Annals of Hepatology

EDITORIAL

October-December, Vol. 10 No.4, 2011: 556-558

Liver cirrhosis and hepatocellular carcinoma in Mexico: impact of chronic infection by hepatitis viruses B and C

Kirvis Torres-Poveda,* Ana I. Burguete-García,* Vicente Madrid-Marina*

* Division of Chronic Infections and Cancer, Centro de Investigación en Enfermedades Infecciosas, Instituto Nacional de Salud Pública, Cuernavaca, México.

Data on the prevalence of chronic liver disease (CLD) in Mexico, derived from selected series of hospitalized patients or from mortality registers, underestimate the prevalence of CLD. The etiology of liver disease is unknown in approximately 10% of patients with abnormal results on liver function tests.[1] Cirrhosis is considered to be the most important risk factor for hepatocellular carcinoma (HCC). Several studies have indicated that 1-4% of all cirrhotic patients per year will develop HCC, according to the leading cause of the cirrhosis as reported by Méndez-Sánchez, *et al.*[2] During 2006 the Ministry of Health in Mexico reported 122,170 (87.3%) avoidable deaths from liver cirrhosis between 2000 and 2004. Liver cirrhosis is the second cause of death in the 15- to 64-year-old age group; being three times higher in men than in women.[3] The liver cirrhosis mortality in Mexico is substantially higher than in high-income countries.[4]

Méndez-Sánchez, *et al.* projected the trends in the prevalence of liver diseases in Mexico from 2005 to 2050 based on mortality data,[5] and analyzed national and regional liver-related mortality trends in Mexico for 2010.[6] In comparison to the previous study of mortality in Mexico[7] and worldwide,[8] the mortality from cirrhosis in Mexico increased since 2000, may be due to better diagnostic methods or better surveillance methods. The epidemiology of liver cirrhosis is characterized by marked differences across sex, ethnic groups, and geographic regions. The nature, frequency, and time of acquisition of the major risk factors for cirrhosis [hepatitis B virus (HBV), hepatitis C virus (HCV)], and alcoholic liver disease, may explain this variation.[5]

Correspondence and reprint request: Vicente Madrid Marina, M.D., Ph.D.
Division of Chronic Infections and Cancer
Instituto Nacional de Salud Pública
Av. Universidad 655. C.P. 62100, Cuernavaca, Morelos, México
Tel.: (+52) 777-3293056. E-mail: vmarina@insp.mx

Manuscript received: May 23, 2011.
Manuscript accepted: July 28, 2011.

More recently, Méndez-Sánchez, *et al.*, in 2010, compared mortality trends according to the type of disease in Mexico, it was found that the incidence of viral hepatitis, tumor and cirrhosis- related mortality increased, whereas that of alcohol-related death decreased, even though it was still the main cause of liver-related mortality. The mortality due to viral hepatitis increased over the study period, being the highest mortalities in Distrito Federal, Baja California and Jalisco.[6]

In Mexico HCC represents > 90% of primary liver neoplasms and develops mainly in patients with liver cirrhosis.[9] HCC will continue as the third leading cause of liver disease in Mexico, contributing 77,098 cases in the coming decades.[5] In 2006 the Ministry of Health in Mexico reported 14,725 (65.7%) avoidable deaths from liver cancer between 2000 and 2004.[3] Méndez-Sánchez, *et al.*, in 2008 reported that the mortality from HCC in Mexico showed an increasing trend in the period 2000-2006.[2] A previous studies in Mexico evaluating cases of HCC reported underlying liver disease secondary to alcohol in 44% and to HCV in 26% and documented cirrhosis in 42%[10] and HCV infection as the main etiological factor.[11]

