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Hepatitis B Virus: Can it be a Vector-Borne Transmitted Infection?

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Abstract

The question of whether hepatitis B virus could be a vector-borne transmitted infection was around in the scientific field since the 1949. The majority of the studies agreed that Hepatitis B virus could be found in the bedbugs for a longer period of time than in the mosquitoes. Moreover, there was evidence that certain species of mosquitoes could transmit hepatitis B virus to animals leading to immunity; however, this did not reflect their ability to transmit the virus to humans because it was done under experimental conditions and on a small number of animals.

Given the great recent advance in the laboratory techniques, more research about this subject needs to be done to identify whether vector-borne transmission of hepatitis B virus can explain the hepatitis B cases with no apparent cause of infection.

Hepatitis B Virus: Can it be a Vector-Borne Transmitted Infection?

The question of whether the hepatitis B virus (HBV) could be a vector-borne transmitted infection puzzled many scientists since 1949 [1]. However, over a period of 29 years, a total of 12 research and two review articles were done to investigate this question. In addition, around five non-English language articles were published during the same period.

The HBV infection is one of the most important infectious diseases worldwide. Annually, around one million persons die of HBV-related causes. Estimates suggest that 40% of the world's population has had contact with HBV carriers or are HBV carriers. Worldwide, HBV prevalence varies from 0.1% up to 20%. According to Wasmuth, the prevalence of HBV is low (0.1-2%) in Western Europe (with wide variation within Europe), United States and Canada, Australia and New Zealand; intermediate (3-5%) in the Mediterranean countries, Japan, Central Asia, the Middle East, and Latin and South America; and high (10-20%) in Southeast Asia, China, and sub-Saharan Africa [2]. The predominant route of transmission of HBV varies in different geographic areas. For example, in low prevalence areas, the routes are mainly unprotected sexual intercourse and intravenous drug use. In contrast, perinatal infection is the predominant mode of transmission in high prevalence areas. In intermediate prevalence areas, the major route of transmission is horizontal transmission in early childhood [2].

HBV DNA is a direct parameter of viral replication and infectivity. HBV has a very high replication with a magnitude of 108 to 1013/ml per day [3]. In addition, a relatively small number of viruses are sufficient to cause infection in humans [3]. Generally, HBsAg carriers are considered contagious, with the degree of infectivity ranging from viraemic, highly infectious carriers to non-infectious carriers.

Given a virus with such high infectivity, can it be similar to other agents, like malaria and leishmania, and be transmitted via vectors, and if not, then why?

Literature Review

In 1975, Newkirk and colleagues studied the fate of HBsAg following a blood meal in two species of mosquitoes (Aedes Aegypti and Culex Tarsalis) and two species of hemiptera (Cimex lectularis and Rhodinus Prolixus). Both mosquito species and hemiptera species were experimentally fed on HBsAg positive blood. In the two mosquito species, the highest concentrations of HBsAg were detected for a maximum of 20 hours after feeding an infected blood. In contrast, the concentrations of HBsAg in the two hemiptera species remained positive for 5 weeks period and elevated after that suggesting a possible replication of the virus. Nevertheless, HBsAg was never detected in the feces of either species. The authors suggested that one possible explanation of these findings was the release of protease trypsin in mosquitoes after blood meal, which destructed the virus. As a result, for the mosquitoes to be effective mechanical transmitters, they would have to be killed during the second feeding within a few hours of incomplete HBsAg positive blood meal, making this route of transmission of low significance. Furthermore, the authors suggested that the potential mode of transmission of HBsAg via hemipteria could be through regurgitation or salivation during feeding or through mechanical transmission by killing the insect during its feeding [1].

One year later, Berquist et al. fed two mosquito species (Culex Tarsalis and Aedes Aegypti) on chimpanzees carrying HBsAg with unknown infectivity and then made them bite HBsAg negative chimpanzees. The mosquito tissues continued to be positive for low levels of HBsAg for few hours after blood meal. However, inoculation of susceptible chimpanzees with macerated pools of Aedes Aegypti mosquitoes after digestion of the blood meal did not produce hepatitis or serological evidence of the infection. Likewise, studying the mechanical transmission by interrupting feeding of Aedes Aegypti from HBs Ag-carrier chimpanzees and transferring them to susceptible chimpanzees did not produce hepatitis. In conclusion, these findings did not support the hypothesis that mosquitoes were involved in either biological or mechanical transmission of HBV [4].

In 1977, Rosa et al. fed triatoma (cone-nosed bugs) on patients with acute viral hepatitis B infection and collected the excreta of triatoma to test them for HBsAg via radioimmunoassay. In the first week after blood meal, 100% of the excreta were positive for HBsAg. Fifteen days later, only 5% of the excreta were positive for HBsAg and all of the samples were negative for HBsAg after thirty days. Meanwhile, individual homogenate of triatoma was negative for HBsAg. The aforementioned results suggested the possibility of passive transmission of HBsAg by feces. In contrast, intracellular replication did not occur [5].

