Clinical outcome of a patient cohort with acute hepatitis B

Laura Alves de Souza, Angelo Alves de Mattos, Maristela Fiorini, Polyanna Ribeiro, Cristiane Valle Tovo

Universidade Federal de Ciências da Saúde de Porto Alegre Post-Graduation Course-Hepatology of (UFCSPA), Porto Alegre/RS, Brazil.

Email: angeloamattos@gmail.com
Tel.: 55 51 3214-8238

INTRODUCTION

Viral hepatitis is a public health problem in Brazil and worldwide. According to the World Health Organization (WHO), 2 billion people have had contact with the hepatitis B virus (HBV); approximately 5% of these individuals are considered carriers (1).

The risk of chronicity after infection is 90% in the newborns of mothers with positive hepatitis B early antigen (HBeAg), 25 to 30% in children under 5 years of age, and less than 5% in adults (2). Chronic carriers have an increased risk (15 to 40%) of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma, resulting in 1 million deaths each year (3).

The most effective hepatitis B preventive measure is vaccination. Since 1998, a policy of universal vaccination has been implemented for children younger than 1 year in Brazil. The policy was subsequently extended to people younger than 20 years (4). Vaccination was also extended to vulnerable populations (e.g., injected drug users or health-care workers) in 2001 and to people up to 29 years of age in 2010 (5). It is estimated that 75% of the under-29 population is vaccinated (6).

Because HBV carriers are the source of infection and chronic hepatitis B is a major cause of cirrhosis and hepatocellular carcinoma, it is important to understand the incidence, prevalence, and chronification associated with HBV infection (7).

The objective of this study was to describe the clinical outcomes of patients with confirmed acute hepatitis B (AHB) in the South region of Brazil in the city of Porto Alegre from 1999 to 2007.

PATIENTS AND METHODS

This retrospective-prospective cohort study was based on secondary data (retrospective data) obtained from the Information System for Notifiable Diseases (SINAN) and primary data collected from patients who completed structured and semi-structured questionnaires (prospective data).

Between 1999 and 2007, 103 confirmed cases of AHB were reported to SINAN in Porto Alegre: 67 (65%) patients were male, and 77 (74.8%) were aged between 20 and 49 years. Of the 103 eligible patients, it was possible to identify outcomes in 78 (75.7%) cases: 56 (71.8%) were considered resolved; 11 (14.1%) became chronic carriers; and 11 (14.1%) died. Four (36.4%) of the 11 deaths (5.1% of the 78 evaluated patients) resulted from fulminant hepatitis.

A case was defined as any individual reported to SINAN in Porto Alegre, a city of 1.5 million inhabitants, from January 1999 to December 2007, and who had positive HBsAg and positive immunoglobulin M antibody to the hepatitis B core antigen (anti-HBc IgM). The patients were contacted at their addresses and phone numbers, and the records of individuals whom we were unable to find were checked through the Mortality Information System or the Health Care Unit registers.

After signing informed consent forms, the patients answered questionnaires evaluating epidemiologic data, the risk factors for hepatitis B acquisition and their participation in consultation and preventive measurements (i.e., vaccination). They were asked to supply copies of laboratory tests performed at least 6 months after their AHB diagnoses. If no information could be obtained, serological tests were performed in a Public Health Service unit.

Patients were considered to have resolved hepatitis B if they had negative HBsAg and positive antibodies to the hepatitis B surface antigen (anti-HBs) after 6 months and, in cases of chronic carriers, if they presented with positive HBsAg in the same period (8).

To determine the number of coinfected patients, the authors examined notification forms with information related to coinfection with hepatitis C virus (HCV) and human immunodeficiency virus (HIV).

This study was approved by the Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre. In the statistical analysis, Pearson’s Chi-squared test was used, with a 5% level of significance.

RESULTS

Between 1999 and 2007, 103 confirmed cases of AHB were reported to SINAN in Porto Alegre: 67 (65%) patients were male, and 77 (74.8%) were aged between 20 and 49 years.

Of the 103 eligible patients, it was possible to identify outcomes in 78 (75.7%) cases: 56 (71.8%) were considered resolved; 11 (14.1%) became chronic carriers; and 11 (14.1%) died. Four (36.4%) of the 11 deaths (5.1% of the 78 evaluated patients) resulted from fulminant hepatitis.

Hepatitis became chronic in patients older than 22 years: 8 of these patients (72.7%) were between 20- and 49-years-old, and 8 (27.3%) were over 50-years-old. The Caucasian race was prevalent, and female patients became chronic carriers more often than males.

