Coll. Antropol. **24** (2000) 1: 211–216
UDC 616.36-036
Original scientific paper

Prognosis for the Patients with Chronic Hepatitis B

V. Čolić-Cvrlje, S. Naumovski-Mihalić, M. Prskalo, A. Čolić, B. Cvjetičanin and B. Šabarić

University Hospital »Merkur«, Zagreb, Croatia

A B S T R A C T

The purpose of the research was to determine the influence of the hepatitis B virus on the progression of the chronic liver disease. In the present paper, 127 patients who were followed up for five years and who had histologically verified chronic liver disease, are described. Fifty two of them were carriers of HBsAg, 75 patients were HBsAg negative, but had other markers typical for a previous infection of HBV in the sera. All the patients were nonalcoholics and no drug addicts. In the sera of these 127 patients markers of HBV were prospectively followed up: HBsAg, HBeAg, anti-HBs, anti-HBc, anti-HBe, HBVDNA, antiHCV for C virus and anti-D for D virus. It was proved by these investigations that HBV provokes very severe chronic hepatitis: CAH (chronic active hepatitis) and CH (cirrhosis hepatis). It was also proved that HBV replicated in 44.20 % patients, namely, HBVDNA was positive in the sera of those patients. In 26.08 % of such patients the mutant form of HBV was present. In spite of progressive liver disease and without any antiviral therapy all the patients with chronic HBV cirrhosis hepatis were, after five year-follow-up, in Child-Pugh A grade. It was found that the patients who were HBsAg negative, but had one or more markers of HBV positive in the sera, had also a severe chronic hepatitis. That group of patients remains our object of further research. The five-years follow-up of all these patients demonstrates that it is necessary to find out an efficient medicament against HBV chronic hepatitis. Obligatory vaccination of the risk population against virus B remains the only prevention against this severe disease.

Introduction

According to epidemiological data there are 350.000.000 carriers of hepatitis B virus in different parts of the world and 3.000.000 people die yearly from different forms of chronic hepatitis caused by this virus. Distribution of HBV is various on different continents, respectively in different countries[1,2]. About 5% of the world population is infected with HBV. HBV belongs to the group of hepadna vi-

Received for publication October 19, 1999.

ruses with the well known structure and genome organization[3]. It is transmitted by parenteral, sexual and perinatal way. It causes acute hepatitis, but through the effect of HBV, chronic hepatitis forms of various intensity develop: cirrhosis hepatis and hepatocellular carcinoma[4,5]. The investigation in Croatia demonstrates that there are 2–7% of the infected population and that HBV is a significant cause of liver disease in our country[6]. Through this investigation we wanted to examine natural history of chronic HBV hepatitis in our patients.

Patients and Methods

We investigated and followed up for 4 years 127 patients who had histologically proven chronic liver disease. Within this group there were 52 positive HBsAg patients and 75 patients who were HBsAg negative, but who had one or more other serum markers of HBV. After 4 years of the follow-up we re-evaluated the serological status of these patients for HBV and in a portion of the investigated patients we performed a control liver biopsy. After that, we followed up the whole group during 12 months, and every 4 months, during clinical control, we determined the HBV markers in their sera. At the end of the investigation we again performed a control liver biopsy in a portion of the same patients. Alcohol abuse was excluded for all patients as well as intravenous drugs. The history of previous acute hepatitis, blood transfusion or other sources of HBV infection were taken. Histological diagnosis was made according to the accepted classification of: chronic persistent hepatitis (CPH), chronic active hepatitis (CAH), cirrhosis hepatis (CH), hepatocellular carcinoma (HCC) or normal findings (N)[7–9]. The sera markers HBsAg, anti-HBs, anti-HBc, HBeAg, anti HBe, were analysed by commercial methods RIA and EIA (BEAD test) Abbot Laboratories, North Chicago, Illinois, USA. HBV-DNA-PCR was performed by the Roche-Amplicor test. Anti HCV-Elisa test by the Ortho Clinical Diagnostic, Rharitan, USA. Anti HD-by RIA Abbot commercial test. The test of significance, ^{2} with Yates correction for small numbers was used. ^{2} was significant if higher than 3.841, $p = 0.05$. The 95% interval of confidence was used for results expressed in percentage. The numbers in brackets mean upper and lower limits of 95% interval of confidence[10].

Results

Out of 127 patients with HBV markers in the sera, 47.24% (33–61%) had cirrhosis, 24.41% (10–43%) had chronic active hepatitis and 23.61% (10–44%) had chronic persistent hepatitis.

