ADVANCES IN HEPATOLOGY

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Delta Virus Infection: Epidemiology and Initiatives to Intercept It

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G&H How prevalent is hepatitis D virus, and does it pose a significant epidemiologic threat in first-world nations?

RG Globally, an estimated minimum of 15 million people are infected with delta virus today. Delta virus does affect first-world countries. For example, the number of deaths due to delta virus infection in Germany is greater than the number of deaths due to HIV infection. The seroprevalence data are scant in the United States because only 2 groups—my research team at the California Pacific Medical Center in San Francisco and a group from Johns Hopkins University School of Medicine—have published data on delta virus, also known as hepatitis D virus (HDV), in the past decade. We really do not know the seroprevalence in this country for 2013, but a proposal has been made to the National Health and Nutrition Examination Survey to look at all the persons in its serum database who are infected with the hepatitis B virus (HBV) and then test those persons for delta virus. The data from that project may be more expansive, but using my seroprevalence data from the Bay Area—which found a seroprevalence rate of 7% for delta virus in our HBV population—it could then be predicted that between 60,000 and 90,000 persons in the United States have delta virus infection today.

As for other countries, Mongolia has the highest prevalence rate of delta virus infection in the world. It also has a very high rate of HBV infection as well, but the delta virus infection rate can approach 30% among persons infected with HBV. In fact, pockets of delta virus infection are found in very interesting places around the world. Some countries in central Africa have a high seropositivity rate for delta virus. There are also 2 pockets of high delta virus seropositivity in the northern part of South America: in the northern region of Amazonia and also the Orinoco River Valley in Venezuela. These locales are not really connected with any other place in the world, and the genotype of the delta virus is different from that found in North America and Africa.

Delta virus seropositivity is also very prevalent in Eastern European countries, such as Bulgaria. There are also pockets of delta virus seropositivity in Russia and central Asia, all the way down to Afghanistan and Pakistan. Wherever there is a relatively high rate of HBV infection, there is also a significant rate of delta infection, as seen in a recent study in Vietnam that found a 15% rate of HDV in a profiled population at a set of tertiary referral centers.

There are multiple genotypes of HDV, and the different regions of the world have unique genotypes. Genotype 1 is prevalent in the United States, Canada, Europe, and Eurasia; genotype 3 is prevalent in South America; genotypes 2 and 4 are prevalent in the Asia Pacific region; and genotypes 5, 6, and 7 are prevalent in Africa. The explanation for these varied genotypes lies in the long history of HDV in humans, human migration, and viral mutation rate.

G&H What are the common mechanisms of transmission?

RG In each of the highly endemic regions mentioned, the transmission pattern is probably a bit different, but in Eastern Europe, transmission is attributed to a mixture

of improperly sterilized medical instruments, including syringes, as well as illicit intravenous drug use and sexual transmission. In Mongolia, nonsterile syringes used for medical injections and scarification and other folk-culture habits that involve breaks in the skin are assumed to be the cause of HBV and delta virus transmission. Similar reasons for delta virus infection in Amazonia have been proposed as well as possible links to new world primate infections that "jump" to humans.

G&H What is the natural history of delta virus infection?

RG Vertically acquired HBV infection is associated with a 25% lifetime risk of cirrhosis or cancer. That rate probably doubles in patients in whom HDV infection then develops. If a patient has adult-acquired HBV infection, the lifetime risk of cirrhosis or cancer is typically 7%, but if the patient is infected with HBV and delta virus, and chronic delta virus infection develops, then the risk of development of cirrhosis or cancer is probably 5 or more times greater. So, chronic delta virus infection results in much more rapid progression to end-stage liver disease, need for liver transplantation, oncogenesis, and death.

Delta virus can both manifest in the presence of HBV or can be a primary coinfection. Patients with primary coinfection may have very severe disease or may experience spontaneous clearance of both HBV and delta virus. If delta virus is superimposed on chronic HBV infection, it is extremely likely that chronic HDV infection will develop, also leading to an accelerated disease pattern.

Delta is an RNA virus, and hepatologists believe that it is curable, whereas HBV is not curable. If HBV is treated with a first-line oral therapy such as entecavir (Baraclude, Bristol-Myers Squibb) or tenofovir, however, it has no effect on delta virus replication. The only treatment now available is interferon therapy. The cure rate with interferon appears to be only 15%.

G&H Could you explain the virology of this virus?

RG HDV is an approximately 40-nm diameter, enveloped RNA virus. Its genome is a single-strand, negative-sense, circular RNA of about 1700 nucleotides. Composed of only 1 protein, the hepatitis delta antigen is known to be expressed and forms a nucleocapsidlike structure with the genome. The genome and protein, in turn, are surrounded by a lipid envelope that is embedded with HBV and which the HDV encodes instead of its own envelope proteins. For this reason, natural HDV infections always occur in the presence of a coexisting HBV infection. The only viral element of HBV that HDV relies on is the hepatitis B surface antigen (HBsAg).

