

Case Control Study

Chronic hepatitis B in children with or without malignancies: A 13-year follow-up

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METHODS: Twenty four children (15 boys and 9 girls) with malignancies, followed up by the pediatric gastroenterology outpatient clinic for CHB between January 2000 and December 2013, were enrolled in the study (Group 1). Group 2 was formed with twenty five children (11 girls and 14 boys) diagnosed with CHB without malignancies. The data from the patients' records were compared between the two groups.

RESULTS: Hepatitis B e antigen (HBeAg)/antiHBe seroconversion was observed in 3 patients (12.5%) in group 1 and 15 patients (60%) in group 2, with annual seroconversion rates of 1.61% and 16.6%, respectively, and the difference was significant ($P < 0.01$). One patient (6.6%) in Group 1 and 9 patients (53%) in Group 2 showed HBeAg/antiHBe seroconversion after treatment and the difference between the two groups was significant ($P < 0.06$) Loss of hepatitis B surface antigen was observed in one patient in each of group 1 and 2. No clinical, laboratory and imaging findings of liver disease were observed in any of the patients at the end of the study.

CONCLUSION: HBeAg/antiHBe seroconversion rate was lower in patients who had recovered from cancer.

Key words: Chronic hepatitis B; Children; Pediatric malignancies; Seroconversion; Course of the disease

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Core tip: Children with hematological cancers have a high risk for hepatitis B virus infection due to immunosuppression secondary to chemotherapy, radiotherapy and multiple blood transfusions. Although there are some studies in the literature addressing the course of chronic hepatitis B (CHB), few studies were conducted on patients with CHB who have been treated for cancer. The aim of our study is to evaluate the clinical characteristics and the course of CHB in a cohort

Abstract

AIM: To evaluate the outcome of chronic hepatitis B (CHB) in children with or without malignancies.

consisting of Turkish children with CHB who had received pediatric cancer therapy and compare the results with children diagnosed with CHB who do not have cancer.

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INTRODUCTION

Following initiation of a universal vaccination program and scanning of blood donors in many countries, the prevalence of hepatitis B virus (HBV) infection has been significantly decreased. However, many children are still being infected every year, and chronic infection frequently develops despite regular follow-ups^[1]. While the course of chronic hepatitis B (CHB) is benign during childhood and adolescence, cirrhosis develops in 3%-5% and hepatocellular carcinoma (HCC) develop in 0.01%-0.03% of chronic patients before adulthood. For whole life, this risk increases to 9%-24% for HCC, and the incidence of cirrhosis increases to 2%-3%/year^[2].

While most children with CHB may be asymptomatic based on normal growth and physical examination findings, normal or minimally abnormal aminotransferase levels and progressive inflammatory changes in liver histology may be seen. In HBeAg-positive children, liver histology usually may reveal mild to moderate inflammation accompanied with minimal fibrosis at any age. During HBe seroconversion, hepatic lobular changes including portal inflammation and fibrosis of various grades with or without piecemeal necrosis develop^[3].

Children with hematological cancers have a high risk for HBV infection due to immunosuppression secondary to chemotherapy, radiotherapy and multiple blood transfusions^[4]. In most of such children, HBV infection is characterized by mild symptoms, and usually leads to chronic hepatitis or prolonged carrier state^[5]. Blood and organ donors with occult HBV infection are possible sources for immunosuppressed hosts. Such patients may show different courses of the disease^[6]. However, severity of hepatic damage in patients following treatment including chemotherapy and radiotherapy is uncertain. Nevertheless, it is well known that chemotherapy suppressing the immune system may cause an increase in HBV DNA (viral load) and may lead to hepatic damage due to lack of immune system control^[7]. Besides, chemotherapy can be directly hepatotoxic, and some chemotherapeutic agents and corticosteroids may cause damage to the liver or may lead to fulminant hepatitis, or to hepatic failure by stimulating viral replication. There is a specific area in the HBV genome which directly stimulates

replication^[7,8].

