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Original Article

Long-term prognosis of chronic hepatitis B virus infection in the childhood

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Abstract

Aim: It was aimed to investigate the modes of transmisson and long-term prognosis of the disease in patients who were followed up with a diagnosis of chronic hepatitis B infection.

Material and Methods: The files of the patients who presented to our outpatient clinic between January 2002 and May 2013 and were being followed up with a diagnosis of chronic hepatitis B virus infection were examined retrospectively and the information related with the age, gender, age at the time of diagnosis, mode of transmission, follow-up period, transaminase levels, the amount of hepatitis B virus-deoxyribonucleic acid and treatment and responses to the treatment given were recorded.

Results: The age at the time of diagnosis of 150 patients (97 males, 64%) included in the study was 14.95±2.94 years. 59 (39.3%) of the patients were inactive carriers, 61 (40.7%) were in the immunotolerant stage and 30 (20%) were in the immunoreactive stage. Vertical transmission was present in 86 (57.3%) patients, horizontal transmission was present in 41 patients (27.3%) and the mode of transmission was not known in 23 patients (15.3%). Response to treatment was obtained in 26 (72.2%) of 36 patients who received treatment. Lamivudine (4 mg/kg/day) was given to 29 of the patients who were given treatment, interferon-α (IFN-α) (6 MU/m^2, three days a week) was given to 3 patients at the same dose and both IFN-α and lamivudine were given to 4 patients. The time to give response to treatment was 24.23±15.23 months (6-50 months). Spontaneous anti-HBe seroconversion occured in four (7.2%) of 55 immuntolerant children who were followed up without treatment. The time to development of seroconversion in these children was 2.50±1.91 years (1-5 years).

Conclusions: Chronic hepatitis B virus infection has a more benign prognosis in children compared to adults, though it may lead to development of hepatic failure, cirrhosis and hepatocellular cancer. In addition, a decrease in the frequency of infection is expected in children in the years ahead owing to vaccination programs. However, we think that studies related with use of different drugs in patients who do not respond to treatment should be performed. (Türk Ped Arş 2014; 49: 117-23)

Key words: Children, hepatitis B virus infection, treatment

Introduction

Hepatitis B virus (HBV) infection is observed commonly in our country and in the world and affects about 1/3 of the world population. Turkey is a moderately endemic area for HBV infection and hepatitis B surface antigen (HBsAg) is positive with a rate of 6.2% in children aged between 6 and 10 years (1). However, the incidence of HBV infection varies by geographical location. While HBsAg positivity is as high as 8.1%-11.5% in children in the eastern region of Turkey, it is 4.6% in the western region (2-4). Infection arising from this virus may be asymptomatic or it may progress from infection to cirrhosis and hepatocellular carcinoma. Most of the individuals infected with chronic HBV acquire the infection at the time of delivery or in the early childhood (5, 6). Interferon- α (IFN), lamivudine or a combination of these are used in chronic HVB treatment in children.

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In this study, it was aimed to investigate the modes of transmisson of HBV infection and long-term prognosis of the disease by examining the file data of the patients who were being followed up with a diagnosis of chronic HBV infection retrospectively.

Material and Methods

One hundred and fifty children aged between 1 and 17 years who were being followed up with a diagnosis of chronic HBV infection between Janurary 2001 and May 2013 in Karadeniz Technical University, Medical Faculty, Division of Pediatric Gastroenterology, Hepatology and Nutrition were included in the study. The information related with the age, gender, mode of transmission, disease status and treatment and responses to the treatment given were recorded from the patient files. The mode of transmission was divided into four groups as vertical (prenatal), horizontal (in-door contact), parenteral and unknown. HBsAg positivity in the mother was considered vertical transmission and HBsAg positivity in the family other than the mother was considered horizontal transmission. Hepatitis B surface antigen (HBsAg), hepatitis B envelope antigen (HBeAg), hepatitis B surface antibody (antiHBs), hepatitis B envelope antibody (antiHBe), HBVDNA(deoxyribonucleid acid) were recorded as serological indicators and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were recorded as biochemical indicators. Hepatitis activity (HAI) index and portal fibrosis score were determined by modified Ishak scoring system on histopathological examination of the patients who underwent biopsy (7). The subjects who had negative HBeAg, a HBVDNA value of <2000 IU/mL and normal transaminases were classified as inactive carriers, the subjects who had positive HBeAg, increased HBVDNA levels and normal or near-normal transaminases were classified as immunotolerant patients and the subjects who had positive HBeAg, increased HBVDNA levels, increased transaminase levels and inflammation and fibrosis on biopsy were classified as immunoreactive patients (8).

