Hepatitis G, Hepatitis TT and Hepatitis Non-A,B,C,D,E,G,TT

Expires Sunday, June 30, 2019 Nursing

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Objectives

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2. Describe the route of transmission, the prevalence, and the potential significance of hepatitis TT.
3. Discuss the possible causes for hepatitis other than hepatitis A through G and TT.

Article

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Objectives: Upon the completion of this CNE article the reader will be able to:

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3. Discuss the possible causes for hepatitis other than hepatitis A through G and TT.

Introduction:

Viruses that primarily infect the liver, producing hepatic dysfunction, jaundice, light colored stools, and abnormal liver function tests, are commonly known as hepatitis viruses. The initial two viruses identified were called Hepatitis A and Hepatitis B. Everything else was essentially called Non-A Non-B viral hepatitis, for which it was thought that two distinct forms existed – one that was similar to A (with an oral-fecal route of transmission) and the other that was similar to B (primarily transmitted percutaneously).

However, the intense work that has occurred in the area of viral study (pushed by the disease AIDS) has resulted in the discovery of many different viral genomes of RNA and DNA composition. This has been true for the hepatitis viruses, as well. No other hepatitis viruses were really identified until Hepatitis C was discovered in 1989 (actually Hepatitis D was discovered in 1977, but is considered a defective virus that cannot exist without the presence of Hepatitis B). "E" was reported in 1990. For some reason, we skipped F and now we possibly have two more – G and TT. This article talks about these two new viruses and covers the issue of whether they are really pathologic or not.

Background on Hepatitis G:

In 1967, Deinhardt et al initiated human viral hepatitis transmission studies in marmoset monkeys. They identified an unknown (possibly infectious) agent they called "GB" in the blood of a 34-year-old surgeon (with the initials GB) who had developed acute hepatitis from an unknown source. No further significant work was really reported on this "GB agent" until 1995.

In 1995, Simons et al identified 2 flavivirus-like genomes in tamarin marmosets after passage with this "GB agent". They called them GBV-A and GBV-B. GBV-C was identified in a patient with unknown hepatitis shortly thereafter. They were found to be single-stranded RNA viruses that were distinct from the Hepatitis C virus. GBV-A, GBV-B, and GBV-C are now (collectively) often called Hepatitis G (HGV). Another caveat of the tremendous work that has been performed in the area of viral study is the isolation of different genome sequences, suggesting variants. For HGV, it has now been proposed that there are 5 distinct variants (or possibly six). Genotype 1 is West Africa, genotype 2 is USA/Europe, genotype 3 is Asia, genotype 4 is Southeast Asia, and genotype 5 is South Africa. A possible sixth genotype is the Pacific

Islands.

Once the core viral genome was elucidated, studies were performed on the actual prevalence of the virus. These studies examined the blood of high-risk patients and found a fairly high positive rate. For example, Zuckerman et al published their results in 1995, involving 101 multi-transfused patients, 112 intravenous drug users, and 1300 West African patients. The overall positive rate was 14% for the multi-transfused population, 12% for the intravenous drug user group, and 27% for the West African population. This study and others have shown that there is a fairly high prevalence (ranges of 2% to 40%) of this viral group in the patient populations that are at high risk for blood-borne infections.

Significance of Hepatitis G:

An important point to understand regarding the study of viruses in patient populations at high risk for certain diseases, is that if a virus is present, it does not necessarily mean that it is causing the problem. Often times in the push to find the answers, entities are guilty by association. Once hepatitis C and E were discovered, it was thought the answer to non-A non-B hepatitis was found. Indeed, a significant portion of non-A non-B hepatitis was caused by these two viral infections. However, cases of non A-E hepatitis still existed (and still occur today). In some of these patients, hepatitis G viral genomes were discovered and it was assumed that these entities were the cause.

However, several studies in the past couple of years have challenged whether or not hepatitis G is actually pathologic. It has been shown that the virus is transmitted from person to person percutaneously through blood products, IV drug abuse, and high risk sexual activity (similar to hepatitis B and C). It has been shown to replicate within the hepatocyte; however, it does not appear to damage the cell or affect liver function in the majority of patients. Both acute and chronic infections have been reported and the virus is sensitive to interferon.

Another finding that has been reported with hepatitis G is the presence of an anti-E2 antibody. This antibody is seen in patients who are no longer positive for the viral genome in the bloodstream. This probably means that this antibody is protective and can effectively rid the body of replicating virus. The significance of this is the potential for the development of a vaccine (if it is determined that one is needed). To quickly review, hepatitis B and C are very similar in their mode of transmission and their potential for long-term sequela in chronic carriers (cirrhosis and hepatocellular carcinoma). Fortunately with hepatitis B, if one is vaccinated and becomes immune, they are protected from the potential adverse effects of the virus. However, with hepatitis C there is no vaccine, which makes management and treatment more complicated and often less satisfying.

