infection to be highly endemic.

The Waorani are a semi-nomadic indigenous group of approximately 1,600 members. They live dispersed among tributaries of the Napo and Curaray Rivers in the Amazon basin of eastern Ecuador, some 70 to 100 km northeast of the town of Shell, in the province of Pastaza. The first sustained peaceful contact with the Waorani was made by North American missionaries in 1958. Since that time the Waorani have had limited but increasing contact with outsiders, including government teachers, health workers, military personnel, scientists, tourists, and petroleum workers and with other indigenous groups. Individuals or groups of men periodically leave their communities for several weeks to months to live and work in small towns or as petroleum workers in jungle camps. Although their culture is experiencing dramatic changes, the majority of the Waorani still maintain most of their traditional social structure and lifestyle: speaking their own distinct language, living in thatch homes, hunting game, fishing in the rivers, and tending small garden plots. Their semi-nomadic lifestyle has been expanded geographically by modern transportation. At the time of this study, there were 22 Waorani villages: 11 had airstrips that were accessible by light aircraft, five were within several hours of an airstrip by canoe or on foot, and six were accessible by road. Most of the villages with airstrips had solar-powered two-way radios.

Though sanitation practices vary somewhat between communities, most of the Waorani drink water from feeder streams and few have adequate latrines. Primary health care (including the administration of some injectable medications) is provided by Waorani health workers who have been trained by missionary nurses. Several Waorani have been trained to do dental extractions, fillings, and cleanings. Vaccination campaigns against measles and yellow fever have been conducted in the Waorani territory. Oil company physicians and dentists provide periodic visits to the communities to administer polio and DPT vaccines to children and to provide primary medical and dental care. To our knowledge, vaccination has been done with single-use, disposable needles and syringes. Patients with serious medical conditions are generally transported by light aircraft to Hospital Vozandes del Oriente in Shell.

MATERIALS AND METHODS

The outbreak. During the first four months of 1998, four Waorani with severe acute hepatitis were admitted to Hospital Vozandes del Oriente, a 30-bed mission hospital in Shell, Pastaza, Ecuador. The patients, three males and one female, ranging in age from 15 to 30 years came from three different communities. All were icteric upon admission, with elevated serum total bilirubin (7.9–21.0) and transaminase levels (SGOT 233–1950 IU/L, SGPT 122–3706 IU/L), and were positive for serum hepatitis B surface antigen (HBsAg). Three of the four patients had prolonged prothrombin times.
Of the two patients with encephalopathies, one subsequently died due to massive pulmonary and gastrointestinal hemorrhage. The remaining three patients eventually recovered with supportive care. There were reports of many jaundiced individuals in Waorani communities, and one additional death. The medical staff at the hospital was alarmed by this cluster of cases of HBsAg-associated fulminant hepatitis, and sought the assistance of the provincial ministry of health and others in investigating the cause and extent of the epidemic.

**Investigation of the outbreak.** An outbreak investigation was approved by the leadership of ONHAE (the Waorani indigenous organization) and the provincial director of the Pastaza ministry of health. Between April 16 and May 15, 1998, teams of physicians and nurses from Hospital Vozandes del Oriente and the ministry of health flew to all eleven airstrips in the Waorani territory, where they evaluated 1,225 people from 16 Waorani villages. With the help of village health workers and one of the investigators (PMK) who is fluent in their language, all individuals who were currently or recently jaundiced (defined as jaundice within the past six months) were identified. Many healthy persons were reluctant to provide blood samples, making it impractical to conduct either a mass screening or to obtain samples from randomized sub-groups of the population. Blood samples were drawn from all 16 of the currently jaundiced people and all 35 of the recently jaundiced individuals, and from 60 healthy volunteers. Demographic information was recorded, as well as histories of possible exposure to hepatitis cases and risk factors for transmission. Due to concerns about spread of the disease and suspicion that hepatitis B was involved, an initial dose of recombinant hepatitis B vaccine was given to all villagers seen.

The following month, the teams made a second visit to the same airstrips, where they evaluated 991 people from the initial 16 communities. No additional cases of jaundice were recorded, as well as histories of possible exposure to hepatitis cases and risk factors for transmission. During the first round of visits that evaluated 1,225 individuals, 16 people were observed by physicians to be jaundiced. During this time period, questionnaires were administered to 28 Waorani who had previously given blood samples. The questionnaires inquired about receiving injections, tattoos or dental work, using needles or thorns to remove insect larvae from their skin, visiting or working in oil company camps, contact with female sex workers, or having had a sexually-transmitted disease.