Returning of ALT values to the normal ranges (<40 U/L) in the follow-up or at the end of treatment was considered biochemical response, elimination of HBeAg and occurence of Anti-HBe was considered seroconversion, decrease of serum HBVDNA to an undetectable level and loss of HBeAg and occurence of Anti-HBe in HBeAg positive patients was considered virological response, presence of biochemical and virological response (seroconversion and loss of HBVDNA) together was considered full response and loss of biochemical response, virological response and HBsAg and occurence of antiHBs was considered full viral eradication. Continuance of the response type one year after the end of treatment was considered permanent response (9).

Statistical analysis

The data were evaluated using Statistical Package for the Social Sciences (SPSS, Inc, Chicago, USA) 13,0 statistical package program. Mean±standard deviation (SD) were used as descriptive statistics. Independent T-test for two samples was used for normally distributed variables and Mann-Whitney U test was used for the variables which did not show normal distribution in comparison of two groups. In comparison of three or more groups, ANOVA test was used for normally distributed variables and Kruskal Wallis variance analysis was used for the variables which did not show normal distribution. In comparison of categorical variables, chi-square test was used. A p value of <0.05 was considered statistically significant.

Results

Ninety-seven (64%) of 150 patients who were included in the study were male and 53 (36%) were female. The mean age at the time of diagnosis was 14.95±2.94 years (1-17 years). The follow-up period of the patients ranged between 6 months and 11 years (5.72±3.39 years). The mean±SD (median) ALT, AST and HBVDNA levels at the time of diagnosis were found to be (log mean±SD) 54.53±77.85 U/L (28,0 U/L), 42.38±43.42 U/L (30 U/L) and 5.98±3.11 (7.86), respectively. 59 (39.3%) of the patients were inactive carriers, 61 (40.7%) were immunotolerant, 30 (20%) were in the immunoreactive stage. Verti-

Table 1. Characteristics of the patients included in the study (n=150)

Age (years), Mean±SD	14.95±2.94
Gender (male), n (%)	97 (64)
ALT (U/L), Mean±SD (median)	54.53±77.85 (28)
AST(U/L), Mean±SD (median)	42.38±43.42 (30)
HBVDNA (logIU/mL)	5.98±3.11
Mode of transmission, n (%)	
Horizontal	41 (27.3)
Vertical	86 (57.3)
Unknown	23 (15.3)
Disease status, n (%)	
Inactive carrier	59 (39.3)
Immunotolerant stage	61 (40.7)
Immunoactive stage	30 (20)
Patients who underwent biopsy, n (%)	19 (12.6)
HAI score, Mean±SD	5.9±2.6
Portal fibrosis, Mean±SD	2.68±1.94
Mode of treatment, n (%)	
Lamivudine	29 (80.5)
IFN	3 (8.3)
IFN+Lamivudine	4 (11.2)

ALT: alanine aminotransferase, ST: aspartate aminotransferase, HBV: hepatitis B virus; DNA: deoxyribonucleic acid; HAI: hepatitis activity index; IFN: interferon; Mean±SD: Mean±standard deviation

Table 2. Characteristics of the patients who received and who did not receive treatment

