

Frequency of antibodies against the hepatitis C virus in patients with hepatic cirrhosis in Yucatan, Mexico

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Frecuencia de anticuerpos contra el virus C de la hepatitis en pacientes con cirrosis hepática en Yucatán, México.

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Abstract

Objective. To report the prevalence of antibodies against the hepatitis C virus (anti-HCV) in a group of patients with hepatic cirrhosis (HC). **Material and Methods.** A prospective transversal and descriptive study was carried out from March 1998 to May 1999. Study subjects were 153 patients; 117 (76%) male and 36 (24%) female, diagnosed with HC. They were attended at the General Hospital Agustín O' Horan and at Regional Research Center Doctor Hideyo Noguchi, in Merida, Yucatan, Mexico. A clinical-epidemiologic questionnaire completed by interview was used for data collection. Anti-HCV were detected using a 2nd generation enzyme-linked immunosorbent assay (ELISA-2). To confirm diagnosis, a second generation recombinant immunoblot assay (RIBA-2) was used. Hepatitis B surface antigen (HbsAg) and antibodies against the hepatitis B core antigen (anti-HBc) were determined using ELISA. The presence of anti-HCV was related to the epidemiologic variables of study subjects. The prevalence of anti-HCV was obtained and the frequency of the characteristics obtained by interview were compared among the positive and negative patients through the χ^2 test and the Fisher's exact test, as needed. **Results.** Among patients with HC (35/117 (30%) male and 14/36 (39%) female), 32 % were positive to anti-HCV. Alcoholism was present in all seroreactive males and absent in all positive females ($p < 0.001$). Data obtained

Resumen

Objetivo. En este estudio reportamos la prevalencia de anticuerpos contra el virus C de la hepatitis (Ac-VCH) en un grupo de pacientes con cirrosis hepática (CH). **Materiales y métodos.** Se hizo un estudio prospectivo, transversal y descriptivo, de marzo de 1998 a mayo de 1999. Se estudiaron a 153 pacientes (117 (76%) hombres y 36 (24%) mujeres) con diagnóstico de CH, que eran atendidos en el Hospital General Agustín O' Horan y en el Centro de Investigaciones Regionales Doctor Hideyo Noguchi, en la ciudad de Mérida, Yucatán, México. Se aplicó un cuestionario con datos clínico-epidemiológicos y se determinó la presencia de Ac-VCH (ELISA de 2^a generación y RIBA-2 para confirmar el diagnóstico) a cada paciente. Se determinó también el antígeno de superficie de la hepatitis B (AgHBs) y anticuerpos contra el antígeno central de la hepatitis B (Anti-HBc) mediante el método de ELISA. La presencia de Ac-VCH fue relacionada con las variables epidemiológicas de los sujetos. La prevalencia de anti-HCV y la frecuencia de características se compararon entre los pacientes positivos y negativos con las pruebas de χ^2 y exacta de Fisher. **Resultados.** El 32% de los pacientes con CH (35/117 (30%) hombres y 14/36 (39%) mujeres) fueron positivos para los Ac-VCH. El alcoholismo estuvo presente en todos los hombres serorreactivos y en ninguna de las mujeres positivas ($p < 0.001$). Ninguna de las variables epidemiológicas anali-

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through an interview were not associated with seropositivity. Anti-HBc was found in 16% of patients positive to anti-HCV and in 12% of seronegatives ($p=0.69$). **Conclusions.** The prevalence found was greater than previous reports in the general population in the Yucatan Peninsula (1.3%). The high prevalence of anti-HCV in these patients suggests that HC is more frequently associated with HCV in Yucatan, Mexico than hepatitis B. Alcoholism probably acts as a cofactor for the development of HC in males. The English version of this paper is available too at: <http://www.insp.mx/salud/index.html>