**Serologic analysis.** Upon collection in the field, blood samples were put on ice in a cooler, then transferred to a refrigerator within eight hours. Samples were centrifuged the morning after their collection, and the sera were subsequently analyzed for HBsAg at Hospital Vozandes del Oriente using the Hexagon HBsAg 1 Step test, manufactured by Human Gesellschaft Biochemica und Diagnostica MBH, Weisbaden, Germany. The remainder of each serum sample was frozen for later evaluation. HBsAg results were confirmed by enzyme-linked immunosorbent assay (ELISA) testing using Abbott Lab Commercial test kits at the U.S. Naval Medical Research Center Detachment (NMRCDD) in Lima, Peru.

Serum samples collected between April 16 and June 20, 1998 were sent to Laboratorio Izqueta Perez in Guayaquil, Ecuador where ELISA tests for IgM antibody to dengue, and IgM and IgG antibodies to yellow fever were performed. All of these initial serum samples that were positive for HBsAg were sent to NMRC for hepatitis D serology. Testing for HBc IgG and IgM antibodies was also done at NMRC. HDV genetic sequence analysis was performed at Georgetown University Medical Center in Rockville, Maryland using previously reported techniques.

**RESULTS**

During the first round of visits that evaluated 1,225 individuals, 16 people were observed by physicians to be jaundiced, and an additional 35 people were identified by family members and village health workers as having been icteric during the previous six months. These 51 currently or recently jaundiced Waorani ranged in age from one to 52 years (mean = 23); 36 were males and 15 were females. Fourteen of the 16 (88%) people with current jaundice lived in one of four communities (identified here as Communities A, B, C and D) as did 30 of the 35 (86%) reported to have been recently jaundiced. During the following year, only seven additional Waorani developed jaundice. Each one lived in a different community.

In total, blood samples from 173 people living in 15 different Waorani communities were tested for HBsAg. Forty-seven (27%) were positive; 31 males and 16 females, who ranged in age from one to 51 years (mean = 20). Thirty-one of the 57 (54%) currently or recently jaundiced individuals tested were positive for HBsAg. HBsAg was found in 16 of the 116 (14%) people tested who had not recently been jaundiced. Eight of 56 (14%) asymptomatic males and 8 of 60 (13%) asymptomatic females were carriers of HBsAg. Five of 45 (11%) asymptomatic females of reproductive age (defined as 15 to 45 years) were positive for HBsAg.

Five of the 159 (3%) serum samples tested were positive for HBe IgM antibody, and 150 of the 156 (96%) samples tested for HBe IgG antibody were positive. Of the 105 people tested who were not currently or recently jaundiced, 100 (95%) were positive for HBe IgG antibody (Table 1). A high prevalence of HBe IgG antibody was found in all age groups and in all communities sampled.

Sera from 23 of the 32 (72%) individuals found to be HBsAg-positive during the first round of visits were tested for HDV RNA and HDV antibody. Sixteen of these people...
that they had used a needle or thorn to remove insect larvae. It is interesting to note, however, that 16 of 28 responders stated that one of these camps worked clearing trails between Communities A, B, C, and D. Seven of the samples were collected from males and one was from a female, whose ages ranged from 2 to 35 years (mean = 16) (Table 2). All 16 individuals who had positive HDV serology had current or recent jaundice, and only two of the seven (29%) with negative HDV serology had been jaundiced. Therefore, among carriers of HBsAg, being jaundiced was strongly associated with the presence of an HDV marker ($P = 0.0006$). The 16 people with positive HDV serology lived in either Community A ($n = 6$), B ($n = 5$), C ($n = 3$), or D ($n = 2$), and included three pairs of siblings aged 15 or less (Patients 2 and 3, 7 and 8, 10 and 11), and a father and his 8-year-old son (Patients 12 and 14).

The interviews designed to identify the source of HDV were inconclusive. Members of Communities A, B, and D all reported that prior to the outbreak of delta hepatitis, men from their villages had come in contact with jaundiced workers in at least three different petroleum camps. Teams from one of these camps worked clearing trails between Communities A and B. An insufficient number of HDV-infected individuals completed questionnaires, making statistical comparison of potential risk factors impossible. It was interesting to note, however, that 16 of 28 responders stated that they had used a needle or thorn to remove insect larvae from their skin, with six of these 16 also admitting to sharing the needle or thorn with someone else.

