Research Article

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DOI: 10.4274/vhd.galenos.2024.2024-3-2
Viral Hepatitis Journal 2024;30(1):13-18

Evaluation of Demographic Data, Clinical and Laboratory Findings, and Treatments Administered to Children Followed Up with a Diagnosis of Chronic Hepatitis B Infection

Kronik Hepatit B Enfeksiyonu Tanısıyla izlenen Çocukların Demografik, Klinik ve Laboratuvar Bulguları ile Birlikte Aldıkları Tedavilerin Değerlendirmesi

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ABSTRACT

Objectives: This study examined the demographic and clinical features of children who were followed up with a diagnosis of chronic hepatitis B virus (HBV) infection.

Materials and Methods: The study included 374 children who were followed up with a diagnosis of chronic HBV infection in our clinic between 2005 and 2023.

Results: The study included 249 (66.6%) males and 125 (33.4%) females. The frequency of chronic HBV infection seen in the siblings of females with chronic HBV infection was determined to be significantly higher than that in male patients (p=0.017). Chronic active hepatitis was present in 147 (39.3%) patients. The route of infection was perinatal in all cases. Of the study cases, 79% were born in or before 2003 and 20% were born after 2003. The treatments administered to the cases were tenofovir disoproxil fumarate in 61 cases, lamivudine in 54, interferon 2α in 53, and entecavir in 10. The frequency of active chronic HBV infection was significantly higher in children born in or after 2006 (p=0.036). Similarly, the incidence of inflammation was significantly higher in those born in 2006 and later (p=0.049). The rate of anti-hepatitis

ÖZ

Amaç: Bu çalışmada kronik hepatit B virüs (HBV) enfeksiyonu nedeniyle izlenen çocukların demografik ve klinik özelliklerinin incelenmesi amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya 2005-2023 yılları arasında kliniğimizde kronik HBV enfeksiyonu tanısı ile izlenen 374 çocuk alındı.

Bulgular: Olguların %66,6'sı (n=249) erkek, %33,4'ü (n=125) kız idi. Kronik HBV enfeksiyonu olan kızların kardeşlerinde kronik HBV enfeksiyonu görülme sıklığı erkek hastalardan istatistiksel olarak anlamlı düzeyde daha yüksekti (p=0,017). Çalışmaya alınan olguların %39,3'ünde (n=147) kronik aktif hepatit vardı. Olguların tümünde bulaş perinatal yolla olmuştu. Olguların %79'u 2003 yılı ve öncesinde doğan çocuklardan oluşmaktaydı. Buna karşın, olguların %20'si ise 2003 yılından sonra doğan çocuklardan oluşmaktaydı. Olguların 61'i tenofovir disoproksil fumarat, 54'ü lamuvidin, 53'ü interferon 2α ve 10'nu entekavir tedavisi almıştı. 2006 yılı ve sonrası doğumlularda aktif kronik HBV enfeksiyonu sıklığı daha önce doğanlara göre istatistiksel olarak daha yüksekti (p=0,036). Benzer şekilde, 2006 yılı ve sonrası doğumlularda enflamasyon

Cite this article as: Deveci U, Doğan Y, Kayaokay AM, Akgeyik Ş, Karakoç F, Hayırlıdağ M. Evaluation of Demographic Data, Clinical and Laboratory Findings, and Treatments Administered to Children Followed Up with a Diagnosis of Chronic Hepatitis B Infection. Viral Hepatitis Journal 2024;30(1):13-18

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A virus immunoglobulin G positivity was statistically significantly higher in children born between 2003 and 2006 than in other age groups (p=0.003).

Conclusion: Family members of these children should be screened for HBV infection. Because of studies in Türkiye in recent years, there has been a significant decrease in the frequency of HBV infection in children.

Keywords: Children, hepatitis B virus, infection, vaccination

görülme sıklığı anlamlı olarak daha yüksekti (p=0,049). 2003-2006 yılları arasında doğanlarda ise anti-hepatit A virüs immunoglobulin G pozitiflik oranı diğer yaş gruplarına göre istatistiksel olarak daha yüksekti (p=0,003).