Table 1. Key Concepts About Hepatitis D Virus (HDV)

- HDV is the smallest human virus and is the causative agent of the most severe form of human viral hepatitis.
- HDV has a unique RNA genome, encoding its only known protein, the delta antigen. The genome and protein are encapsulated in a lipid envelope containing hepatitis B surface antigen (HBsAg), acquired from a requisite hepatitis B virus (HBV) coinfection.
- HDV presents as either an acute coinfection with HBV or as a superinfection in a patient with chronic HBV infection.
- The risk factors and clinical course of HDV are not different from those of the HBV infection, except that HDV tends to worsen the acute disease and accelerate the progression of chronic disease to cirrhosis, cancer, and death.
- There are no approved medications for HDV; historically, only therapies capable of completely eradicating HBsAg can abrogate HDV. Interferon α is the only available therapy for HDV, but prolonged treatment is required to achieve limited efficacy, and relapse is common.
- Understanding the molecular virology has advanced the development of potential new therapies, some of which are expected to soon enter the clinic.

During genome replication, 2 isoforms—1 small and the other large—form. The small delta antigen isoform promotes HDV genome replication, and the large delta antigen isoform has the ability to transdominantly inhibit viral replication. The large delta antigen isoform also contains a mechanism that encourages a prenylation reaction that is catalyzed by host cell farnesyltransferase. Prenylation of the large delta antigen is needed for it to interact with HBsAg and the HDV particle formation process. Inhibition of prenylation may deactivate HDV replication and is an avenue of research to lead to a cure of HDV infection irrespective of issues related to HBV infection. Table 1 notes key concepts about HDV.

G&H Given the low cure rate achieved with peg-interferon α, what is the prognosis for patients with chronic HDV infection?

RG In clearing HDV, the patient may have reversal of fibrosis or stabilization of liver disease. If the HBV can be controlled with oral therapies, there also can be further improvement in the liver disease status.

G&H What diagnostic tests are available for HDV infection?

RG Currently, commercially available tests are delta antibody and delta antigen serology. Patients with acute delta virus infection will be delta immunoglobulin M–positive, and those with chronic disease will be delta

immunoglobulin G–positive. Testing for delta antigen typically reflects the level of viral replication. If the HDV clears, delta antigens should be undetected. If delta RNA levels are moderate to high, delta antigen levels would be moderate to high as well.

An in-house, research-use–only method for delta RNA quantification via polymerase chain reaction testing has recently been published by the Centers for Disease Control and Prevention (CDC). Detection of HDV RNA will confirm active infection. In delta RNA testing, if delta RNA remains positive, then the risk of cirrhosis, cancer, and death and the need for liver transplantation is high, whereas if HDV clears, the chance of these complications is much lower. Thus, delta RNA testing is a very good prognostic tool.

Links for the forms and requirements for HDV RNA testing through the CDC are listed in Table 2. Providers with an interest in HDV also are invited to submit their delta cases to http://hepatitis-delta.org or contact the organization for more information at info@hepatitis-delta.org.

Table 2. Links for Forms and Requirements for HDV RNA Testing Through the CDC

- www.cdc.gov/search.do?queryText=delta+hepatitis&action=search&searchButton.x=0&searchButton.y=0
- www.cdc.gov/laboratory/specimen-submission/pdf/form-50-34.pdf
- www.cdc.gov/laboratory/specimen-submission/index.html

CDC, Centers for Disease Control and Prevention; HDV, hepatitis D virus.

G&H What initiatives are in place for public education about and prevention of delta virus infection?

RG The initiatives that are in place have to do with global HBV and hepatitis C virus management. If HBV transmission is prevented, delta virus transmission is prevented. If a person is immunized against HBV and does not get HBV, he or she cannot acquire delta virus infection. The initiatives include such programs as World Hepatitis Day, which occurs annually on July 28th and is sponsored through the World Hepatitis Alliance (see www.worldhepatitisalliance.org/en/who-what-where-when-and-how.html), Coalition to Eradicate Viral Hepatitis in Asia Pacific (www.cevhap.org/index.php/en/), and the European Association for the Study of the Liver (EASL), which has put together a global delta virus working group called the Hep-Net International Delta Hepatitis Study Group.

The American Association for the Study of Liver Diseases has not been that active in regards to education on delta virus infection, although it did present a satellite symposium at last year's meeting that was well attended. In addition, a European group led by Dr Jean-Michel Pawlotsky, the former secretary general of EASL, is developing a standardized assay system for the World Health Organization so that clinicians and laboratories around the world will be using the same primers, promoters, and other tools and techniques for delta virus screening to help ensure consistency and reproducibility of assays across the world.

G&H What is happening regarding clinical research in the management of delta virus infection?

RG Only 2 new treatments are currently in development, and they work through the same pathway. They are called prenylation inhibitors, and they are being researched at the National Institutes of Health (NIH). The NIH is looking for patients with HDV infection who are willing to travel to Washington, DC to be treated in a randomized, placebo-controlled, clinical trial of lonafarnib. Lonafarnib (Sarasar, Schering-Plough) is a farnesyltransferase inhibitor. The treatment course for patients meeting the eligibility requirements will be 28 days, and the NIH will cover some travel and housing expenses for eligible patients. Contacts are Christopher Koh at christopher.koh@nih.gov and Theo Heller at TheoH@intra.niddk.nih.gov.

Dr Gish has no conflicts of interest to disclose.

Suggested Reading

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