Genotyping revealed that the HDV isolated from the Waorani is of Type III. Genetic sequence analysis of a segment of the HDV genome from eight of the HDV positive samples was performed, using two samples from each of Communities A, B, C, and D. Seven of the samples were from males and one was from a female, whose ages ranged from two to 35 years (mean = 20). None of the individuals tested were from the same nuclear family. The HDV sequences in seven of the eight samples (Patients 1, 6, 11, 12, 13, 15, and 16 [Table 2]) were 100% identical, and the remaining sample (Patient 9) was less than 0.5% different from the others.

We are aware of the deaths of four Waorani during 1998 and 1999, all of whom reportedly had been jaundiced. Two were brought to Hospital Vozandes del Oriente and found to be positive for HBsAg. Three additional Waorani required hospitalization for hepatitis during the same two years; HDV serology was positive in two patients and not performed in the third. Seven of the individuals with confirmed delta hepatitis were re-evaluated seven to 11 months after their acute illness. None had clinical signs or symptoms of hepatitis at the time of follow-up. SGOT levels were normal to mildly elevated (range 23–83 IU/L, mean = 57 IU/L) in four patients, and moderately elevated (range 118–432 IU/L, mean = 294 IU/L) in three patients.

Only two of the 151 (3%) serum samples tested for IgM antibody to dengue were positive. Neither of these individuals had been jaundiced recently. None of the 151 sera tested showed IgM antibody to yellow fever, however 56 of 151 (63%) were positive for IgG antibody to yellow fever virus.

**Table 1**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Not jaundiced no. (%)</th>
<th>Jaundiced no. (%)</th>
<th>Total no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>4/4 (100)</td>
<td>7/7 (100)</td>
<td>11/11 (100)</td>
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<td>6–10</td>
<td>7/8 (88)</td>
<td>6/6 (100)</td>
<td>13/14 (93)</td>
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<td>11–15</td>
<td>9/10 (90)</td>
<td>7/7 (100)</td>
<td>16/17 (94)</td>
</tr>
<tr>
<td>16–20</td>
<td>11/12 (92)</td>
<td>4/4 (100)</td>
<td>15/16 (94)</td>
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<tr>
<td>&gt;20</td>
<td>60/71 (97)</td>
<td>26/27 (96)</td>
<td>95/98 (97)</td>
</tr>
<tr>
<td>Total:</td>
<td>100/105 (95)</td>
<td>50/51 (98)</td>
<td>150/156 (96)</td>
</tr>
</tbody>
</table>

* Currently or recently jaundiced.

(70%) were also positive for an HDV marker; 12 were males and 4 were females, and their ages ranged from 2 to 35 years (mean = 16) (Table 2). All 16 individuals who had positive HDV serology had current or recent jaundice, and only two of the seven (29%) with negative HDV serology had been jaundiced. Therefore, among carriers of HBsAg, being jaundiced was strongly associated with the presence of an HDV marker ($P = 0.0006$). The 16 people with positive HDV serology lived in either Community A ($n = 6$), B ($n = 5$), C ($n = 3$), or D ($n = 2$), and included three pairs of siblings aged 15 or less (Patients 2 and 3, 7 and 8, 10 and 11), and a father and his 8-year-old son (Patients 12 and 14).

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**Table 2**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Community</th>
<th>IgM antiHBc</th>
<th>HDV RNA AntidHDV</th>
<th>Any HDV marker</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>11</td>
<td>A</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<tr>
<td>2</td>
<td>M</td>
<td>10</td>
<td>A</td>
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<td>F</td>
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<td>4</td>
<td>M</td>
<td>9</td>
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<td>5</td>
<td>F</td>
<td>26</td>
<td>A</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<tr>
<td>6</td>
<td>M</td>
<td>16</td>
<td>A</td>
<td>–</td>
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<tr>
<td>7</td>
<td>F</td>
<td>4</td>
<td>B</td>
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<td>8</td>
<td>M</td>
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<td>2</td>
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<td>M</td>
<td>25</td>
<td>C</td>
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<td>M</td>
<td>27</td>
<td>C</td>
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<td>M</td>
<td>35</td>
<td>D</td>
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**DISCUSSION**