Key words: hepatitis C virus; hepatitis B virus; liver cirrhosis; carcinoma hepatocelular; Mexico

zadas estuvo asociada con la seropositividad. Los anti-HBc se encontraron en 16% de los pacientes positivos para Ac-VCH y en 12% de los seronegativos ($p=0.69$). **Conclusiones.** La prevalencia encontrada fue mayor a los reportes previos realizados en población general de la Península de Yucatán (1.3%). La alta prevalencia de Ac-VCH en este grupo de pacientes sugiere que la CH está más frecuentemente asociada con el VCH en Yucatán, México, que con el virus B de la hepatitis. El alcoholismo probablemente actúa como un cofactor en el desarrollo de CH en los hombres. El texto completo en inglés de este artículo también está disponible en: <http://www.insp.mx/salud/index.html>

Palabras clave: virus de la hepatitis C; virus de la hepatitis B; cirrosis hepática; carcinoma hepatocelular; México

Probably more than 100 million people worldwide are infected with the hepatitis C virus (HCV). This virus has the unique ability to cause persistent infection in immunocompetent hosts after parenteral or percutaneous transmission.^{1,2} HCV was discovered in 1988; it is an RNA single-strand virus belonging to the flavivirus family.³ There are at least 6 different genotypes of HCV; of these, type 1b is reportedly the most prevalent in studies carried out in Europe, the United States, and Mexico.^{4,7} There is no association between a particular HCV genotype and the progression to hepatic cirrhosis (HC) or hepatocellular carcinoma (HCC).⁸

Approximately 80% of people who become infected fail to clear the virus, and thus progress to chronic infection. Only 6% to 26% of these people progress to potentially serious end-stage liver disease, the critical sequel being cirrhosis within an average of 18 to 25 years.^{1,2,6} In patients with HCV infection, HCC occurs almost exclusively in the presence of cirrhosis,⁹ and the risk of developing HCC in a cirrhotic liver by HCV increases at a rate of 3 to 10% per year.⁸ In contrast, HCC related to hepatitis-B virus (HBV) occurs in HBV-infected patients, who may or may not suffer from cirrhosis,¹⁰ and several studies have suggested an oncogenic action combining both viruses.¹¹

In Yucatan, Mexico, a preliminary study on the healthy population showed a prevalence of antibodies against HCV (anti-HCV) of 1.3%.¹² On the other hand, HC ranks 13th as a cause of morbidity and 5th as a cause of death in the state of Yucatan, Mexico. Moreover, hospital admissions for hepatic cirrhosis represent approximately 25% of all the cases admitted in the Departments of Internal Medicine in Merida, Yucatan, Mexico, with a male to female proportion of 3:1. In the

majority of these cases, a diagnosis of nutritional alcoholic cirrhosis is given based on the patient's history. However, the absence of alcoholism in the majority of the women questions this diagnosis and leads to consideration of viral participation in these cases, even in those cases in which the disease is apparently related to alcohol intake.

The objective of this study was to determine the prevalence of anti-HCV in a group of patients with HC to define the association of this infection with chronic hepatopathy in Yucatan, and in this way contribute to the knowledge of the epidemiological profile of HCV in Mexico. The prevalence of HBV coinfection was also determined, as well as risk factors associated with infection by these viruses and the development of HC.

Material and Methods

A prospective, cross-sectional, descriptive study was carried out from March 1998 to May 1999. Study subjects were 153 patients originally from and residents of the Yucatan Peninsula diagnosed with HC. All of them were recruited at the General Hospital Agustín O'Horan of the Department of Health and at the Regional Research Center Dr. Hideyo Noguchi of Universidad Autónoma de Yucatán (Autonomous University of Yucatan), in the city of Merida, Yucatan, Mexico. Patients who met the following criteria were eligible for the study: having been diagnosed with alcoholic HC or cryptogenetic HC; unknown virological status of HCV and HBV, and voluntary consent to participate in this study. HC diagnosis was based on histopathological criteria from a hepatic biopsy and/or clinical criteria (jaundice, edema, coagulopathy, splenomegaly, signs of portal hypertension), and hematological and

biochemical findings (anemia and/or other cytopenias, delayed prothrombin time, elevated levels of aspartate-aminotransferase and alanine-aminotransferase, hypoalbuminemia, and increased serum globulin).¹³