Out of 127 patients, 62.20% (48–73%) were men. In the group of 52 HBsAg positive patients, at the first medical checkup, 34.61% (15–60%) had cirrhosis and 30.76% (11–58%) had chronic active hepatitis. After 48 months we performed a control biopsy on 9 of those patients: two of them with previous normal findings developed CPH and CAH, 4 patients with previous CAH developed cirrhosis and from 3 patients with previous CPH one remained CPH and two developed the CAH. It means that after 48 months of the follow-up in this HBsAg positive group 46.15% (25–67%) had cirrhosis hepatis and 63.46% (4–79%) of them were men. Women had cirrhosis in 36.54% (69–88%) cases. The replication tests were positive in 44.23% (24–68%) among all 52 patients. In these patients where HBV replicated most of them had cirrhosis hepatis and were male in 69.56% (60–88%) cases. Most of our patients had anicteric acute phase of HBV hepatitis because 11.53% (5–23%) of patients had a history of previous acute hepatitis. 15.38% (2–60%) patients received blood

transfusion and 40.38% (20–63%) probably had other unknown source of infection. In 52 patients, followed up by us for 5 years, we performed control liver biopsy in 16 patients at the and of the investigation. Three patients with CPH developed CH, four with CAH also developed CH and one patient with previous CH developed HCC. Three patients in this HBsAg positive group died after a 5-year follow-up, one with HCC and two with CH (Table 1). In 75 patients who were ABsAg negative but were positive for other markers of HBV, 48% (30–66%) had cirrhosis hepatis and 22.67% had CAH (6–48%). Average age of these patients was 55.4 for male and 53.4 for female. 45.3% (26–63%) of these patients were younger than 50. Most of these patients had only anti-HBC in the sera and they had cirrhosis hepatis (Table 2). After 5 years of following up we did 13 control liver biopsy in this group of 75 HBsAg negative patients. Four of them with CPH developed progressive hepatitis: one of them developed CAH, three developed cirrhosis. One patient with previous CPH developed HCC, one patient with previous CPH had a normal finding at the control biopsy and one patient with the previous normal finding, after 5 years, developed HCC. All the patients who developed progressive hepatic disease had anti-HBC positive (Table 3).

Serological markers of HBV in the group of these 75 patients did not change during that 5-year follow up. There was no statistical significant difference in the group with HBsAg positive patients with severe hepatic disease in relation to HBsAg negative patients ($^2 = 0.0619$). In the HBsAg positive patients who were

TABLE 1
HISTOLOGICAL DISTRIBUTION OF SERA HBSAG POSITIVE PATIENTS DURING 5 YEARS OF FOLLOW-UP

Histology	First check	%	4 years	%	5 years	%
CH	18	34.61	24	46.15	30	57.69
CAH	16	30.76	14	26.92	10	19.23
CPH	12	23.07	10	19.23	7	13.46
N	6	11.53	4	7.69	4	7.69
HCC			0	0.00	1	1.92
Total	52		52		52	100.00

TABLE 2
DISTRIBUTION OF ANTI HBV ANTIBODIES AT PATIENTS ACCORDING TO HISTOLOGICAL DISTRIBUTION

Histology	AntiHBs	AntiHBc	AntiHBs AntiHBc	AntiHBs AntiHBc AntiHBe	AntiHBe AntiHBc	Total	%
CH	7	13	12	2	2	36	48.00
CAH	2	7	5	1	2	17	22.66
CPH	4	4	10	2	0	20	26.67
N	0	1	0	1	0	2	2.67
Total	13	25	27	6	4	75	100.00

TABLE 3
HISTOLOGICAL DISTRIBUTION OF HBSAG SERA NEGATIVE PATIENTS BUT POSITIVE FOR ANTI-HBV ANTIBODIES DURING 5 YEARS OF FOLLOW-UP

Histology	First check	%	4 years	%	5 years	%
CH	30	40.00	36	48.00	39	52.00
CAH	20	26.67	17	22.67	18	24.01
CPH	17	22.67	20	26.67	14	18.67
N	8	10.66	2	2.66	2	2.66
HCC	0	0	0	0	2	2.66
Total	75		75		75	100.00

also HBVDNA positive, but were male and younger than 50 there was no significant difference in relation to the group of male patients who had no markers if viral replications (^{2} = 2.6331). There was a significant difference between the female patients who had such characteristics (^{2} = 3.9327, p 0.05). It is interesting that there is no significant difference in relation to the patients who were HBsAg positive and HBV DNA positive and the group which was HBsAg positive and HBVDNA negative (^{2} = 0.3421).