Little is known about the impact of chronic infection with HBV and HCV in cirrhosis and HCC development in Mexico. Although is likely to be less important numerically than non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease, the rates of liver diseases from infectious origin may be underestimated, because traditionally a cirrhotic patient in Mexico is being investigated mostly on any history of alcohol consumption and the assessment of a possible infectious origin is not performed in all cases. Alcohol consumption is sometimes considered consuetudinary when there are no metabolic alterations or symptoms. Hence, it is very necessary; establish the real incidence of HCV and HBV infections, since prevalence data are contradictory in the Mexican population.[12-14] HBV and HCV are the most common causes of CLD world-wide.[15] Both

viruses cause a wide spectrum of clinical manifestations ranging from healthy carrier state to acute and chronic hepatitis, liver cirrhosis, and HCC. HBV and HCV infections may induce a proinflammatory state conducive to liver damage and accumulation of lipids.[16] From 2000 to 2007 the Ministry of Health reported 192,588 cases of hepatitis, 3.3% HBV, 6% HCV and 12% without a specific etiologic factor.[17]

A recent population study in Mexico among users of primary and secondary health clinics, with a questionary-trigger sampling reported a seroprevalence of HCV of 1.5% (95% CI: 1.3-1.7). Of these individuals, 60.9% had a history of transfusion, 28.3% reported to have relatives with cirrhosis, 25.2% had tattoos or piercings, and 6.9% referred having used drugs. Male gender and blood transfusion were significantly associated with HCV seropositivity. Among seropositive subjects the prevalence of HCV RNA, which showed chronic active infection in 48.3%.[18] The seroprevalence of HCV found in the Mexican population seems to be consistent with that previously estimated by the World Health Organization (1-2.5%) and contribute to the external validity of these results, because they correlate with previous studies.[12,19]

Regarding to the prevalence of HBV infection in Mexico is 1.4% (measured using the HBVc-Ab)[20,21] and 0.1-0.47% if the HBVs-Ag is considered.[19] Carrier rates for HBsAg vary geographically and Mexico, like other Latin American countries, is considered a low endemic-city area (< 2% of population are carriers).[22] However, high anti-HBc prevalence (91.1%) has been reported in populations on Mexico's southern border[23] and a high anti-HBc against a low hepatitis B surface antigen (HBsAg) seroprevalence is the reported characteristic of native Mexicans.[24] A recent study on the distribution of the anti-HBc based a national serosurvey from 10 Mexican states showed that a anti-HBc prevalence greater among men and association with age, residence in a rural area, low socio-economic status and illiteracy. On the other hand, clusters of very high anti-HBc prevalence were found in several rural communities where the prevalence of anti-HBc in adults was 3 to 20 times the national average.[25] Due to high endemic areas for HBV infection in native Mexican population, limitations in the diagnostic sensitivity and specificity of the serological immunoassays used to date and presence of occult hepatitis B in the country, the real prevalence of HBV infection could be even higher than HCV in Mexico.[17]

Chronic infections caused by HBV and/or HCV are the main risk factors for the development of HCC in humans.[26] The rate at which HCC occurs in the individual chronically infected with HBV- or HCV-associated cirrhosis is between 1 and 6% per year.[27] There are clearly features that unify HCC occurring in a background of HBV and HCV. HCC due to HBV and HCV may be an indirect result of enhanced hepatocyte turnover that occurs in an effort to replace infected cells that have been immunologically attacked. Viral functions may also play a more direct role in mediating oncogenesis.[26] In the latter case chronic exposure to aflatoxin B1, alcohol, and other factors may be considered as putative etiological factors. Primary evidence for a close interrelationship between these viruses and HCC has been obtained during accurate epidemiological studies, which have recognized increased risk for HCC in patients infected with HBV and HCV compared with non infected individuals.[28] In fact, HBV positive patients generally acquire their infection at an earlier age (at birth or during the first years of life) compared with those who are HCV positive (rarely before age 20 years). Thus, the duration of the two infections may be the same regardless of the significantly more advanced age of HCV-infected subjects. The strong association between HCC development and these two viral infections suggests that HBV and HCV exert a strong oncogenic effect on liver cells.[29]