A clinical-epidemiological questionnaire was applied by interview to collect data on age, previous diagnosis of hepatitis, blood transfusion, family history of liver disease, and chronic alcoholism (40 g alcohol/day for at least the past five years). A 2-ml sample of venous blood was drawn from each patient for detection of anti-HCV, using commercial equipment (HCV enzyme immunoassay (EIA) 2nd generation, Abbott Laboratories, North Chicago, IL, USA), following the manufacturer's instructions. This assay uses a recombinant antigen (C-100-3) as well as proteins from structural and non-structural portions of the HCV genome. If a sample reacted on two different occasions, an assay by second generation recombinant immunoblot (RIBA-2) (Ortho Diagnostic Systems Inc., Raritan NJ, USA) was carried out. This assay determines the presence of four HCV recombinant antigens. A patient was considered positive when reactive to at least two antigens, indeterminate if there was a reaction to only one antigen, and negative if there was no reaction.¹⁴ The presence of surface hepatitis B antigen (HBsAg) and antibodies against the hepatitis B core antigen (anti-HBc) were determined by EIA, (Abbott Laboratories, North Chicago, IL, USA).

The prevalence of anti-HCV was obtained and the frequency of the characteristics obtained by interview were compared among the positive and negative patients through the χ^2 test and the Fisher's exact test, as needed.

Results

Table I shows the demographic and risk factor data in relation to the prevalence of anti-HCV. Seventy-six percent (117) of the 153 patients were male and 36 (24%) were female. All patients had a low socioeconomic status. The average age of the group was 52 (range 18-85) years of age. In 120 patients (111/117 -95% - male and 9/36 -25% - female, $p < 0.0001$) the diagnosis of alcoholic cirrhosis was found and 33 patients (6 -5% - male and 27 -75% - female, $p < 0.0001$) were diagnosed with cryptogenetic cirrhosis. The average time of HC diagnosis was 4 (2-6) months.

Anti-HCV was identified in 49 (32%) cases (35/117 -30% - were males and 14/36 -39% - females). A history of hepatitis was more frequent in patients with no anti-HCV (10% vs. 2%, $p = 0.05$). A history of alcoholism was present in 35/35 (100%) male patients and in 0/14 (0%) female patients with anti-HCV ($p < 0.001$).

Table I
DEMOGRAPHIC AND RISK DATA IN RELATION TO THE PREVALENCE OF ANTIBODIES AGAINST THE HEPATITIS C VIRUS IN 153 PATIENTS WITH HEPATIC CIRRHOSIS IN YUCATAN, MEXICO

	Seropositive (n=49)		Seronegative (n=104)		p*
Males (%)	35/117	(30)	82/117	(70)	0.42*
Females (%)	14/36	(39)	22/36	(61)	
Age (interval)	54	(30-72)	49	(18-85)	0.30
Personal history of hepatitis (%)	1	(2)	10	(10)	0.008
Family history of hepatopathy (%)	11	(22)	18	(17)	0.59
Alcoholism (%)	35	(71)	85	(82)	0.21
Alcoholism among females (%)	0/14	(0)	9/22	(41)	0.006
Alcoholism among males (%)	35/35	(100)	76/82	(93)	0.17
History of blood transfusions (%)	11	(22)	23	(22)	0.87
Anti-HBc (%)	8	(16)	13	(12)	0.69
HBsAg	0	0			

A family history of hepatopathy was found with similar frequency among the seroreactive and non-seroreactive patients (11/49 -22% - vs. 18/104 -17% -, $p = 0.59$). In the cases considered as having alcoholic cirrhosis, anti-HCV was present in 35/120 (29%), while in those considered as having cryptogenetic cirrhosis, anti-HCV was present in 14/33 (42%) ($p = 0.14$).

