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Low prevalence of hepatitis E infection among pregnant women in Madrid, Spain

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SUMMARY:

Hepatitis E virus, a cause of sporadic hepatitis in developed countries is present in Spain. The aims of this study were to determine whether the prevalence of IgG anti-hepatitis E virus antibodies has increased in recent years in Spain and the prevalence in a study population at risk of developing the disease following the infection. Serum samples from 1040 women in the first trimester of pregnancy were studied. The prevalence rate of 3.6% has not increased significantly since 1999 in spite of the large number of immigrants from endemic regions. IgM anti-HEV antibodies were detected in 0.67% of the patients suggesting that although subclinical infection exists the prevalence is very low. The reasons for the differences in the morbidity of HEV in pregnant women in different geographical areas remain unclear. Good hygienic measures and public health conditions are important factors for ensuring low prevalence of hepatitis E in Spain.

INTRODUCTION

Hepatitis E virus (HEV) is a major cause of acute viral hepatitis in developing countries. In Europe many cases of autochthonous hepatitis E have been recognized recently in

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patients without any evidence of travel to endemic areas; this has been suggested as a distinct clinico-epidemiological entity and the name of ¨indigenous to developed countries hepatitis E¨ (IDC HE) has been proposed (Teo,2006). Acute infection by HEV generally causes mild and self-limiting hepatitis but it can also result severe clinical fulminant hepatic failure in pregnant women and is associated with very high mortality particularly during the third trimester in endemic areas (Mushahwar, 2008). Interestingly, this feature has never been reported in industrialized countries where genotype 3 is the prevalent genotype in contrast to genotypes 1 and 2 which are found most frequently in developing countries. The reasons for the differences in the morbidity and outcome of HEV in pregnant women in individual countries remain unclear. Prevalence studies conducted in Spain have reported a wide range of prevalence rates from 0.6% in pregnant women in the north of Spain (Suarez Gonzalez et al, 2004) to 7.3 % in the general population of Catalonia (Buti et al, 2006).

There has been a large influx of immigrants to Madrid in recent years with figures in June, 2009 as high as 17.1% of the total population and 27.3 % in some of the poorer neighbourhoods (Consejeria de Inmigración, 2009). Since a large number of pregnant women in Spain come from endemic countries and hepatitis E is more severe in this group of patients, it is important to determine the characteristics of HEV infection in this risk group.

The aim of this study was to investigate the seroprevalence of HEV infection in a representative sample of pregnant women and determine the clinical features in relation to the presence of IgM anti-HEV antibodies in the blood of the patients.

PATIENTS AND METHODS

Serum samples from 1040 pregnant women, who attended the Obstetric Department of the Ramon and Cajal Hospital (Madrid, Spain) for routine screening were included in this study. Serum was taken from the patient during the first trimester of pregnancy during routine antenatal check-ups. One hundred and eighty one patients were studied in 2007, 588 patients in 2009 and 271 patients in 2010. Habitat (rural or urban), age, ALT and AST and clinical symptoms were assessed in all patients. The sample size for an expected prevalence of IgG HEV antibodies of 2.9% in Madrid (Mateos, 1999), an alpha error of 5% and a precision of + 0.001 was 1,046 pregnant women.

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IgG anti-HEV antibodies were detected in serum by a commercial enzyme immunoassay (EIA) (HEV Ab, DiaPro Diagnostic Bioprobes, Milan, Italy) following the manufacturer's instructions. All positive samples were studied further for the presence of IgM anti-HEV antibodies (HEV IgM, Dia.Pro Diagnostic Bioprobes, Milan, Italy). A result was considered positive by both tests when the ratio of the sample optical density and the cut off value was higher than 2. Positive results by EIA were confirmed by Western blot analysis (RecomBlot HEV IgG/IgM, Mikrogen, Martinsried, Germany). In addition, HEV RNA was amplified by reverse transcriptase (RT)-nested PCR (Fernández Barredo et al, 2006) in all serum samples with IgM anti-HEV.
The Institutional Ethic Committee approved the study and written informed consent was obtained from all the patients.