In 1978, a cross sectional study of the prevalence of HBsAg in Cimex Lectularis at six localities in northern Transvaal (Messina, Waterpoort, Louis Triachardt, Pietersburg, Letaba, Potgietersrus). A total of 1,368 bedbugs of the species Cimex lectularius were collected mainly from huts in villages or on farms and then were tested in pools of 10 for the presence of HBsAg. None of 20 pools from Pietersburg was HBsAg-positive, but 32 out of 120 pools from the remaining localities were HBsAg-positive. Estimated infection rates per 1,000 bugs were 17,1 (Messina); 24,9 (Waterpoort); 28,4 (Letaba); 54,5 (Potgietersrus); and 67,0 (Louis Trichardt), with an overall rate of 30,6 per 1,000 bedbugs. Moreover, the engorged bugs showed an infection rate of 34, 8 per 1,000 bedbugs. Similarly, the unengorged bugs showed an infection rate of 25, 3 were HBsAg-positive. These very high infection rates, even in unengorged bugs, suggested that C. lectularius could be a vector of hepatitis B virus in the Transvaal. In addition, HBV transmission between humans via infected bedbugs might explain the high HBsAg-positivity among the residents of houses with bedbug infestations [6].

In 1979, Jupp and McElligott provided HBsAg positive blood meals to a colony of the common bedbug (Cimex lectularius L) in a series of five experiments. They found that the HBsAg persisted in the bugs for at least seven and a half weeks, but was undetectable after 18 weeks. They also were able to observe a trans-stadial transmission through one moult only while transovarial transmission did not occur. Moreover, adult bugs successfully transmitted the antigen into 3 out of 35 canisters of HBsAg-negative blood. HBsAg positive bedbugs were placed in a glass centrifuge tubes with closed tops and inverted into the ear of a rabbit and into the shaved abdomen of 10 guinea pigs. Antibody of HBsAg was detected in the serum from a rabbit on which HBsAg-positive adult bugs had fed as well as in the serum of two out of ten guinea-pigs on which HBsAg-positive 4th and 5th nymphal instars had fed. Generally, the results showed that biological multiplication and biological transmission did not occur in C. lectularius, but mechanical transmission did occur and was probably an important means of hepatitis B virus transmission among humans in South Africa [7].

In another study in 1979, a groups of researchers fed colony-reared Cimex hemipterus (Fabr.) once on blood positive for HBsAg from renal dialysis patients. In addition, they fed the insects on HBsAg negative blood from rabbits multiple times thereafter. In addition, they sampled the insects were at intervals and tested for HBsAg by radioimmunoassay. They found that the HBsAg was positive up to six weeks in the bedbug's body after the HBsAg positive blood meal. These results might explain the high rates of infection in bedbugs and might provide a support to the hypothesis that bedbugs might have a role in the transmission of HBV [8].

In 1993, in French Polynesia, researchers were concerned about the exceptionally high prevalence of HBV infection in children (74%), particularly in Nuku-Hiva Island. In addition, there was an evidence of a horizontal transmission pattern among the population of Marquesas archipelago. Therefore, they conducted a cross sectional study of 506 children (age range 2-11 years) and examined for the presence of skin lesions. Moreover, they attempted to detect HBV DNA in and on blackflies using two polymerase chain reaction methods. Although small amounts of HBV DNA were detected on the blackflies, the results did not support direct transmission of HBV by the blackfly S. buissoni as an explanation for the high infection rate on Nuku-Hiva Island. Nevertheless, the results suggested an indirect role of this fly through causing scratching of lesions on children. Contamination by close contact between children and or by means of contaminated hands and fingernails was proposed as a more likely explanation [9].

A couple of years later, another experimental study into which three genera of mosquitoes (Culex fatigans, Anopheles Stephensi, and Aedes Albopictus) were fed HBV infected blood and then let to bite the Tupaia Belangeri monkeys to search for evidence of infection in serological and liver biopsy samples. Not only was there both serological and liver biopsy evidence of HBV transmission via both Anopheles Stephensi and Aedes Albopictus, but there was also evidence of induced immunity against HBV [10].

In 2001, two experimental studies explored the possibility of HBV transmission via insects. In the first study, Cimex Lectularius L. were fed directly on patients with high titres of HBV and control uninfected patients. In contrast, Rodnius Prolixus were fed on HBV infected and HBV uninfected blood. Insects and insect excrement were collected at weekly intervals and tested for HBV DNA using the polymerase chain reaction. HBV DNA was persistently found in Cimex Lectularius L. (bedbugs) and excrement for up to six weeks after feeding on an infected meal. In contrast, although Rodnius Prolixus (kissing bugs) also showed persistent evidence of HBV DNA, HBV DNA could not be tested in excrement after day 14 because kissing bugs did not excrete fecal material two weeks after feeding. The results suggested that there was evidence that HBV DNA persist in Hemiptera [11].