	Patients who received treatment (n=16)	Patients who were monitored	p value
Age (years), Mean±SD	14.88±3.04	14.97±2.92	0.960
Gender (male), n (%)	21 (58.3)	76 (66.6)	0.366
ALT (U/L), Mean±SD (median)	124.22±123.18	33.14±37.50	<0.001
AST(U/L), Mean±SD (median)	72.24±73.11	33.09±21.95	<0.001
HBVDNA (logIU/mL)	8±1.62	5.33±3.20	<0.001
HAI score, Mean±SD	6.33±2.51 (16)	5.81±2.68 (3)	0.692
Portal fibrosis score, Mean±SD	2.87±2.06	1.66±0.57	0.218
Mode of transmission, n (%)			
Horizontal	26 (72.2)	66 (57.8)	
Vertical	7 (19.4)	28 (24.5)	0.009
Unknown	3 (8.3)	20 (17.5)	

ALT: alanine aminotransferase, ST:aspartate aminotransferase, HBV: hepatitis B virus; DNA: deoxyribonucleic acid; HAI: hepatitis activity index; IFN: interferon; Mean±SD: mean±standard deviation

cal transmission was present in 86 (57.3%) of the patients, horizontal transmission was present in 41 (27.3%) and the mode of transmission was unkonw in 23 (15.3%). Parenteral transmission did not occur in any of our patients. Accompanying hepatitis D and C virus infection was not present in any of our patients. Biopsy was performed in 19 patients (12.6%). While 16 (84.2%) of the patients in whom biopsy was performed were in the immunoreactive stage, 3 (15.8%) were in the immunotolerant stage. Histological activity index and fibrosis score (mean±SD) were 5.9±2.6 and 2.68±1.94, respectively (Table 1).

While treatment directed to HBV infection was given to a total of 36 patients (24%), no treatment was given to 114 patients (76%). When the mean age, ALT, AST, HBVDNA (log) levels, mode of transmission, HAI and fibrosis score were compared between the patients who received and did not receive treatment, it was found that ALT (124.22±123.18 U/L), AST (72.24±73.11 U/L), HBVDNA log levels (8.00±1.62) were significantly higher in the patients who received treatment compared to the patients who did not receive treatment (p<0.001). In addition, the rate of inititating treatment was higher in the patients with vertical transmission (p=0.009). In comparison of the groups, independent T-test for two samples was used for normally distributed variables, Mann-Whitney U test was used for the variables which did not show a normal distribution for numerical data and chi-square test was used in comparison of categorical variables (Table 2). Treatment was inititated in 2008 and before in 27 of the patients (75%), while only 9 patients (25%) started to be treated in 2009 and afterwards. Biopsy was performed in 16 of the patients (44%) who were given treatment and treatment was started without performing biopsy in 20 (56%) patients. The mean HAI and fibrosis score values were found to be 6.33±2.51 and 2.87±2.06, respectively in the patients who were given treatment.

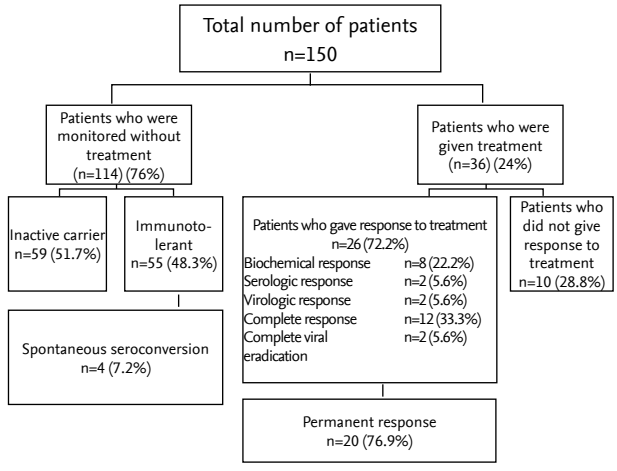

Figure 1. Prognosis in the patients with hepatitis B virus infection

Among the patients who were given treatment, lamivudine (4 mg/kg/day) was given to 29 patients (80.5%), IFN-α (6 MU/m², three days a week) was given to 3 (8.3%) patients and both IFN-α and lamivudine (complementary treatment) was given to 4 patients (11.2%). While interferon-α was given for a period of 6 months, lamivudine was given for a period of at least one year and continued for 6 months further after antiHBe seroconversion was provided. In complementary treatment, IFN-α was given for 6 months in combination with lamivudine. The mean time of lamivudine treatment was 30.05±15.55 months (12-60 months). While response to treatment was obtained in 26 (72.2%) of 36 patients who were given treatment, no response was obtained in 10 patients (27.8%). The time to obtain response to treatment was

