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The Mystery of Hepatitis E Seroprevalence in Developed Countries:

Is There Subclinical Infection due to Hepatitis E Virus?

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One of the mysterious aspects of hepatitis E virus (HEV) is the high seroprevalence of antibody to HEV (anti-HEV) IgG in developed countries where the infection is not endemic, despite the seldom-reported cases of acute clinical hepatitis caused by HEV in these countries. The reasons for this discrepancy are not clear, but different hypotheses have been proposed, including the low specificity and cross-reactivity of the anti-HEV IgG assays, the presence of avirulent HEV strains, and the high frequency of asymptomatic HEV infection.

In this issue of *Clinical Infectious Diseases*, Christensen et al. [1] reported the prevalence of anti-HEV among farmers and blood donors in Denmark in 1983 and among blood donors 20 years later. The study confirmed the high seroprevalence of anti-HEV IgG in Denmark, where clinical HEV infection is not endemic. The prevalence of anti-HEV IgG ranged from 30%-50% among blood donors and farmers who had samples obtained in 1983 to 20% among blood donors who had samples obtained in 2003. However, only 0-2 cases per year of acute hepatitis E are reported in Denmark. Christensen and colleagues concluded that the discrepancy was attributable to the high number of persons with asymptomatic HEV infection in Denmark and is not attributable to the nonspecific reaction of the serum samples. Age, contact with horses, and the presence of antibody to hepatitis A virus were associated with anti-HEV positivity in their study. The authors argued against ongoing low-level exposure as a mechanism for the association between age and prevalence of anti-HEV, because the prevalence of anti-HEV among the same age group depended on the year of serum sample collection. Persons born before World War II were more likely to be exposed to HEV than were those born after World War II. Consequently, Christensen and colleagues assumed that the reason for this birth cohort effect is improved sanitation. To our knowledge, their study is the first to report a birth cohort effect on the prevalence of anti-HEV. The study clearly identified that the dynamics of HEV seroprevalence among developed countries where HEV infection is not endemic are different. In some areas, such as Japan, the seroprevalence did not changed between 1974 and 1994, suggesting low-level exposure [2], although in Denmark, the seroprevalence of anti-HEV IgG has decreased in recent years. However, Christensen et al. [1] were not able to exclude the presence of low-level exposure to zoonotic HEV genotypes in Denmark as an explanation for the high seroprevalence (20%) despite improved sanitation.

The long-lasting anti-HEV IgG response reported by Christensen et al. [1], compared with the half-life of IgG (28 days) and with findings reported in other studies [3,4], needs clarification. Long-term immune responses have been reported in viral diseases, such as measles and hepatitis B; however, there is evidence of persistent infection in these diseases that supports

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continuous stimulation of the immune responses and long-lasting immunity. In the context of HEV infection, there has been no evidence of persistent infection in an immunocompetent host. Nevertheless, the mechanism of the long-term presence of anti-HEV IgG could be explained by the presence of low-level exposure, especially to zoonotic strains. The association of HEV seroprevalence with contact with animals and horses supports this hypothesis.

The role of HEV infection in the morbidity associated with pre-existing liver diseases in developed countries is an intriguing topic. In regions of endemicity, such as the Indian subcontinent, super-infection due to HEV in patients with cirrhosis may cause acute decompensation and may be associated with significant mortality [5-9]. Determination of the presence or absence of anti-HEV IgG would be valuable in countries of endemicity to decide whether cirrhotic patients should be vaccinated to prevent reversible worsening liver functions when a vaccine against HEV becomes commercially available. However, in industrialized countries, the significance of HEV superinfection has not been fully explored, despite the high prevalence among the general population. It would be interesting to examine the prevalence of HEV infection among cirrhotic patients in industrialized countries and to evaluate whether HEV infection correlates or affects morbidity associated with liver diseases.

Although subclinical infection was speculated to serve as a probable HEV reservoir in countries of endemicity, it may serve a similar role in industrialized countries. In a report from Japan [10], 2 individuals who experienced seroconversion developed infection without any elevation of liver enzyme levels and/or symptoms. These individuals were part of a follow-up study that used serum samples obtained periodically from healthy individuals over a 25-year period. The only abnormalities detected were the development of IgA antibodies and detection of HEV RNA for genotype 3 strains in the absence of IgM antibodies [10]. Similarly, in a study of HEV infection in patients from Japan who were receiving hemodialysis, 4 patients who acquired de novo HEV infection after the initiation of hemodialysis did not have elevations in enzyme levels, did not have symptoms, and did not develop anti-HEV IgM during or after the appearance of anti-HEV IgG in their serum samples [11]. Moreover, in a previous report from our laboratory, subclinical infection was associated with HEV-specific IFN-γ immune responses and seroconversion without clinical symptoms [12]. In contrast to previously published studies, a recent study from Japan reported that subclinical infection was associated with elevations in liver function levels, and the authors reported that 3% of participants with elevated liver enzyme levels (e.g., alanine aminotransferase level) had evidence of subclinical infection [13]; these findings raise a question about the definition of subclinical infection in healthy individuals. Is subclinical infection associated with anti-HEV seroconversion and/or elevation of liver enzyme levels or with only anti-HEV seroconversion without clinical signs of liver inflammation? Animal studies have revealed that subclinical infections cause an increase in liver enzyme levels or elicit a humoral immune response, compared with clinical disease in countries of endemicity [14].

The mechanisms for subclinical infection are still unclear. Such infection may be attributable to low-level exposure to infectious virus, the presence of existing protective immunity in the host, or the genotypes of the viruses. Exploration of those different mechanisms of subclinical infection requires diagnosis of subclinical infection and isolation of the viruses from the subclinically infected individuals; however, this has proven to be difficult.

The differences between genotypes producing symptomatic infection and genotypes producing subclinical infection could also be an important factor. HEV genotypes correlate with the severity of infection [15-17]. Genotype 3 does not cause disease in swine and appears to be attenuated in experimentally infected primates [18,19]. Furthermore, accumulating evidence suggests that HEV genotypes 3 and 4 are less pathogenic in humans, compared with genotype 1. During epidemics of infection due to genotype 1, the number of asymptomatic HEV

infections was estimated to be greater than the number of symptomatic cases. For example, during the recent outbreak of HEV infection in Darfur, the number of persons with mild symptoms was 6-fold higher than the number of persons with severe symptomatic cases, and more individuals had subclinical infections than had clinical symptomatic infections [20]. In outbreaks in Pakistan [21] and Nepal [22], the ratios of patients with mild anicteric symptoms to patients with severe jaundice were 4:1 and 3:1, respectively. Human infection due to HEV genotypes 3 and 4 may be much less virulent than infection due to other genotypes, with a ratio of asymptomatic infections to cases of acute viral hepatitis of ≥100:1. Thus, genotypes 3 and 4 have not been reported to cause outbreaks of acute viral hepatitis. However, a small number of genotype 3 and 4 isolates have been sequenced sporadically in samples obtained from patients with acute viral hepatitis in the United States, Europe, and other regions where HEV infection is rare [23-27].

Subgenotype differences or genotype shifts could also be the reason for the varying virulence of HEV viruses [28]. For example, asymptomatic subclinical infection can become significant if there is a genotype shift in industrialized countries; this phenomenon has been reported in the context of other viral infections.

In the absence of reports of high incidence of symptomatic infection in industrialized countries, the high seroprevalence of HEV may be merely a surrogate marker of subclinical infection. In summary, HEV infection is one of the newly emerging zoonotic infectious diseases that has not yet been fully explored, and it might have an unrecognized role in liver diseases in industrialized countries.

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