Seventeen (16.5%) of the 103 reported patients had associated coinfections: 12 (70.6%) had HIV; 4 (23.5%) had HIV/HCV; and 1 (5.9%) had HCV. There was no association...
Table 1 - Studies that have assessed the chronicity of acute hepatitis B in adult populations.

| Reference | Author          | N    | Chronicity (%) | Assessed population                  |
|-----------|-----------------|------|----------------|--------------------------------------|
| 9         | Barker          | 172  | 7.0            | Prisoners                            |
| 10        | Beasley         | 37   | 2.7            | Students: Taiwan                      |
| 11        | Ferraz          | 357  | 1.7            | Acute hepatitis B: Brazil            |
| 12        | Gimeno          | 63   | 0              | Drug addicts                         |
| 13        | Hoofnjagle      | 149  | 4.7            | Prisoners                            |
| 14        | Kent            | 35   | 0              | Acupuncture                          |
| 15        | Kuruuzum        | 240  | 4.6            | Acute hepatitis B: Turkey            |
| 16        | Lavarini        | 150  | 4.0            | Acute hepatitis B: Italy             |
| 17        | McMahon         | 48   | 10.4           | Eskimos (Alaska)                     |
| 18        | Rinker          | 28   | 0              | Women who received contaminated blood|
| 19        | Roumeliotou*    | 13   | 0              | Women with heterosexual contact       |
| 20        | Roumeliotou*    | 58   | 12.0           | Acute hepatitis B: Germany           |
| 21        | Schomerus*      | 28   | 0              |                                      |
| 22        | Wiedmann*       | 507  | 0.2            | Acute hepatitis B: Greece            |
| 23        | Tassopoulou*    | 17   | 0              | Oncologic staff                      |
| 24        | Tassopoulou*    |      |                |                                      |

*Studies published on the same population. Only data from studies with the greatest number of individuals were considered.

between the type of coinfection and patient outcomes, chronicity, resolutions or deaths (p = 0.747). Two of the patients who became chronic carriers were coinfect ed, 1 with HIV and 1 with HIV/HCV.

**DISCUSSION**

Since the early 70s, several published studies have evaluated the chronicity of AHB in adult patients (Table 1) and shown an evolution to chronicity of up to 12% (9-25). A meta-analysis of 10 studies with adult heterogeneous populations, without adjusting for potential differences between them, showed that the risk of chronicity was higher than 10% in 2 studies, 5% in 1 and less than 5% in 7 (7).

Note that the chronicity in this study was high (14.1%) compared to the literature. This discrepancy could most likely be explained by the fact that the evolution to chronicity is inversely proportional to the age at which infection occurs (16). For example, some authors have reported that approximately 10% of patients who become infected with HBV as adults would not clear HBsAg after 6 months (21). As shown in our sample, all the patients were older than 22 years, which could justify a higher chronicity. Note that other studies have also observed high frequencies of chronicity (10,15,17). Several factors are associated with the increased risk of chronic HBV infection, including male gender, various causes of immune deficiency, genome variations, and genetic, hormonal and nutritional factors (7).

Differences in chronicity can also be explained by the manner in which it was calculated. In the present study, the evolution to chronicity was calculated based on patients who had complete follow-ups, similar to other studies (15,24). However, some authors did not specify whether there were losses in the follow-up (17) or if they calculated the progression to chronicity based on the total number of patients or only those with completed follow-ups (11). The results of the present study could be overestimated because some patients were lost to follow-up.

Regarding deaths, it is relevant that 5.1% of patients (4 of 78) died of causes related to fulminant hepatitis. Clearly, this result is most likely overestimated by the under-reporting of AHB.

Implementing the HBV vaccination over the last 30 years in several countries, such as the United States in 1981, Taiwan in 1984 and Brazil in 1998, has promoted a change in patient outcomes (13,18,26,27).

Of the AHB patients, 77 (74.8%) were aged between 20 and 49 years; this age range is not included in the National Immunization Program. Our findings suggest the importance of revising the inclusion criteria used in the vaccination schedule currently used in Brazil.

Regarding ethnicity, the Caucasian race was prevalent. Regarding gender, female patients were more likely to become chronic carriers, although this difference was not statistically significant. This result was not in alignment with other studies, which have reported a higher evolution to chronicity in male individuals (28,29,30).