In children who have been treated for cancer or without cancer, HBV infection may show an acute and self-limiting course or a fulminant course progressing to hepatic failure with high mortality rate, or may persist for more than 6 mo progressing to chronic infection. Therefore, current anti-viral agents are used to eradicate HBV in children infected with HBV. These anti-viral agents, albeit not having sufficient efficacy, can prevent progression of liver damage. Treatment strategies for children with CHB focus on inhibition of viral replication to prevent active liver damage, and induce HBe Ag seroconversion^[9].

Although there are some studies in the literature addressing the course of CHB, few studies were conducted on patients with CHB who have been treated for cancer. The aim of our study is to evaluate the clinical characteristics and the course of CHB in a cohort consisting of Turkish children with CHB who had received pediatric cancer therapy and compare the results with children diagnosed with CHB diagnosis who do not have cancer. The study had a case-controlled and comparative design.

MATERIALS AND METHODS

The study included 24 patients (15 males, 9 females) with CHB who had received cancer therapy (group 1), and 25 patients (14 males, 11 females) with CHB who had not received cancer therapy. The patients were followed-up by the pediatric gastroenterology outpatient clinic of Sisli Hamidiye Etfal Training and Research Hospital between January 2000 and December 2013.

Five (20.8%) of the patients in Group 1 were diagnosed with solid tumors, and 19 (79.1%) were diagnosed with leukemia/lymphoma. All patients included in the study were in remission and had not received chemotherapy for at least 12 mo. During the therapy, each patient had received 19.19 ± 17.44 units (1-80 units) blood and blood products on average. The average duration of hepatitis B surface antigen (HBsAg) seropositivity after cancer therapy was 24.05 ± 19.52 mo (3-96 mo) in the patients in group 1. The patients included in the study were routinely tested for HBV markers as well as HCV during chemotherapy and at the end of the therapy. All patients in group 1 had serological markers for CHB for longer than 6 mo. None of the subjects had a history of liver disease or had received blood or blood products before the onset of cancer.

The mean age of the patients in group 2 at diagnosis was 9.11 ± 3.69 years. Their serological markers for CHB had been positive for longer than 6 mo. With respect to transmission route of the disease in the patients in group 2, 6 were born to a mother with hepatitis B, 9 were cases of intrafamilial transmission, and 4 had a history of dental extraction. The transmission routes for 6 patients were unknown. The

demographics of the patients in both groups are shown in Table 1.

Those who had a concomitant systemic disease, and those with accompanying hepatitis C, delta hepatitis, HIV infection or other liver disease (*e.g.*, liver disease associated with α -1 anti-trypsin deficiency, Wilson's disease, autoimmune hepatitis, cystic fibrosis and celiac disease) were excluded from the study. All patients were asymptomatic at diagnosis and none of those included in the study had cirrhosis or HCC.

Method

The physical examination findings, liver function tests, risk factors for HBV infection, ages, clinical findings of liver disease, complete blood counts, virological markers (*e.g.*, HBsAg, anti-HBs, HBeAg, anti-HBe and serum HBV DNA levels), α -fetoprotein levels and auto-antibodies of all patients at diagnosis were collected from their medical records. Serum aspartate aminotransferase and alanine aminotransferase (ALT) levels were evaluated using standard methods (upper limit of normal: 50 IU/L).

All patients were monitored through physical examination, liver function tests and virological tests every 3 to 6 mo. Ultrasonographic examinations and α -fetoprotein tests were done at 6 to 12-mo intervals.

Liver biopsy was performed in patients with increased ALT levels (NX2 or above) for longer than 6 mo, increased HBV DNA, and HBe Ag (+) during the follow-up. After consent forms were obtained, the liver biopsy materials were evaluated by the same liver pathologist blinded to the clinical and biochemical data of the patients. The biopsy materials were evaluated for fibrosis scores using necroinflammatory activity and Knodell histological activity index (HAI).

Patients whose liver biopsy revealed moderate to severe necroinflammation and/or findings beyond mild fibrosis were treated. Pre-treatment ceruloplasmin, α -1 anti-trypsin, autoimmune antibodies and HCV values were normal. Fifteen patients from group 1 and 17 patients from group 2 were given treatment. The patients assigned to receive treatment were administered recombinant interferon (5 MU/m² per day, three times a week for 6 mo subcutaneously, and lamivudine (maximum 100 mg, for at least 1 year). Treated patients were monitored through monthly physical examination, complete blood count, liver enzymes, viral serological markers (at the initiation of the treatment, month 3 and month 6), autoimmunity markers at 6-mo intervals, and annual ultrasonography and alpha fetoprotein levels.