The presence of anti-HBc was detected in 21/153 patients (14%) with HC (8/49 (16%) cases positive to anti-HCV and in 13/104 (12%) patients seronegative to anti-HCV, $p = 0.69$. Reactivity to HBsAg was not observed in any case.

Discussion

Although 70% to 80% of people infected with HCV become chronic carriers, most develop a mild form of the disease with slow progression.¹ However, HCV infection is currently the most common cause of liver fibrosis and cirrhosis.¹⁵ Approximately 6 to 26% of people who acquire HCV progress to cirrhosis.^{1,16,17} The frequency of cirrhosis is greater in transfusion-related patients than in those with a history of community-acquired HCV.¹⁸ Some predictive factors of cirrhosis have been identified: duration of infection (greater than 20 years), the age at contamination (greater than 40 years), chronic alcohol consumption, male gender, and human immunodeficiency virus co-infection.^{2,19} In patients who have cirrhosis, the 5-year risk of hepatocellular carcinoma is about 10%.⁸

The relationship between HCV and chronic hepatic disease has also been evaluated by studies showing a high prevalence of anti-HCV in cirrhotic patients. Also, a prevalence of 31% to 68% of anti-HCV has been reported in cirrhotic patients in different countries around the world²⁰⁻²⁷ compared with 1 to 2% in healthy population.¹ On the other hand, the presence of HCV viral genome was identified with a frequency of 50% from autopsy archives in one study in Italy.²⁸

In this study the prevalence of anti-HCV in this group of patients was 32% for patients with HC. This prevalence is significantly higher than that reported in the healthy general population in the Yucatan Peninsula (1.3%).¹² Some facts were notable among this group of patients. The history of acute hepatitis in these patients with anti-HCV is mostly subclinical. The prevalence in relation to gender was not statistically significant, which demonstrates that the infection has no predisposition towards either gender. On the other hand, although the frequency of some recognized risk factors associated with transmission of HCV (personal history of hepatitis, family history of liver disease, and history of blood transfusion) among the patients with or without anti-HCV is not statistically different, these factors in the transmission of HCV in Yucatan cannot be ruled out. Contact with asymptomatic household members and a low socioeconomic level may participate in an important way in the transmission of HCV in this group of cirrhosis patients and non-intravenous drug users.

The absence of alcoholism in females with anti-HCV suggests that HCV itself is able to produce hepatic damage that leads to HC, even in the absence of alcoholism. However, in patients with HCV infection, it is known that alcoholism acts as a co-factor for the development of HC and HCC, as has been demonstrated in other studies.²⁹⁻³¹ Also, the prevalence of anti-HCV in patients diagnosed with alcoholic cirrhosis has been reported as frequently as in non-alcoholics with cirrhosis.³²

The prevalence of anti-HBc was 14% in all patients, which is significantly lower than the prevalence of anti-HCV. Our study suggests an association between HCV and HC in one third of patients. That is to say that infection by HCV is more frequently associated with HC than with HVB in the Peninsula of Yucatan, just as has been reported in the international medical literature.³³ The impact of HCV infection in the development of HCC in the Yucatan was undefined until now.

HC associated with HCV infection is considered end-stage liver disease and the most important risk factor for HCC. However, recent reports on the treatment of HCV-related cirrhosis using interferon alfa³⁴⁻³⁶ or the

new formulation peginterferon alfa-2a,³⁷ suggest that these therapeutic schemes may be effective in the treatment of HC (decreased cumulative incidence of worsening of the Child-Pugh score, sustained virological response, histological response, biochemical response, and higher overall survival) at least in 31% of the patients treated with interferon alfa-2a and in 54% of the patients treated with peginterferon alfa-2a.³⁷ HCC prevention in patients with HCV-related cirrhosis is effective in 73% of them.^{38,39} This progress against HCV-linked HC has been significant and justifies the detection of this virus among patients with HC.

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