Table 3. Characteristics and treatment responses of the treatment groups

	Lamivudine (n=29)	IFN-α (n=3)	Complementary treatment (n=4)
Age (years), Mean±SD	14.93±2.95	13.33±5.50	15.75±1.89
Gender (male), n (%)	17 (58.6)	2 (66.6)	2 (50)
ALT (U/L), Mean±SD (median)	134.34±132.84	96.00±6.00	54.66±30.28
AST (U/L), Mean±SD (median)	77.22±79.46	57.33±36.35	42.33±10.96
HBVDNA (logIU/mL), Mean±SD	7.98±1.72	7.06±1.13	8.80±1.15
HAI score, Mean±SD	5.58±2.53	9.00±1.41	4.60±2.82
Portal fibrosis score, Mean±SD	2.42±1.31	3.50±0.70	5.00±5.65
Mode of transmission, n (%)			
Vertical	12 (41.3)	0 (0.0)	1 (25.0)
Horizontal	12 (41.3)	2 (66.6)	2 (50.0)
Unknown	5 (17.4)	1 (33.4)	1 (25.0)
Positive treatment response, n (%)	19 (65.5)	3 (100)	4 (100)
Mode of treatment response, n (%)			
Biochemical response	7 (36.8)	0 (0.0)	1 (25)
Serologic response	1 (5.2)	1 (33.3)	0 (0.0)
Virologic response	2 (10.4)	0 (0.0)	0 (0.0)
Complete response	8 (42.4)	1 (33.3)	3 (75)
Complete viral eradication	1 (5.2)	1 (33.3)	0 (0.0)

ALT: alanine aminotransferase, ST:aspartate aminotransferase, HBV: hepatitis B virus; DNA: deoxyribonucleic acid; HAI: hepatitis activity index; IFN: interferon; Mean±SD: mean±standard deviation

24.23±15.23 months (6-50 months). Biochemical response occured in 8 (22.2%) of the patients in whom response to treatment was obtained, while serological reponse occured in 2 (5.6%), viral response occured in 2 (5.6%), full response was obtained in 12 (33.3%) and full viral eradication occured in 2 (5.6%) (Figure 1). Permanent response occured in 20 of these patients (76.9%). Demographic, laboratory, histological properties and treatment responses of the treatment groups are shown in Table 3. No statistically significant difference was found between the groups in terms of pre-treatment age, laboratory values (ALT, AST and HBV DNA) and histological evaluation (HAI and portal fibrosis score) ($p>0.05$). Kruskal Wallis Variance analysis was used in comparison of the groups. No statistically significant difference was found between the groups in terms of pre-treatment demographic properties, laboratory values, histological evaluation and treatment responses ($p>0.05$). No difference was observed in treatment responses in the patients in whom treatment was inititated after performing biospy and the ones in whom treatment was inititated without performing biopsy ($p=0.111$).

Spontaneous HBeAg seroconversion occured in 4 (7.2%) of the patients (n=55) who were being followed up without treatment. The mean time to occurence of seroconverison in these patients was 2.50±1.91 years (1-5 years) (Table 4).

Hepatocellular cancer or mortality related with HBV did not occur in any of our patients during the follow-up.

Discussion

Hepatitis B virus causes to acute and chronic liver disease in children and adolescents worldwide. Infection in the childhood is associated with decompensated liver disease, increased morbidity and mortality related with cirrhosis and hepatocellular carcinoma in the advanced period of life.