Chronic carriers of active viral replication with hepatitis G have been reported even though they do not seem to have hepatic dysfunction. Some of these patients have been followed for the potential development of cirrhosis or hepatocellular carcinoma, and this has also not been shown to develop at the present time.

Vertical transmission (also called perinatal transmission) of viruses from an infected mother to the baby during a pregnancy is another concern when dealing with blood-borne infections. Feucht et al in 1996 reported transmission of the virus to 3 babies (33%) delivered of 9 HGV infected mothers. In 1999, Wejstal et al reported on the perinatal transmission of the Hepatitis C virus and the Hepatitis G virus. Of 59 HCV infected mothers who delivered 71 children, only 2 became infected with HCV, a transmission rate of 2.8%. However, of 16 HGV infected mothers who delivered 20 children, 16 infants (80%) became HGV-RNA positive. Therefore, the perinatal transmission rate was much higher for G when compared to C. However, none of the 16 children developed any clinical or biochemical signs of active hepatitis (a finding that is similar to the studies in adults mentioned above).

Similarly, Palomba et al in 1999 published a report on 56 HIV positive and HCV positive pregnant women. Of these women, 41% were completely HGV negative and antibody negative and 30% were HGV negative but anti-E2 antibody positive. The remaining 29% (or 16 patients) were HGV-RNA positive (anti-E2 antibody negative). These 16 HGV-RNA positive women delivered 20 children. Nine (45%) of these children also became HGV-RNA positive (and 2 also became infected with Hepatitis C and 1 with HIV). In the 6 infants who only became infected with HGV, none developed clinical or biochemical signs of active hepatitis.

Summary of Hepatitis G:

The positive detection rate for the HGV virus in the bloodstream of high-risk patients in most studies is higher than that for Hepatitis C and Hepatitis B. The transmission is very similar to that of Hepatitis B and C, however, at this time, it

does not seem to have the same potential for future long-term disorders. Perinatal transmission also appears to occur with a range of 30% to 80% depending upon any co-infections with HCV or HIV the mother may have. Most studies that have analyzed umbilical cord blood for the virus at delivery are negative (which suggests a transmission from the mother to the baby through the birth process – again similar to hepatitis B and C). The presence of the anti-E2 antibody appears to be associated with the absence of HGV-RNA and may be a protective antibody. If this is true, the development of a vaccine is much more feasible, if it is determined that HGV is capable of producing disease.

The real question is whether or not this virus is pathologic or is it basically associated with patients who have a history of intravenous drug usage, blood exposure, or other related blood-borne viral infections (HIV, HCV, HBV, etc.). The overall consensus from most investigators is that HGV is a distinct RNA virus that can be transmitted between people and be found to actively replicate. However, at this time, it does not appear to be a cause for acute hepatitis nor does it produce liver dysfunction. If this virus is pathologic in some individuals (or becomes pathologic in the future – discussed below), it may require some other inducing agent or co-infection or some other substance in order produce clinical disease.

Background on Hepatitis TT:

Nishizawa and Okamoto et al in 1997 reported their identification of a non-enveloped single-stranded DNA virus in the blood of a patient with the initials "TT" who had post-transfusion hepatitis. They subsequently identified this virus in the blood of a few other patients with Non-A through G post-transfusion hepatitis in Japan. The virus has 3,739 nucleotides and now, up to 4 genotypes each with subtypes have been identified. It most closely resembles the Parvovirus group of viruses.

Prevalence studies were then performed on the TT virus. Simmonds et al in 1998 detected this virus in the blood of 1.9% of 1000 blood donors in Scotland who were HIV, HCV, and HBV negative. Naoumov et al in 1998 detected the TT virus in 25% of 72 patients with chronic liver disorders, but also discovered it in the blood of 10% of 30 laboratory personnel in London, and again questioned whether the virus was pathologic. Also in 1998, Charlton et al reported their results on a group of patients in the United States (from the Mayo Clinic). They detected the TT virus in 1% of blood donors, in 15% of patients with cirrhosis of the liver for unknown reasons, in 27% of patients with idiopathic liver failure, in 18% of patients transfused blood products, and in 4% of patients waiting for a liver transplant for other reasons. Finally, Okamoto et al in 1998 noted the association of this virus in the blood of patients with similar viral infections (such as HIV, HCV, HBV, and HGV) but also reported the detection of the virus in stool samples of viremic patients, suggesting the possibility of an oral-fecal transmission as well.