Follow-up and definitions

The treated patients in both groups were followed up every 3 mo after the completion of treatment. Also the untreated HBeAg (+) patients were followed up every 3 mo. Patients with HBeAg/anti-HBe seroconversion, normal ALT levels and HBV DNA < 2000 IU/mL were followed up every 6 mo.

Inactive carrier state was defined as patients with HBeAg (-), anti-HBe (+) HBV DNA (-) or < 2000 IU/mL, and normal ALT levels. Biochemical response was defined as a normalization of ALT levels. Serological response for HBeAg was considered to be disappearance of HBeAg and development of anti-HBe antibody in HBeAg (+) patients. The serological response for HBsAg was a disappearance of HBsAg and development of anti-HBs antibody while the virological response was HBV DNA levels that were non-detectable or < 2000 IU/mL 6 mo after the completion of the treatment. A sustained virological response was a continuance of the virological response for at least 12 mo after cessation of the treatment, while a complete response was prolonged HBsAg loss along with virological response, without treatment^[1].

The initial findings at diagnosis, response to treatment in treated patients, liver biopsy findings and final state of the disease were compared between the two groups.

Informed consent was obtained from the patients and their guardians before procedures.

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, United States) were used for statistical analysis. For evaluating the study data, besides descriptive statistical methods (mean, standard deviation, median, frequency, ratio), an independent samples test was used to compare parameters that showed normal distribution and Mann-Whitney *U* test was used to compare parameters that were not distributed normally between groups. Pearson χ^2 test, Yates Continuity Correction and Fisher's Exact test were used to compare qualitative data. *P* < 0.05 was accepted as statistically significant. Kaplan Meier analysis and log rank test were used to evaluate seroconversion rates.

RESULTS

The rate of the cases detected to be HBsAg (+) among the pediatric oncology patients who had been followed up for the last 13 years was 6%.

Forty-nine patients (group 1 = 24 patients, group 2 = 25 patients) with CHB diagnosis who had been followed up at the outpatient clinic for a period of 13 years were included in the study. The demographics of the patients are shown in Table 1.

The initial laboratory results of the patients in both groups are shown in Table 2. No significant difference was found in ALT levels, HBV DNA, albumin, INR, α -fetoprotein, HAI or fibrosis staging between the two groups (*P* > 0.5).

Throughout the follow-up period, interferon (5 MU/m² per day, three times a week for 6 mo) and lamivudine (maximum 100 mg for at least 1 year) were initiated in 15 patients with active hepatitis infection from group 1, and 17 patients with active

Table 1 Main characteristics of the patients with chronic hepatitis B in both groups *n* (%)

	Groups	
	Group 1, <i>n</i> = 24	Group 2, <i>n</i> = 25
Gender		
Female	9 (37.5)	11 (44.0)
Male	15 (62.5)	14 (56.0)
mean age at diagnosis (yr, mean ± SD)	10.89 ± 2.67	9.11 ± 3.69
Solid tumour	5 (20.8)	
Leukemia/lymphoma	19 (79.1)	
Diagnosis time after chemotherapy	2.00 ± 1.92	
Number of transfusions (mean ± SD)	19.19 ± 17.44	
Route of transmission		
HBsAg(+) mother	0	5 (20)
History of dental extraction	0	3 (12)
Family contact	0	5 (20)
Unknown	24	12 (48)

Group 1: Patients cured of malignancy with chronic hepatitis B (CHB); Group 2: Children diagnosed CHB without malignancy.