Hepatitis B virus is transmitted by parenteral contact with infected blood or body fluids (percutaneous), sexual contact, transmission from the infected mother to the newborn and close contact with infected people which does not include sexuality (5, 6). In our country, prenatal transmission was found predominantly (43.9%) in children in a study performed by Canpolat et al. (9) in 2013. Similar to the literature, prenatal transmission was found more frequently also in our study (57.3%). However, the rate of prenatal transmission is expected to decrease in future years in our country with the effect of the vaccination program.

Inactive carriers (39.3%) constitute an important portion of our patients. As a result of the studies performed in different coun-

Table 4. Demographic and laboratory findings of the patients with spontaneous seroconversion

	First patient	Second patient	Third patient	Fourth patient
Gender	Female	Male	Male	Male
Age (years)	12	3	7	10
Mode of transmission	Horizontal	Vertical	Unknown	Unknown
ALT (U/L)	19	14	65	19
AST (U/L)	21	76	60	28
HBVDNA log (IU/mL)	3.56	7.27	6.78	2.62
Seroconversion period (years)	1	5	1	3

ALT: alanine aminotransferase, ST: aspartate aminotransferase, HBV: hepatitis B virus; DNA: deoxyribonucleic acid; HAI: hepatitis activity index

tries, the incidences of chronic active hepatitis and cirrhosis were found to be 1.6% and 0.7%, respectively and development of severe liver disease was observed rarely in these patients (10, 11). Cirrhosis or severe liver disease did not develop in any of our inactive carrier patients. 40.7% of our patients were in the immunotolerant stage. In this stage when the immune system has not matured yet, HVB multiplies with a high rate, but necroinflammation and fibrosis do not develop in the liver (12). As the immune system matures, immune response develops against HBV antigens generally in the adolescence or adulthood and hepatocellular damage starts (13). This stage is called the immunoreactive stage. While some patients are completely asymptomatic in this stage, some may have attacks which mimic acute hepatitis and which even progress to fulminant hepatic failure (14). Cirrhosis and hepatocellular cancer may develop in advanced years in these patients (15). In our study, the patients in the immunoreactive stage were found with the lowest rate and cirrhosis or hepatocellular cancer did not develop in any of them in the follow-up.

Although liver biopsy is recommended to be performed before treatment before hepatitis B infection is initiated, some authors think that biopsy is not necessary, since it is an invasive procedure and does not affect the treatment decision (16-18). It has been stated that treatment can be initiated without performing biopsy in HBeAg positive patients with an alanine aminotransferase level higher than 2-fold of the normal value and serum HBVDNA above 20 000 IU/mL (16). In these patients, liver biopsy may provide additional useful information, but does not change the treatment decision. Use of a non-invasive procedure to confirm or exclude presence of cirrhosis and to estimate the degree of fibrosis may be useful in patients in whom treatment has been inititated without performing liver biopsy. In our department, it was observed that no difference was present in treatment responses in the patients in whom treatment was inititated after performing biopsy and the patients in whom treatment was inititated without performing biopsy.