Significance of Hepatitis TT:

Several recent studies on Hepatitis TT (like Hepatitis G) have again questioned whether or not this virus is pathologic or just a marker for high-risk groups. Many patients with documented transmission do not show any clinical or biochemical signs of active hepatitis. Tuveri et al recently reported data regarding a large number of Hepatitis TT infected patients and concluded that it was commonly found in certain high-risk groups, but overall it was only weakly pathologic and was possibly only responsible for a few cases of active or chronic hepatitis. Chronic carriers of active viral replication have also been reported with the TT virus; however, to date, no protective antibody has been discovered.

Regarding the perinatal transmission of the Hepatitis TT virus, the results are similar to that of Hepatitis G. Sugiyama et al tested 70 children in Japan born to women who were either HBV or HCV positive. Five of these children and 4 siblings were TT virus DNA positive. The first positive detection of viral DNA occurred at or after 6 months of age, suggesting that transmission occurred at the time of delivery. None of the nine children, however, demonstrated any clinical or biochemical evidence of hepatitis.

In a conflicting study, however, Schroter et al published the results of the children delivered of 22 women who were HTTV-DNA positive in Germany. They detected the virus in the blood of every newborn except one. They also detected the virus in 74% of the breast milk samples from viremic mothers. However, the virus was detected in the bloodstream of most of the newborns (shortly after delivery) prior to the start of breast-feeding and therefore they felt that discouraging breast-feeding in viremic patients was not indicated.

Summary of Hepatitis TT:

Again, this virus like Hepatitis G is commonly found in the blood of patients at high risk for other parenteral related viral infections, such as HIV and Hepatitis C. This virus however, has been detected in some stool samples and may also be passed by the oral-fecal route. In addition, like HGV, it is not certain that this virus is actually pathologic. It appears to be found in patients with liver disorders but may not actually be the cause of the problem.

It is important to note, that for both HGV and HTTV, none of the studies have actually tested the blood of patients (adults or children with a documented transmission) on a daily basis to see if there is a short lived transient elevation of liver enzymes. It is possible that these viral infections in most instances are very mild and short lived. In addition, the long-term effects are still unknown and again, maybe they are only pathologic when combinations of factors, substances, or other viral infections are present.

Hepatitis Non-A, Non-B, Non-C, Non-D, Non-E, Non-G, Non-TT etc. etc.:

There still are numerous reported cases of acute fulminant hepatitis, unexplained hepatic failure, and cryptogenic cirrhosis (cirrhosis from unknown causes) that occur in patients who are negative for Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Hepatitis G, and Hepatitis TT. Therefore, other viruses probably exist that have yet to be discovered. It is also possible that many of these cases of acute hepatitis for unexplained reasons occur in individuals with exposure to hepatotoxins unrelated to viruses or some combination of all of the above.

Final Conclusion:

Upon reading the above information regarding these two new viruses, one might come to the conclusion that they are not important because they do not really produce any significant disease. However, we should never forget the potential of the future. HIV is probably the best example of this situation. As most people know, HIV is a very significant, debilitating, life-threatening infection. It came upon the world in the late 1970's and early 1980's as a new disease and as an unknown entity. However, once the viral genome was identified, studies have gone back and analyzed blood that had been saved from prior studies (performed 30 to 40 years ago) and HIV has been detected. However, there was no evidence that it was pathologic years ago. Something changed in its genetic makeup leading us to the HIV related diseases we know today. As healthcare professionals, it is important for us to know that Hepatitis G and Hepatitis TT are distinct replicating viruses that can be transmitted between people, similar to other viral infections. Therefore, continued education and safety measures on preventing viral transmission need to be taught and enforced. Hepatitis G and Hepatitis TT may become more pathologic in the future.

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About the Author(s)

Dr. Towers is currently Professor and Vice Chair of the Department of Obstetrics & Gynecology at University of Tennessee Medical Center Knoxville in the Division of Maternal-Fetal Medicine. He is still clinically active managing numerous high-risk pregnancies. He is also actively involved in research with over 90 publications in major medical journals. Though his research has spanned many areas in obstetrics, he has primary interests in drugs in pregnancy, infections in pregnancy, fetal heart monitoring, bleeding in pregnancy, and fetal lung maturity.

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She received her BSN and then her MSN from Wichita State University followed by a postmaster’s Women’s Health Nurse Practitioner Certification from Arizona State University. She has provided several presentations regarding nursing concerns related to Women’ Health Care and has frequently lectured on normal and high-risk obstetrical issues. She has practiced clinically in Kansas, California, and Arizona.