CONCLUSIONS

Liver related mortality has increased significantly in Mexico at the provincial and national levels and it is estimated that it will continue to increase. Liver cirrhosis has a critical impact on public health in Mexico, representing the third greatest cause of death in the general population, and predicted trends for the next five decades are not promising. Similarly, HCC will continue as the third leading cause of liver disease in Mexico, according to the mortality trend data. The burden of liver disease caused by infection has been underestimated in the absence of molecular studies in patients with cirrhosis or dying from this disease which show the presence or absence of the HBV and HCV. It therefore requires molecular studies of the HBV and HCV both in subjects with a diagnosis of cirrhosis and in those who die from cirrhosis, to have more accurate data in Mexico. If the emphasis is on early diagnosis of HBV and HCV, it will be more likely of success in controlling viral hepatitis epidemia, where a third of

the world's population is exposed to the types B and C. Given the epidemiological transition of CLDs in Mexico, it is necessary to gain accurate knowledge about the demography of liver diseases for the formulation of health-care policies to prioritize health interventions and research, and to allocate resources adequately.

REFERENCES

1. Méndez-Sánchez N, Aguilar-Ramírez JR, Reyes A, Dehesa M, Juárez A, Castañeda B, Sánchez-Avila F, et al. Etiology of liver cirrhosis in Mexico. *Ann Hepatol* 2004; 3(1): 30-3.
2. Méndez-Sánchez N, Villa A, Vázquez-Elizondo G, Ponciano-Rodríguez G, Uribe M. Mortality trends for liver cancer in Mexico from 2000 to 2006. *Ann Hepatol* 2008; 7(3): 226-9.
3. Secretaría de Salud. La mortalidad en México, 2000-2004. Muertes evitables: magnitud, distribución y tendencias. 2006. Available from: http://www.salud.gob.mx/apps/htdocs/estadisticas/descargas/pdf/LaMortalidadEnMexico2000 2004.pdf
4. Stevens G, Dias RH, Thomas KJ, Rivera JA, Carvalho N, Barquera S, Hill K, et al. Characterizing the epidemiological transition in Mexico: national and subnational burden of diseases, injuries, and risk factors. *PLoS Med* 2008; 5(6): e125.
5. Méndez-Sánchez N, Villa AR, Chávez-Tapia NC, Ponciano-Rodríguez G, Almeda-Valdés P, González D, Uribe M. Trends in liver disease prevalence in Mexico from 2005 to 2050 through mortality data. *Ann Hepatol* 2005; 4(1): 52-5.
6. Méndez-Sánchez N, García-Villegas E, Merino-Zeferino B, Ochoa-Cruz S, Villa AR, Madrigal H, Kobashi-Margáin RA, et al. Liver diseases in Mexico and their associated mortality trends from 2000 to 2007: A retrospective study of the nation and the federal states. *Ann Hepatol* 2010; 9(4): 428-38.
7. Narro-Robles J, Gutiérrrez-Ávila H, López-Cervantes M, Borges G, Rosovosky H. La mortalidad por cirrhosis hepatica en México I. Características epidemiológicas relevantes. *Sal Púb Méx* 1992; 34(4): 378-87.
8. Bosetti C, Levi F, Luccini F, Zatonski WA, Negri E, La Vecchia C. Worlwide mortality from cirrhosis: an update to 2002. *J Hepatol* 2007; 46: 827-39.
9. Velázquez R, Rodríguez M, Navascués CA, Linares A, Pérez R, Sotorríos NG, Martínez I, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 2003; 37: 520-7.
10. Ruelas-Villavicencio AL, Vargas-Voracková F. In whom, how and how often is surveillance for hepatocellular carcinoma cost-effective? *Ann Hepatol* 2004; 3(4): 152-9.