Regarding the 17 coinfected patients, 12 (70.6%) had HIV, 4 had HIV/HCV, and 1 had HCV. HBV/HIV coinfection occurs in many patients, and it is explained by the common routes of transmission for these 2 viruses, primarily sexual, parenteral and vertical (31). A study conducted in Porto Alegre involving 587 HIV patients showed that 14 of 306 (4.6%) had positive HBsAg (32).

Note that 2 patients who became chronic carriers were coinfect ed. Literature reports suggest that worse outcomes are more frequent in coinfect ed patients (33).

The abovementioned results suggest the utmost importance of control measures and epidemiological assessments of HBV patients because in the evaluated population, there were high levels of chronicity and mortality related to liver injury. Effective actions, such as universal vaccination, break the transmission chain of HBV. The appropriate follow-up of patients and their contacts (home and/or sexual) is essential for improving the well-being of our population.

**AUTHOR CONTRIBUTIONS**

Souza LA was responsible for all the phases of the study from conception to the manuscript draft. Mattos AA was responsible for the general coordination of the study, draft and critical review of the manuscript. Fiorini M and Ribeiro P were responsible for collecting the data and organizing the database. Tovo CV participated in drafting and critical review of the manuscript.
REFERENCES

1. European Association for the Study of Liver. EASL. Clinical practice guidelines: management of chronic hepatitis B. J Hepatol. 2009;50(2):227-42.

2. Damaj T, Alavi S, Hamdi M, Assaf M, Chetouane H, Ghiara P. A multicenter controlled trial of lamivudine in patients with chronic hepatitis B in Lebanon. J Viral Hepat. 2007;14(7):549-54.

3. McMahen BJ. Natural history of chronic hepatitis B – clinical implications. Medscape J Med. 2006;8(4):91.

4. Sokal JE, Sokal RR. A statistical method for linear regression analysis of the toxicity of compounds. J Pharmacol Exp Ther. 1956;118(2):393-405.

5. Beasley RP, Hwang LY, Lin CC, Ko YC, Twu SJ. Incidence of hepatitis B infection in Taiwan, 1968-1976: a population-based study. J Infect Dis. 1985;151(4):599-603, http://dx.doi.org/10.1093/infdis/151.4.599.

6. Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B in the United States. JAMA. 1983;249(25):3147-52, http://dx.doi.org/10.1001/jama.1983.03320250047007.

7. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. Clin Infect Dis. 1995;20(4):992-1000, http://dx.doi.org/10.1093/clinids/20.4.992.

8. Lok AS, McMahon BJ. AASLD Practice guideline update. Chronic Hepatitis B: Update 2009. Hepatology. 2009;50(1-36).

9. Barker LF, Murray R. Acquisition of hepatits-associated antigen. Clinical features in young adults. JAMA. 1971;216(12):1970-6, http://dx.doi.org/10.1001/jama.1971.10318030028006.

10. Beasley RP, Hwang LY, Lin CC, Ko YC, Twu SJ. Incidence of hepatitis B among students at a university in Taiwan. Am J Epidemiol. 1983;117(2):213-22.

11. Ferraz MLG, Yoradjian A, Barbieri A, Figueiredo V, Lopes Neto E, Cruz DP, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. BMJ. 1983;287(6401):1254-6, http://dx.doi.org/10.1136/bmj.287.6401.1254.

12. Gimeno V, Escudero A, Gonzalez R, Serra MA, Del Olmo JA, Wassel A, et al. Serum inhibitory factors (SIF) are of prognostic value in acute viral hepatitis. Lancet. 1985;1(8424):309-12, http://dx.doi.org/10.1016/S0140-6736(85)90839-9.

13. Tassopoulos NC, Papaevangelou GJ, Roumeliotou-Karayannis A, Tilehurst JR, Feinstein SM, Purcell RH. Search for hepatitis B virus DNA in sera from patients with acute type B or non-A, non-B hepatitis. J Hepatol. 1986;2(3):410-8, http://dx.doi.org/10.1016/0160-0805(86)90052-6.

14. Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Roumeliotou-Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. Gastroenterology. 1997;92(6):1844-50.

15. Wands JR, Walker JA, Davis TT, Waterbury LA, Owens AH, Carpenter CC. Hepatitis B in an oncology unit. N Engl J Med. 1974;291(26):1371-5.

16. Kao JH, Chen DS. Global control hepatitis B virus infection. Lancet Infect Dis. 2002;2(7):395-403, http://dx.doi.org/10.1016/S1473-3099(02)00313-8.

