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Comparison of hepatitis E virus seroprevalence between HBsAg-positive population and healthy controls in Shandong province, China

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Abstract

Background: Persons with chronic hepatitis B (CHB) infection were reported to suffer severe disease after hepatitis E virus (HEV) superinfection, but the studies regarding HEV seroprevalence in this population were limited. A recent study in Vietnam found higher HEV seroprevalence among CHB patients compared with healthy controls.

Methods: A community-based case-control study was conducted in two counties of Shandong province, China, where hepatitis E incidence was at the highest (Rushan) and lowest (Zhangqiu) in the province based on data from routine public health surveillance. Four townships were selected randomly from each county and all residents in these townships were tested for hepatitis B surface antigen (HBsAg). Those tested positive for HBsAg (CHB group) and the 1:1 age and sex-matched HBsAg-negative residents (control group) were included. Anti-HEV IgM and IgG were tested and positive rates of IgG and IgM were compared between the CHB group and the control group.

Results: In total, 2048 CHB participants and 2054 controls were included in the study. In the CHB group, HEV IgG seroprevalence was 9.16% (95% *CI*: 7.47–11.09) in Zhangqiue and 38.06% (95% *CI*: 35.07–41.19) in Rushan ($P < 0.001$); the corresponding rates of IgM were 0.1% (95% *CI*: 0.002–0.54) and 1.57% (95% *CI*: 0.90–2.53), respectively ($P < 0.001$). HEV IgG seroprevalence was similar between CHB group and the control group in both counties ($P = 0.21$, $P = 0.47$, respectively) and the same results were found for the positive rate of IgM ($P = 0.103$, $P = 0.262$, respectively). Multivariable analysis showed the status of HBsAg was not independently associated with the status of anti-HEV IgG in either Zhangqiu or Rushan [$P = 0.187$, $OR = 1.23$(95% *CI*: 0.90, 1.68); $P = 0.609$, $OR = 1.05$ (95% *CI*: 0.87, 1.26)].

Conclusions: The seroprevalence of HEV varies greatly in different geographic areas, but the seroprevalence is similar between populations with and without CHB. CHB patients residing in high HEV endemic areas might be at higher risk for HBV-HEV superinfection.

Keywords: Hepatitis E virus, Chronic hepatitis B, Seroprevlance, Superinfection

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Background

Hepatitis E virus (HEV) was discovered in 1980's and has been documented to be prevalent in many countries [1]. HEV seroprevalence among the general population was 1.95% in the Netherlands [2], 5.3% in Japan [3] and 21% in the United States [4]. HEV is among the leading causes of acute viral hepatitis in developing countries [5] and is responsible for approximately 56,600 deaths in the world annually [6]. HEV infection is often asymptomatic, however in some special populations including pregnant women, patients with chronic hepatitis and those who are immunosuppressed, it might cause severe disease or chronic infection [7–9].

Although HEV is primarily transmitted by the faecal-oral route, its transmission by transfusion has already been documented [5]. HEV RNA was detected in 0.001% to 0.33% of blood donors in Australian, the United States and Qatar [10–12], suggesting the risk of HEV infection through transfusion. It is well known that hepatitis B and C could also be transmitted by transfusion. The studies from Turkey and Sweden found the seroprevalence of HEV was significantly higher among chronic hepatitis C patients compared with the general population [13, 14]. A study in Vietnam found significantly higher seroprevalence of HEV among chronic hepatitis B (CHB) patients [15], while the study in France found no difference [16].

Both hepatitis B and hepatitis E are endemic in China. The seroprevalence of hepatitis B surface antigen (HBsAg) and anti-HEV IgG was 7.18% and 23.1%, respectively according to a national survey in 2006 [17, 18]. The estimated number of persons with CHB is up to 90 million in China [17]. Although the superinfection of HBV and HEV has been widely reported in China [19, 20], all available studies are hospital-based focusing on clinical outcomes after superinfection. HEV seroprevalence among persons with CHB is poorly understood in China.

We conducted this study to evaluate HEV seroprevalence among persons with and without CHB in Shandong province, China.

Methods

Study population

Shandong province is located in eastern China. The province has 140 counties and a population of 97 million. The average seroprevalence of anti-HEV IgG was 11% among the general population [21]. This study was conducted during April and July 2014. The study population was selected by two-stage sampling method. First, all counties were ranked by HEV incidence reported through China National Notifiable Disease Reporting System (NNDRS) in 2013 and the county with the highest (Rushan) and the lowest (Zhangqiu) HEV incidence were selected. Second, four townships were selected by simple random sampling from each county. All residents in these townships were tested for HBsAg. All HBsAg-positive inhabitants and 1:1 age and sex-matched inhabitants negative for HBsAg were included in the study. The study flow chart is shown in Fig. 1.

Questionnaire survey

A face-to-face interview was conducted by the staff from the county level Center for Disease Control and Prevention (CDC). The information was collected on age, gender, education attainment, special occupations (seafood cultivation, processing and selling; swine laughter or selling), health habits including washing hands before dining, drinking boiled water and not-eating out of home and the histories of chronic diseases such as hypertension, heart disease, stroke, etc.

Sample collection and testing

Blood samples of 5 ml were collected from each participant. HBsAg was detected using Xinchuang ELISA kits (Xinchuang Biology Co., Xiamen, China). Anti-HEV IgG and IgM were detected using the Wantai ELISA kits (Wantai Biology Co., Beijing, China). HEV RNA was tested by real-time PCR for the serum positive for anti-HEV IgM (Invitrogen, one step qRT-PCR system). All tests were performed following the manufacturers' instructions and were conducted by staff at Shandong Provincial CDC.

Medical examination for HBsAg-positive participants

Further medical examination was carried out for HBsAg-positive participants in local hospitals, including physical examination, Ultrasound examination of liver, testing of HBV serological markers including antibody against HBsAg (anti-HBs), antibody against hepatitis B core antigen (anti-HBc), hepatitis B e antigen (HBeAg) and antibody against hepatitis B e antigen (anti-HBe), and HBV DNA level and Alanine aminotransferase (ALT) level. The participants were classified into HBV carrier, CHB patients, cirrhosis and hepatocellular carcinoma (HCC) according to the above medical examination. HBV carrier was defined as: (1) Tested positive for HBsAg; (2) had no signs and symptoms suggestive of hepatitis; (3) ALT level was within normal limit (< 40 IU/ml) [22]; (4) B ultrasound examination did not find any abnormalities in the liver. A case of chronic hepatitis patient was defined as: (1) HBsAg seropositive status lasted for 6 months or beyond; (2) had signs and symptoms suggestive of hepatitis; (3) HBV DNA was positive and ALT level increased(≥40 IU/ml) and (4) B ultrasound examination showed chronic liver disease. Cirrhosis and HCC were diagnosed mainly according to ultrasound findings.