In the second study, Blow et al. studied transtadial persistence and stercorarial shedding of hepatitis B virus (HBV) in common bed bugs, Cimex lectularius L., by using experimental infectious blood feedings on human volunteers, infectious intrathoracic inoculations, and virus detection by polymerase chain reaction and Southern hybridization. HBV persisted in bed bug bodies for up to 35 days after the infectious blood meal. Moreover, HBV passed transtadially through one molt regardless of instar, was shed in fecal droplets for up to 35 days after the infectious blood meal, but did not pass transovarially. Furthermore, in bugs inoculated intrathoracically, HBV was detected for 21 days after inoculation. In addition, the presence of nucleic acids amplified from a conserved core region of the viral genome in bodies and feces of C. lectularius indicated that the HBV virus could be mechanically transmitted in feces or when bugs were crushed during feeding [12].

Finally, in 2005, Ghoda and Shah hypothesized that "should mosquitoes be responsible for the transmission of HBV, then the incidences of malaria and acute hepatitis due to HBV should show a linkage" [13]. Consequently, they monitored the frequencies of malaria and acute hepatitis B at Gujrat Research and Medical Institute prospectively over three years. They wanted to observe seasonal patterns in the frequencies of the two diseases and to detect any correlation between the seasonal frequencies of two diseases. While malaria occurrence showed a clear seasonal pattern, no similar seasonal pattern for acute hepatitis B was observed.

Limitations

The majority of these studies were done in an experimental environment, where the insects were fed hepatitis B virus infected blood or made to bite highly infectious human patients. Therefore, the ability of the insect to be infected as a result of biting a human cannot be ascertained. Similarly, the ability of the insects to transmit the virus was studied by either exposing the animals directly to large number of infected insects or exposing the animals to a macerated pool of the infected insects, which did not reflect the ability of the infected insects to transmit the virus to humans.

Another important limitation is the small sample size of the animals under study. One of the studies was done on 10 guinea pigs and 1 rabbit. Two of the 10 guinea pigs and the 1 rabbit developed anti-HBs Abs, which might suggest that these insects are playing a role in developing immunity against Hepatitis B virus by inoculating a small amount of the virus that is enough to trigger the immune system and develop antibodies instead of developing infection.

In addition, the cross sectional study that examined the relationship between skin lesions and blackflies, lacked an objective assessment of the hepatitis B status among the children. Nevertheless, the theory that the contaminated finger and fingernails could be the mode of transmission of hepatitis B was plausible and needed to be further explored.

Lastly, the 2005 cross sectional study that examined the seasonal distribution of both malaria and hepatitis B ignored the fact that malaria has a short incubation period of about 14 days while hepatitis B virus has incubation period that may reach up to 180 days. Consequently, if mosquitoes transmitted hepatitis B virus, hepatitis B infection would not have shown the same seasonal distribution as malaria.

Most of the studies that were done between the 1970s and 2000 used neutralization and hemagglutination assays, which were usually affected by the stability of the agents used in the analysis. In addition, these assays usually required strict adherence to the protocol to get accurate results [1,4,6-8]. In contrast, some of experimental and epidemiologic studies done during the 1990 and 2000 used molecular technology methods, which had better sensitivity and specificity than the traditional methods used at that time to detect HBV in humans as well as in arthropods [9-11]. Nevertheless, false positive results due to contamination as well as false negative results from failure of the process are possible alternative explanation of the results [12-14]. It is also worth to notice that the detection range of the hybrid capture and signal amplification methods varies between 3,300 copies/ml to 1,400,000 copies/ ml [9-11,15]. The variability in the detection range might have affected the results, especially in the arthropods.

Since 2005, the possibility of HBV transmission via vectors had been addressed through reviews only, which emphasized that HBV could be detected in bedbugs but did not confirm HBV transmission via bedbugs [16-21].

Conclusion

Hepatitis B virus can persist in the bedbugs, but not in the mosquitoes. The role of the bedbugs in the transmission of HBV from infected humans to other uninfected humans is not clear yet and needs further studies. Similarly, the role of the bedbugs in causing mild infection that ends with immunity is still vague and unexplored enough. Since 2005, no further studies investigated this issue experimentally despite the significant technological developments in the viral detection and sequencing technologies in arthropods and humans. Therefore, collaboration between entomology, epidemiology, veterinary, and biology scientists is of utmost importance to clarify the nature of HBV transmission via bedbugs.

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