Table 2 Initial laboratory and liver biopsy findings of the patients in both groups

	Group 1, <i>n</i> = 24	Group 2, <i>n</i> = 25	<i>P</i> value
HBsAg (+)	24/24	25/25	
HBsAg (+)	24/24	25/25	
¹ HBV DNA > 10 ⁵ copies/mL	24/24	25/25	
¹ ALT N	9	8	0.350
ULNX2	11	10	
ULNX3	4	7	
² Alpha fetoprotein	2.35 ± 1.84 (1.84)	1.66 ± 0.54 (1.60)	0.053
Albumin	4.27 ± 0.22	4.22 ± 0.32	0.654
INR	1.08 ± 0.07	1.07 ± 0.07	0.894
² Hepatitis activation index (mean ± SD)	5.41 ± 2.94 (5.00)	5.91 ± 2.52 (5.00)	0.644
² Fibrosis (mean ± SD)	1.38 ± 1.15	1.04 ± 0.64	0.441
Treated patients (INF-α and LAM)	15	17	

¹χ² test; ²Mann Whitney *U* test. HBsAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis-B virus; ALT: Aminotransferase.

hepatitis infection from group 2. One patient (6.6%) in Group 1 and 9 patients (53%) in Group 2 showed HBsAg/antiHBs seroconversion after treatment and the difference between the two groups was significant (*P* < 0.06) (Table 3).

No treatment was initiated in 9 patients from group 1 and 8 patients from group 2, because they had HBs Ag (+), anti-HBs (-), normal ALT levels, HBV DNA > 10⁵ copies/mL. At the end of the study, HBsAg/anti-HBs seroconversion developed in 2 of these patients from group 1 and 6 of 8 patients in group 2. When all patients were evaluated for HBsAg/anti-HBs seroconversion at the end of the study (treated and untreated), HBsAg/

Table 3 Seroconversions to anti hepatitis B e and anti-hepatitis B surface in both groups *n* (%)

Seroconversions	Groups		<i>P</i> value
	Group 1	Group 2	
Treatment induced ¹			
HBsAg to HBsAb	1 (6.6)	9 (53)	0.006
Treatment induced			
HBsAg to HBsAb	0	0	
Total HBsAg to HBsAb ¹ (treatment induced and spontan seroconversion)	3 (12.5)	15 (60)	0.002
Total HBsAg to HBsAb ¹ (treatment induced and spontan seroconversion)	1 (4.1)	1 (4)	1.000

¹Fisher's Exact test. HBsAg: Hepatitis B e antigen.

Table 4 Evaluation of hepatitis B e antigen/anti- hepatitis B e seroconversion with Kaplan-Meier analysis *n* (%)

	<i>n</i>	HBsAg(-)/antiHBs(+)	HBsAg (+)/ anti-HBs(-)	Seroconversion annual Rate
Group 1	24	3 (12.5)	21 (87.5)	1.61%
Group 2	25	15 (60.0)	10 (40.0)	16.66%
Total	49	18 (36.7)	31 (63.3)	8.33%

Kaplan-Meier analysis. HBsAg: Hepatitis B e antigen.

antiHBs seroconversion was observed in 3 patients (12.5%) from group 1 and 15 patients (60%) from group 2, with annual seroconversion rates of 1.61 and 16.6%, respectively. The difference between the two groups was significant (*P* < 0.002). No HBV DNA was detected in 12 of these patients, and HBV DNA was < 2000 IU/mL in 6. HBsAg-anti-HBs and HBsAg/anti-HBs seroconversions in both groups are listed in Table 3. E-seroconversion levels determined using Kaplan-Meier analysis are shown in Table 4.

When the transmission routes for patients who developed HBsAg/anti-HBs seroconversion in group 2 were evaluated, it was seen that 6 of them were cases of intrafamilial transmission and 4 had a history of dental extraction. The transmission routes for 5 patients were unknown.

At the end of the study period, s-seroconversion (anti-HBs (+)/HBs Ag (-)/HBV DNA absent or < 2000 IU/mL per normal ALT) was observed in 1 patient from group 1. HBs Ag seroconversion developed in 1 patient from group 2 (anti-HBs (+) HBV DNA not detected and ALT was normal).

For 21 subjects from group 1 and 10 subjects from group 2, HBsAg (+) anti-HBs (-) HBV DNA > 10⁵ copies/mL and normal ALT levels were observed at the end of the study.

No clinical, laboratory and imaging findings of liver disease were found in any of the patients at the end of the study.