Discussion

At the Gastroentero-hepatologic division of the University hospital »Merkur« in Zagreb, the patients with chronic HBV hepatitis have been investigated for 25 years. In 1974 it was determined that 15% of the patients with histologically proven chronic liver disease was positive for the HB antigen[11]. In 1981, when very sensitive RIA method for determination of serologic markers of HBV was used for the first time, we were surprised by the number of the patients who had HBV chronic hepatitis. HBsAg was positive in 105 out of a total of 401 investigated patients (26%).

In 247 of all patients we founded one or more markers for HBV[12]. We controlled our patients in hospital and outpatients introducing new methods of testing for HBV in order to make better diagnosis of chronic HBV hepatitis. This investigation shows that our patients with serological HBV markers have very severe chronic hepatitis and that the virus hepatitis B is a very significant factor for developing chronic hepatitis. 5-years survival for cirrhosis and chronic active hepatitis is 55% for the patients under 65 years of age. Such severe hepatic disease has a fatal end and the question of therapy for the patients with chronic HBV hepatitis is a challenge[13].

Antiviral therapy with interferon has been applied for a few decades and hundreds of patients were cured with various doses of interferon at different degrees of chronic hepatic disease with various success[14]. During our investigations we did not cure our HBV-patients with antiviral therapy, although our patients had all predictors for introducing such kind of therapy: active hepatic disease, no cirrhosis, female gender, infection with B-virus at adult age, low-grade of HBVDNA in sera, and anicteric acute hepatitis. Most of our patients, nevertheless, have cirrhosis hepatis and it is very risky to apply antiviral therapy at such patients. But, for example, Hoofnagle et al.[15] gave interferon to the patients with Child Pugh B and C-grade. In 35% of the patients HBVDNA converted and biochemistry parameters in the patients improved. Better effect was achieved in the group of

patients with Child Pugh A-degree. The results of Perillo et al. with interferon at the patients who had decompensated cirrhosis hepatis were similar, but a number of the patients died because of complications of liver disease during the therapy[16]. All our patients with cirrhosis hepatis were at the beginning of investigation in Child Pugh A-degree. Although antiviral therapy was not applied with these patients, they were in the same degree of disease after 5-years follow-up.

It is interesting that in our patients who were HBsAg positive at the beginning of investigation there was no spontaneous sero-conversion of HBsAg, neither HBeAg. That had no effect on disease development. In our investigation we also defined a group of patients with mutant B-virus which is characteristic for the Mediterranean area. Such patients have very progressive liver diseases but are also very resistant to antiviral therapy[17,18].

Our group of patients who are HBsAg negative, but positive for other serological markers, is especially interesting. They have severe chronic hepatitis disease and our opinion is that B virus is ethiologically a cause of liver disease because alcohol and C virus are excluded. Among them, there is a high percentage of patients (33%) who have only anti-HBc positive and 44% of them have cirrhosis hepatis. With this research we have contributed to recent investigations which points to a conclusion that it is necessary for such patients to look for B virus with the help of new high sensitive methods[19–21].

Conclusions

We did not apply antiviral therapy in our patients, but the investigation and the results point to the necessity of discovering of a new and more efficient therapy for the HBV chronic hepatitis. Until that time, a recommendation of WHO for obligatory vaccination against B virus among risky population as well as in areas with 7% infection is the only protection measure against this virus[22,23].