17. Daniels D, Guldal S, Wasley A. Centres for Disease Control and Prevention CDC. Surveillance for acute viral hepatitis - United States. 2007. MMWR Surveill Summ. 2009;58(3):1-27.

18. Kim WR, Benson JT, Therneau TM, Torgerson DA, Yawn BP, Melton LJ. Changing epidemiology of hepatitis B in a U.S. community. Hepatology. 2004;39(3):811-6, http://dx.doi.org/10.1002/hep.20098.

19. Roumeliotou A, Tassopoulos N, Richardson SC, Kalafatap G, Papaevangelou G. How often does chronic liver disease follow acute hepatitis B in adults? Infection. 1985;13(4):174-6, http://dx.doi.org/10.1007/BF01628006.

20. Roumeliotou A, Papaevangelou G. Chronic liver disease rarely follows acute hepatitis B in non-immunocompromised adults. Infection. 1992;20(4):221-3, http://dx.doi.org/10.1007/BF02036063.

21. Schuermann H, Wiedmann KH, Döpke W, Peerenboom H, Strohmeyer G, Balzer K, et al. (>)-Cyaniqonol-3 in the treatment of acute viral hepatitis: a randomized controlled trial. Hepatology. 1984;4(2):331-5, http://dx.doi.org/10.1002/hep.1840040226.

22. Wiedmann KH, Bracting NW, Diao GD, Schuermann H, Döpke W, Berg PA. Serum inhibitory factors (SIF) are of prognostic value in acute viral hepatitis. Lancet. 1985;1(8424):309-12, http://dx.doi.org/10.1016/S0140-6736(85)90839-9.

23. Tassopoulos NC, Papaevangelou GJ, Roumeliotou-Karayannis A, Tilehurst JR, Feinstein SM, Purcell RH. Search for hepatitis B virus DNA in sera from patients with acute type B or non-A, non-B hepatitis. J Hepatol. 1986;2(3):410-8, http://dx.doi.org/10.1016/0160-0805(86)90052-6.

24. Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Roumeliotou-Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. Gastroenterology. 1997;92(6):1844-50.

25. Wands JR, Walker JA, Davis TT, Waterbury LA, Owens AH, Carpenter CC. Hepatitis B in an oncology unit. N Engl J Med. 1974;291(26):1371-5.

26. Kao JH, Chen DS. Global control hepatitis B virus infection. Lancet Infect Dis. 2002;2(7):395-403, http://dx.doi.org/10.1016/S1473-3099(02)00313-

27. Daniels D, Guldal S, Wasley A. Centers for Disease Control and Prevention CDC. Surveillance for acute viral hepatitis - United States. 2007. MMWR Surveill Summ. 2009;58(3):1-27.

28. Kim WR, Benson JT, Therneau TM, Torgerson DA, Yawn BP, Melton LJ. Changing epidemiology of hepatitis B in a U.S. community. Hepatology. 2004;39(3):811-6, http://dx.doi.org/10.1002/hep.20098.

29. Meire F, Le Strat Y, Delarocque-Astagneau E, Dubois F, Antonia D, Lemasson JM, et al. Prevalence of hepatitis B and hepatitis C virus infections in France in 2004: social factors are important predictors after adjusting for known risk factors. J Med Virol. 2010;82(4):546-55, http://dx.doi.org/10.1002/jmv.21734.

30. Taylor BC, Yuan JM, Shamliyan TA, Shaukat A, Kane RL, Wilt TJ. Clinical outcomes in adults with chronic hepatitis B in association with patient and viral characteristics: a systematic review of evidence. Hepatology. 2009;49(5 Suppl):S85-95, http://dx.doi.org/10.1002/hep.22929.

31. Souza MG, Passos ADC, Machado AA, Figueiredo JFC, Esmeraldino LE. Co-infection HIV and virus de hepatitis B: prevalência e fatores de risco. Rev Soc Bras Med Trop. 2003;36(2):56-62, http://dx.doi.org/10.1590/S0037-86822003000200002.

32. Toyo CV, Santos DE, Mattos AZ, Almeida PRL, Mattos AA, Santos BR. Prevalência ambulatorial em um hospital geral de marcadores para hepatites B e C em pacientes com infecção pelo vírus da imunodeficiência humana. Arq Gastroenterol. 2006;43(2):73-6, http://dx.doi.org/10.1590/S0004-28032006000200002.

33. Sherman M. Strategies for managing coinfection with hepatitis B virus and HIV. Cleve Clin J Med. 2009;76 Suppl 3:S30-3, http://dx.doi.org/10.3949/ccjm.76.s.3107.