DISCUSSION

CHB continues to be a global health problem. In Turkey, a vaccination program for hepatitis B was initiated in 1998^[10]. In our country, the prevalence of HBV infection in the healthy population was reported to be 5.4%-8.2% (moderately endemic)^[10,11]. In children with hematological diseases and malignancies receiving chemotherapy and multiple transfusions, the prevalence was reported to be 2%-11.6%^[5,7,12]. In our study, we found the HBsAg seropositivity to be 3.07%, which is consistent with the literature, in hemato-oncological cancers.

Transmission routes of CHB infection vary among different zones of the world. While either vertical/perinatal transmission or horizontal transmission during early childhood is observed in the highly endemic areas (mainly in Asian countries), HBV infection is seen in all age groups in the moderately endemic areas and parenteral and sexual transmission are observed more frequently in individuals close to adulthood in the low-level endemic zones^[6]. In our cohort, although the transmission routes in the patients in group 1 are not known exactly, when the transmission routes were examined in the patients in group 2, the rates were found as follows: vertical transmission 24%, horizontal transmission 36% and dental extraction history 16%. The transmission routes could not be determined in 24% of the patients.

Three phases were determined for CHB infection in children: immune tolerant, immune active and inactive carrier^[13]. HBeAg seroconversion is accompanied by a reduction in HBV DNA levels; histological findings in liver biopsy demonstrate mild to moderate inflammation with minimal fibrosis^[2,4]. Although it occurs during childhood, spontaneous HBeAg seroconversion is rarely seen in children under 3 years of age. In many cases, this process is seen during adolescence and early adulthood. In the early stages of HBeAg seroconversion, children are still asymptomatic or show mild non-specific symptoms^[2,6]. All of our subjects in both groups were between 4 and 14 years of age. Our subjects were asymptomatic, and no chronic liver disease findings and no development of liver cancer were noted during the 13-year follow-up.

In the literature, it is reported that inflammation that begins in various grades at any age increases and progresses with age^[3]. Pre-treatment biopsies were taken from our subjects, and the histopathological examinations of the biopsy specimens showed that means of fibrosis were 1.38 ± 1.15 in group 1 and 1.04 ± 0.64 in group 2. The difference between the two groups was not significant. HAI scores were 5.41 ± 2.94 (5.00) (group 1) and 5.91 ± 2.52 (5.00) (group 2). The difference between the two groups was not considered significant.

There are long-term studies in the literature relating to the natural course of the disease in children^[14-20]. In the studies relating to this, effects of ethnicity and

the transmission route of infection on HBeAg/anti-HBe seroconversion were significant^[14,18]. The study conducted by Popalis *et al.*^[14] included a multiethnic group, and it was reported that younger, non-Asian origin children with increased ALT levels show more e-seroconversion. The authors reported a rough rate of 41% for e-seroconversion. In the study of Zacharakis *et al.*^[18], HBeAg/anti-HBe seroconversion rate (43%) was lower in Muslim children than the other ethnicities. In a study conducted among Chinese children, a more homogenous group, e-seroconversion rate was 7%^[15]. In the study of Marx *et al.*^[16] e-seroconversion rate was reported to be 40.2%. Their study included children of different ethnicities, and low HBeAg-AntiHBe seroconversion was found in Asian patients with vertical transmission route. Our study group consisted of patients of a homogenous group in terms of ethnicity. Our patients were of Asian origin and Muslim. In our study, the cumulative HBeAg/anti-HBe seroconversion rate in both groups was 36.7% (8.33%/year). In group 1, the rate was significantly low; *i.e.*, 12.5% (1.61%/year). In group 2, the rate was 60% (16.6%/year). The patients in group 1 had been treated for cancer. The low seroconversion rate in the subjects in group 1 may be explained by the facts that anti-cancer drugs can inhibit both humoral and cellular response and immunosuppressive effects of chemotherapy may be relevant in the proliferation and persistence of HBV. In the literature, there are few studies investigating the natural course of infection in children with CHB who have been treated for cancer. Immune function is believed to have a key role in the severity of HBV infection. Anti-cancer drugs inhibit both humoral and cellular responses. The immunosuppressive effect of chemotherapy on cell-mediated functions may be effective in the proliferation and persistence of HBV.