REFERENCES

1. ALTERR, M. J., E. E. MART, Clin. N. Am., 33 (1994) 437. — 2. KANE, M., Gut, 34 Suppl. (1993) S10-S12. — 3.LAU, I. Y. N., T. L. WRIGHT, Lancet, 342 (1993) 1335. — 4. PERRILLO, R. P., Gut, 34 Suppl. (1993) S48-S49. — 5. FATTOWICH, G., Hepato-Gastroenterology, 45 (Suppl. 3) (1988) 1206. — 6. PERIŠIĆ, V., S. ČERLEK, V. ČOLIĆ-CVRLJE, M. KATIČIĆ, B. PAPA, M. DOMINIS, Proc. of XV Meeting of EASL (1980) 1. — 7. KNODELL, R. G., K. G. ISHAK, W. C. BLACK, Hepatology, 1 (1981) 431. — 8. ISHAK, K. G., Hepatology, 22 (1995) 693. — 9. DESMET, V. J., M. GERBER, J. H. HOOFNAGLE, M. MAMMS, P. I. SCHEUER, Hepatology, 19 (1994) 1513. — 10. WULF, H. R.: Rational diagnosis and treatment. (Blackwell Scientific Publications, Oxford, 1986.). — 11. CVRLJE, V., M. DOMINIS, D. JURIŠIĆ, F. MUŠTOVIĆ, F. TADEJ, D. VRHOVSKI, Proc. Clin. Bioch. Diagn. Liver Dis. (Cavtat, 1974). — 12. ČOLIĆ-CVRLJE, V.: Antigen and antibodies of Hepatitits B and Hepatitis A viruses in chronic liver disease. M. S. Thesis. In Croat. (University of Zagreb, Zagreb, 1981). — 13. LEE, W. M., N. Engl. J. Med., 337 (1997) 1733. — 14. HOOFNAGLE, J. H., Digestion, 59 (1998) 563. — 15. HOOFNAGLE, J. H., A. M. DIBISCEGLIE, Gastroenterology, 104 (1993) 1106. — 16. PERRILLO, R. P., C. TAMBURO, F. REGENESTEIN, Hepatology, 16 (1992) Abstract A126. — 17. BRUNETTO, M. R., M. STEMMLER, F. SCHODEL, Ital. J. Gastroenterol., 21 (1989) 151. — 18. BRUNETTO, M. R., F. OLIVERI, A. DEMARTINO, P. L. CALVO, P. MANZINI, T. ORRANI, F. BONINO, J. Hepatol., 13 (1991) 58. — 19. SMITH, H. M., I. Y. N. DAVIES, S. E. DANIELS, G. Y. M. ALEXANDER, R. WILLIAMS, J. Med. Virol., 36 (1992) 16. — 20. THOMAS, H. C., Journal of Viral Hepatitis, 5 (Suppl. 2) (1998) 31. — 21. LINDENSCHMIDT, E. G., Proc. of Vth Intl. Conf. Current Trends in Chronical Evolving Viral Hepatitis, Lyon (1997) Abstract 7. — 22. DOBSON, S., JAMA, 274 (1995) 1209. — 23. KANE, M. A.: Hepatitis B control through immunization (SAGE). Global programme for vaccines and immunization. (WHO, Geneva, 1995).

V. Čolić-Cvrlje

University Hospital »Merkur«, Zajčeva 19, 10000 Zagreb, Croatia

PROGNOZA KOD OBOLJELIH OD KRONIČNOG B HEPATITISA

S A Ž E T A K

Svrha rada bila je utvrditi utjecaj hepatitis B virusa na razvoj kronične bolesti jetre. U navedenom radu praćeno je tijekom 5 godina 127 bolesnika s histološki verificiranom kroničnom bolešću jetre. 52 su bili nosioci HBsAg, a 75 su bili HBsAg negativni, ali su imali druge biljege u serumu za preboljelu infekciju hepatitis B virusa. Svi bolesnici bili su nealkoholičari i neovisnici o uzimanju intravenoznih droga. U svih 127 bolesnika prospektivno su praćeni biljezi hepatitis B virusa: HBsAg, anti HBs, anti HBc, HBeAg, HBVDNK, kao i anti HCV za C hepatitis virus i anti D za D virus. Istraživanjem je dokazano da B virus izaziva izuzetno teške bolesti jetre: kronični aktivni hepatitis i cirozu. Ustanovljeno je također da se hepatitis B virus i dalje replicira u 44.20% bolesnika. U 26.08% takovih bolesnika dokazana je prisutnost mutantne forme hepatitis B virusa. Unatoč progresivnoj bolesti jetre i bez antiviralne terapije s kroničnom HBV cirozom jetre bili su nakon 5 godina u kliničkom Child Pugh A stadiju oboljenja. Ustanovljeno je da HBsAg negativni, ali s jednim ili više biljega B hepatitisa u serumu također imaju teška oboljenja jetre te ostaju predmetom daljnjeg istraživanja. Petogodišnje praćenje ovih bolesnika pokazuje da je neophodno iznalaženje efikasnog lijeka protiv hepatitis B virusne bolesti jetre, a da je obavezno cijepljenje ugroženih skupina za sada jedina prevencija od ovog teškog oboljenja.