RESULTS

All the patients included in this study were living in urban areas in Madrid. The age range was 14 to 45 years (media: 30.6 years). None of the patients presented clinical symptoms associated with hepatitis when the blood sample was drawn. IgG anti-HEV antibodies were found in 2.1% (5/181) of the 2007 group, in 4.08 % (24/588) of the 2009 group and in 3.3% (9/271) of the 2010 group. The overall prevalence was 3.6% (38/1040). IgM anti-HEV antibodies were detected in 0.67 % (7/1040) suggesting acute or recent infection. ARN HEV was negative in all 7 samples IgM anti-HEV positive tested. None of them presented clinical symptoms related to viral acute hepatitis. ALT and AST had normal values in all the patients who presented IgG and IgM anti-HEV in serum. Six oh those patients were Spanish and 1 was from Egypt.

DISCUSSION

HEV circulates in Spain. The virus has been isolated from sewage (Pina S et al, 2000) and it is considered a zoonotic disease and the most probable reservoir for the human population is swine (Fernández Barredo et al, 2007). HEV has been the cause of sporadic acute hepatitis E in Spain (Perez-Gracia et al, 2004) and is considered as an occupational disease (Perez Gracia et al, 2007). However in industrialized countries, the transmission routes for autochthonous HEV infections remain unknown although

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food and environmental routes are considered the most important (Teo, 2010). Since all the patients included in this study were living in urban settings, direct animal contact was not a probable transmission route. Obviously, exposure to food in the kitchen to raw pork or poultry cannot be excluded neither can shellfish which is consumed frequently in Spain. The prevalence of IgG anti-HEV antibodies was 2.1 %, 4.08% and 3.3 % in the group of patients studied in 2007, 2009 and 2010 respectively. The overall prevalence was 3.6%. In studies conducted in 1999 in the same area, a prevalence of 2.9% was found (Mateos et al, 1999). The odds ratio was 0.8 and the 95% CI was 0.67-1.73. This difference was not statistically significant ($p< 0.810$). Interestingly, seven (0.67 %) patients presented IgM anti-HEV antibodies in blood. All of them were asymptomatic cases of hepatitis E occurring during the first trimester of pregnancy. Unfortunately it was not possible to test any further blood samples since these patients were healthy during pregnancy. No risk factors for transmission were found by interviews held with these infected patients. In contrast, pregnant women in endemic areas suffer very frequently severe hepatitis and even death. The reasons for the difference in the outcome of HEV in different geographical areas remain unclear but it could be the result of early childhood exposure to HEV, producing long-lasting immunity and/or modified subsequent responses of exposure to the virus. Alternatively, the predominant HEV genotypes in Spain could be less virulent than those in developing countries. The HEV genotypes circulating in endemic areas, mainly genotype 1 and 2, are very uncommon in industrialized countries. In conclusion, the data obtained during this study demonstrate that asymptomatic hepatitis E occurs in pregnant women in non-endemic countries at a very low rate (0.67 %). The HEV genotypes and subtypes circulating in different countries can be responsible for the different geographical morbidity in pregnant women (Navaneethan et al, 2008); seroprevalence of IgG HEV antibodies has not increased in Spain in these recent years (3.6 %), considering the seroprevalence studies conducted in the same area in 1999 (2.9%) (Mateos et al, 1999). Discrepancies between the prevalence rates found in Spain by other authors (0.6%-7.3%) (Suarez Gonzalez et al, 2004; Buti et al, 2006) may be due to epidemiological characteristics of the patients studied (rural or urban areas, gender, age, profession), methodology and lack of confirmation with other tests such as Western blot. The geographical situation inside the country can also have a role since a very high prevalence has been reported in south west France (Mansuy et al, 2008). The good hygienic measures and public health conditions in Spain may be the most

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important factors in maintaining the low prevalence rate of hepatitis E which is not considered a major health problem at the moment. Nonetheless if the number of clandestine immigrants from endemic countries continues to increase in Spain and the route of transmission of HEV is not established completely in order to prevent the spread of HEV, this favourable epidemiological situation may change in future years.

Conflict of interests

The authors declare that there is not any conflict of interest in the present report.

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