The vertical transmission route adversely affects HBeAg/anti-HBe seroconversion^[16,18]. In the study of Bortolotti *et al.*^[17], the e-seroconversion rate was high (84%) during a 13-year follow-up period on average. However, patients with vertical transmission accounted for a small number of their patients. Although one of the limitations of our study was that we could not exactly evaluate the transmission routes of the patients in group 1, none of the three patients who developed seroconversion in this group had a history of vertical transmission. No vertical transmission was observed in any of the patients who developed HBeAg/antiHBe seroconversion in group 2. Another limitation of the study was that the moment of infection was not known.

Similarly with adults, the target of CHB treatment in children is to increase long-term survival, and to improve quality of life by decreasing the risk of progressive liver disease and HCC^[2]. Antiviral therapy (with interferon or lamivudine) is effective during the immune clearance phase of the infection to suppress viral replication and to induce HBeAg seroconversion, and is indicated in the immune active phase of the

infection^[2,21]. In our patients, we used a combination of interferon and lamivudine. The post-treatment HBeAg/antiHBe seroconversion rates in subjects in group 2 and group 1 were 53% and 6.6%, respectively. The difference between the two groups was statistically significant. In many studies relating to CHB conducted on children with cancer, the efficacy of treatment was questioned. Koçak *et al.*^[22] reported HBeAg/anti-HBe seroconversion in two (25%) of eight patients receiving recombinant interferon α therapy. Kasirga *et al.*^[23], reported HBeAg/anti-HBe seroconversion in three (27.3) of 11 patients receiving interferon α -2b therapy. These studies were not long-term studies. In their study, Saltik-Temizel *et al.*^[24] reported the results obtained 5 years after CHB treatment in children with cancer, and reported HBeAg/anti-HBe seroconversion in 33.3% (4/12) of the patients. In their study, one patient showed HBeAg/anti-HBe seroconversion at the end of the treatment, and three during the follow-up. However, in the literature, we could not identify studies on the natural course and follow-up of HBV infection in children treated for cancer. When we compared the two groups after a follow-up period of 13 years, treatment-induced and total e-seroconversion were lower in patients with cancer.

Spontaneous HBsAg/antiHBs seroconversion is quite rare during childhood (0.6%-1%/year)^[2,16,21]. Loss of HBsAg and development of anti-HBs were observed in 2 patients in both groups. In the study of Zacharakis *et al.*^[18], the rate was 1%/year. In a Japanese cohort, no s-seroconversion was seen during observation periods^[19]. Ruiz-Moreno *et al.*^[20] reported that clearance of HBsAg was observed in only 5% of 103 Spanish children with CHB in a follow-up period of 6.3 years.

In conclusion, we found that both post-treatment and spontaneous HBeAg/antiHBe seroconversion rates are lower in subjects recovered from cancer. However, we observed a mild clinical course in the patients in both groups after a follow-up period of 13 years. We think that CHB infection show a more benign course during childhood, but the number of subjects with long-term follow-up periods should be increased to obtain more healthy results.

COMMENTS

Background

Children with hematological cancers have a high risk for hepatitis-B virus infection due to immunosuppression secondary to chemotherapy, radiotherapy and multiple blood transfusions. Although there are some studies in the literature addressing the course of chronic hepatitis B (CHB), few studies were conducted on patients with CHB who have been treated for cancer.

Research frontiers

The clinical characteristics and the course of CHB were evaluated in a cohort consisting of Turkish children with CHB who had received pediatric cancer therapy and compare the results with those of children diagnosed with CHB without malignancies.

Innovations and breakthroughs

In this present study we found that both post-treatment and spontaneous

HBeAg/antiHBe seroconversion rates are lower in subjects who had recovered from cancer. However, the authors observed a mild clinical course in the patients in both groups after a follow-up period of 13 years.

Applications

The studies on the natural course of chronic hepatitis B in a special patient group can help to understand the disease better.

Terminology

HBe/antiHBe seroconversion is important in the course of chronic hepatitis B in children.

Peer-review

A well-performed case control study, with similar clinical and virological features between both groups.

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