11. Mondragón-Sánchez R, Ochoa-Carrillo FJ, Ruiz-Molina JM, Herrera-Goepfer R, Oñate-Ocaña LF, Aiello-Crocifoglio V. Hepatocellular carcinoma. Experience at the Instituto Nacional de Cancerología. *Rev Gastroenterol Mex* 1997; 62(1): 34-40 [Article in Spanish].
12. Santos-López G, Sosa-Jurado F, Vallejo-Ruiz V, Meléndez-Mena D, Reyes-Leyva J. Prevalence of hepatitis C virus in the Mexican population: A systematic review. *J Infect* 2008; 56(4): 281-90.
13. Valdespino JL, Conde-González CJ, Olaiz-Fernández G, Palma O, Kershenobich D, Sepúlveda J. Seroprevalencia de la hepatitis C en adultos de México: ¿un problema de salud pública emergente? *Sal Púb Méx* 2007; 49(Suppl. 3): S395, e403.
14. Chiquete E, Panduro A. Low prevalence of anti-hepatitis C virus antibodies in Mexico: a systematic review. *Intervirology* 2007; 50: 1-8.
15. De Flora S, Bonanni P. The prevention of infection-associated cancers. *Carcinogenesis* 2011; 32(6): 787-95.
16. Del Campo JA, Romero-Gómez M. Steatosis and insulin resistance in hepatitis C: A way out of the virus? *World J Gastroenterol* 2009; 15(40): 5016-9.
17. Panduro A, Escobedo-Meléndez G, Fierro NA, Ruiz-Madrigal B, Zepeda-Carrillo EA, Román S. Epidemiology of viral hepatitis in Mexico. *Sal Púb Méx* 2011; 53(Supl. I): S37-S45.
18. Burguete-García AI, Conde-González CJ, Jiménez-Méndez R, Juárez-Díaz Y, Meda-Monzón E, Torres-Poveda K, Madrid-Marina V. Hepatitis C seroprevalence and correlation between viral load and viral genotype among primary care clients in Mexico. *Sal Púb Méx* 2011; 53(Supl. I): S7-S12.
19. Valdespino JL, Conde-González CJ, Olaiz-Fernández G, Palma O, Sepúlveda J. Prevalencia en México de la infección y el estado portador de la hepatitis B en adultos. *Sal Púb Méx* 2007; 49(Suppl. 3): S404-S411.
20. González-Huezo MS, Sánchez-Hernández E, Camacho MC. Prevalencia de marcadores positivos para hepatitis B (Ags-VHB) y hepatitis C (Anti-VHC) en personal de salud del IS-SEMYM (Instituto de Seguridad Social del Estado de México y municipios). *Rev Gastroenterol Mex* 2010; 75(3): 4-11.
21. Fundación Mexicana para la Salud Hepática. Hepatitis C as a public health problem in Mexico. *Sal Púb Méx* 2011; 53(Supl. I): S61-S67.
22. Tanaka J. Hepatitis B epidemiology in Latin America. *Vaccine* 2000; 18(Suppl. 1): S17-S19.
23. Alvarez-Muñoz T, Bustamante-Calvillo E, Martínez-García C, Moreno-Altamirando L, Guiscafre-Gallardo H, Guiscafre JP, Muñoz O. Seroepidemiology of the hepatitis B and delta in the southeast of Chiapas, Mexico. *Arch Invest Med* 1989; 20: 189-95.
24. Roman S, Tanaka Y, Khan A, Kurbanov F, Kato H, Mizokami M, Panduro A. Occult hepatitis B in the genotype H-infected Nahuas and Huichol native Mexican population. *J Med Virol* 2010; 82(9): 1527-36.
25. Juárez-Figueroa LA, Uribe-Salas FJ, Conde-González CJ. Heterogeneous distribution of hepatitis B serological markers in rural areas of Mexico. *Sal Púb Méx* 2011; 53(Supl. I): S26-S31.
26. Block TM, Mehta AS, Fimmel CJ, Jordan R. Molecular viral oncology of hepatocellular carcinoma. *Oncogene* 2003; 22: 5093-107.
27. El Serag HB, Mason AC, Key C. Trends in survival of patients with hepatocellular carcinoma between 1977 and 1996 in the United States. *Hepatology* 2001; 33: 62-5.
28. Conjeevaram HS, Lok AS. Management of chronic hepatitis B. *J Hepatol* 2003; 38(Suppl. 1): 90-103.
29. Barazani Y, Hiatt JR, Tong MJ, Busuttil RW. Chronic viral hepatitis and hepatocellular carcinoma. *World J Surg* 2007; 31: 1243-8.