All cases of fulminant hepatitis evaluated during this outbreak tested positive for HBsAg. Dengue was effectively ruled out as the cause of the epidemic, as was yellow fever. Although a large percentage of the Waorani had IgG antibody to yellow fever, none had IgM antibody. This was likely due to previous yellow fever vaccination or possibly infection by another flavivirus. Seventy-nine percent of the Waorani with current or recent jaundice lived in the four villages where all 16 confirmed cases of HDV genotype III infection were identified. HDV genotype III is unique to northern South America, and has been shown to be a cause of fulminant hepatitis in the region. Being jaundiced was strongly associated with delta virus infection in Waorani who were carriers of HBsAg. Taken together, these data support the conclusion that HDV genotype III was the principal cause of this outbreak of acute hepatitis.

Only two of the 16 patients with positive HDV serology (Patients 7 and 9) tested positive for IgM antibody to HBc, a marker of acute hepatitis B infection. Of interest, both of these patients were young children. The remainder of the individuals with HDV had a serologic pattern that was consistent with HDV superinfection of a chronic carrier of HBV. The absence of HDV RNA in two patients suggests that they may have been in the convalescent phase of infection. Though both of these patients had reportedly been jaundiced earlier, neither was jaundiced at the time their blood sample was obtained.
The fact that 14% of the asymptomatic individuals tested were found to be HBsAg carriers, and 96% of those who were tested showed antibody to HBC, indicate that HBV infection is highly endemic in this population. In fact, the Waorani have the highest HBV prevalence of any Amazonian group investigated to date.1–4,7–9

Many investigators have sought to determine the modes of transmission of HBV, particularly in populations where it is hyperendemic. Vertical (perinatal) transmission alone would not be adequate to produce the high prevalence of HBV infection seen among young Waorani children, among whom sexual activity is not known to occur. Other investigators have also found a high prevalence of HBV infection in young children in Amazonian populations where the disease is hyperendemic.1,4,8–10,11,20,21

Several alternative hypotheses have been proposed to explain the efficient horizontal transmission of HBV and HDV in hyperendemic populations. These include contact with infected skin lesions;24–31 insect vectors;24–31 cultural practices that involve puncturing or cutting the skin, receiving injections, the sharing of beds, razors or other personal items;1,2,31 dental care;22,32,33 and household contact.6

Although the source of delta virus infection in this epidemic could not be determined, several conclusions can be made regarding its transmission. The identical or nearly identical genetic sequences of HDV found in eight individuals from different families in four separate villages means that open skin lesions are very common among the Waorani, and that sharing needles and thorns for this purpose is also common. This practice could facilitate the transmission of HBV and HDV. We concur with previous investigators who found that open skin lesions are very common among the Waorani, particularly in children.10 Transfer of infected secretions from such lesions could potentiate transmission to others in crowded living conditions.8 We conclude that HDV can spread rapidly, possibly through contact with infected secretions from open skin lesions, the sharing of needles or thorns for larvae removal from the skin, or perhaps mechanical transmission by some as yet unidentified insect vector.

The introduction of delta virus into a population in which hepatitis B is highly endemic can have disastrous consequences, including a high prevalence of chronic hepatitis and considerable mortality.16,18 The availability of hepatitis B vaccine, the early lack of serologic data, and the difficulties involved in traveling to remote villages led to the initial decision to vaccinate all the Waorani while simultaneously investigating the cause of the outbreak and the prevalence of HBV infection. Teaching was repeatedly done in every village regarding methods to limit the spread of HBV. Anti-HBc seroprevalence data became available several months into the project and revealed that the vast majority of the Waorani had already been infected with HBV. At that point we opted to complete the series of three hepatitis B vaccines for all children under five years of age. Upon concluding the vaccination campaign in Waorani communities, the ministry of health initiated an ongoing hepatitis B vaccination program for infants of all ethnicities throughout the province. The need to vaccinate outsiders who enter Waorani communities has also been emphasized.

More research is needed to determine the mode of transmission of HBV and HDV in hyperendemic populations such as those found in the Amazon region. The expense and unavailability of local serologic testing, plus cultural resistance to blood sampling, make evaluation of the prevalence of HBV and HDV difficult in isolated Amazonian peoples. Meanwhile, the best long-term strategy for control of delta hepatitis where HBV is highly endemic appears to be universal infant vaccination.

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