Lamivudine which is a nucleoside analog has been used in treatment of chronic HBV for many years. In the study of Jonas et al. (19), the rate of loss of HBeAg and HBVDNA was found to be 23% in the patients who were receiving lamivudine treatment (20). In the study of Canpolat et al. (9), HBeAg loss found with a rate of 39.3% and HBVDNA loss found with a rate of 50% in the Turkish children who received lamivudine. In our study, 65.6% of the children who were given lamivudine treatment gave response to treatment. Full response developed in 34.4% of these patients, biochemical response developed in 17.2%, virological response developed in 6.8%, serologic response developed in 1 (3.4%) and full viral eradication developed in 1 (3.4%). 34.4% of the patients who were given lamivudine did not give response to treatment. Although the time of usage of lamivudine was shorter in the patients who gave response to treatment (28.15±13.75 months), the difference was not statistically significant. In the study of Kuloğlu et al. (21), it was stated that treatment with lamivudine for a mean period of 18 months would be sufficient. Jonas et al. (22) showed that lamivudine could be used safely up to three years. Genetic study directed to lamivudine resistance was not performed in any of the patients who did not give response to lamivudine treatment. Tenofovir treatment was started in one patient who did not give response to lamivudine treatment. However, this patient was lost to follow-up after inititation of treatment, since he entered into the adulthood age group. Another agent used in treatment of children with chronic HBV infection is IFN-α. In studies conducted with Turkish children, HBeAg loss was found with a rate of 26-69% and HBVDNA loss was found with a rate of 26-61.5% with IFN-α treatment (9, 23). In a multi-center study conducted in Turkey, a total of 182 pediatric patients were divided into three groups; IFN-α was administered with a dose of 10 MU/m^2 in the first group for 6 months, a combination of IFN-α at a dose of 5 MU/m^2 and lamivudine at a dose of 4 mg/kg/day was admnistered in the second group for 12 months and a combination of IFN-α at a dose of 10 MU/m^2 and lamivudine at a dose of 4 mg/kg/day was administered in the third group for 12 months. Conclusively, it was concluded that complementary treatment alone was not superior to IFN-α treatment (24). In another multi-center study performed in Turkey, IFN- and lamivudine complementary treatment were administered as two different regimes in 177

children with chronic HBV (25). In the first group, the two agents were started together, IFN- was administered at a dose of 9 MU/m^2 for 6 months and lamivudine was administered until response was obtained. In the second group, lamivudine was started primarily and IFN was added 2 months later with the same dose and for the same period. Response to treatment was found with a rate of 55.3% in the first group and with a rate of 27.6% in the second group. Selimoğlu et al. (26) found treatment response with a high rate (61.5%) with a combination of standard dose IFN-α and lamivudine. In the study performed by Dikici et al. (23), 10 MU/m^2 IFN-α plus 4 mg/kg/day lamivudine combination was admninistered for 12 months in one patient group and 10 MU/m^2 IFN-α was administered for 12 months in the other patient group. They found the combination group more successful in terms of returning of ALT level to normal ranges and loss of HBVDNA at the end of treatment, but they found no significant difference between the groups in terms of permanent response 6 months after the end of treatment. In our study, no significant difference was found between treatment groups in terms of rates of treatment response.

If the immune system of immunotolerant children can produce sufficient response, damage starts to occur in the infected liver cells as a result of interaction between the immune system and the virus. Liver enzymes are increased, HBVDNA level decreases or becomes negative, antiHBe seroconversion develops. Afterwards, transaminases reduce to normal or near-normal values and the disease enters into the inactive carrier stage (27, 28). While spontaneous HBeAg loss is observed with a rate of 10-16% annually in chronically infected children, spontaneous HBsAg loss has been reported to be 0.6% annually (27, 28). In the study performed by Selimoğlu et al. (26), the rate of spontaneous antiHBe seroconversion was found to be 2.8%. The follow-up period ranged between 1 and 11 years in 55 immunotolerant patients whom we followed up without giving treatment (5.80±4.92 years). While spontaneous seroconversion occured in 4 (7.2%) of these patients, antiHBs seroconversion did not develop in any of our patients.

Cirrhosis, progression to active hepatitis or hepatocellular cancer did not develop in any of our patients during the follow-up. This may be related both with the number of subjects and the short follow-up time. In addition, a limitation of our study was the low number of the patients who received treatment. Conclusively, chronic HBV infection has a more benign prognosis in children compared to adults, though it may lead to development of hepatic failure, cirrhosis and hepatocellular cancer. In addition, the incidence of infection is expected to be low in future years in children due to vaccination programs. However, studies related with use of different drugs in cases with no response to treatment should be performed.

Ethics Committee Approval: The study was conducted retrospectively by checking records of the patients. Therefore, there is no ethics committee approval.

Informed Consent: The study was conducted retrospectively by checking records of the patients. Therefore, there is no informed consent.

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