Sonuç: Bu çocukların aile bireylerinin HBV enfeksiyonu yönünden taraması yapılmalıdır. Son yıllarda ülkemizde yapılan çalışmaların sonucu olarak çocuklarda HBV enfeksiyonunu görülme sıklığında belirgin azalma olmuştur.

Anahtar Kelimeler: Çocuklar, hepatit B virüsü, enfeksiyon, aşılama

Introduction

Viral hepatitis is widely observed throughout the world and is a significant health problem of great concern in Turkey. Viral hepatitis is as old as human history and was first clinically described by Hippocrates. With the discovery in 1963 of the hepatitis B virus (HBV) antigen by Blumberg in Australia, a new period opened in the history of viral hepatitis (1). However, HBV infection continues to be a significant global public health problem. According to current estimations of the frequency of HBV infection by the World Health Organization, there is chronic infection in 296 million people. This causes approximately 1.5 million deaths per year because of acute or chronic diseases and viral infection complications (2).

The hepatitis B superficial antigen (HBsAg) seropositivity rate in Türkiye is 4% (3). Each year throughout the world, a new diagnosis of HBV infection is reported in 2 million children under the age of 5 years. The infection has been reported to pass most frequently from mother to child through the vertical route and via the horizontal route in the early period of life (4). To protect against hepatitis B infection, it is aimed for at least 90% of infants to receive the first dose of HBV vaccine within the first 24 hours postnatally and for three or more doses to be administered (5).

The aim of this study was to evaluate the demographic data, clinical and laboratory findings, and treatments administered to children who were followed up with a diagnosis of chronic HBV infection.

Materials and Methods

This study was planned as a retrospective cohort study. The study included pediatric cases with chronic HBV infection with HBsAg antigen positivity for >6 months, who were followed up in the Pediatric Gastroenterology, Hepatology, and Nutrition Polyclinic of Fırat University Medical Faculty Hospital between 2005 and 2023. The demographic, clinical, and laboratory data obtained from examinations of the cases' files were recorded on previously created study forms together with the treatments administered, and were then compared with the literature. This study was approved by the Ethics Committee of Fırat University Faculty of Medicine (approval number: 11/03, date:10/08/2023).

Cases with negative hepatitis B e antigen (HBeAg), HBV-DNA <2000 IU/mL, and normal transaminase levels were defined as the "inactive carrier" group. Those with HBeAg positivity, high HBV-DNA levels, and normal or close to normal transaminase levels were accepted as the "immunotolerance" group. Cases with HBeAg positive, high HBV-DNA and transaminase levels, and inflammation determined by biopsy were defined as the "immunoreactive" group (6).

Statistical Analysis

Data obtained in the study were statistically analyzed using SPSS vn. 22.0 software. The distribution of continuous variables was examined using the Shapiro-Wilk test. Descriptive statistics were stated as mean ± standard deviation and median (minimum-maximum) values for continuous variables and as number (n) and percentage (%) for categorical variables. In the analysis of categorical variables, the chi-square test and/or Fisher's exact test were used. The post-hoc Bonferroni test was applied for paired comparisons. In the comparisons of continuous variables between two independent groups, the Mann-Whitney U test was used. A value of $p<0.05$ was set as statistically significant.

Results

The study included 374 patients diagnosed with chronic HBV infection, comprising 249 (66.%) males and 125 (33.4%) females with a mean age of 10.97±3.87 years. In boys, the average serum alanine aminotransferase (ALT) level was 45.0 U/L and aspartate aminotransferase (AST) level was 41 U/L. In girls, the average serum ALT and AST levels were 42 U/L and 41 U/L, respectively. AST level was 41 U/L. In boys, the average serum HBsAg level was 480 and HBeAg level was 234. In girls, the average serum HBsAg level was 387 and HBeAg level was 259. When evaluated according to gender, no statistically significant difference was determined with respect to mean age, serum ALT and AST levels, and HbsAg and HbeAg positivity (Table 1). There was no statistically significant difference between the two genders with respect to chronic HBV infection, the presence of inflammation, and anti-hepatitis A virus immunoglobulin G [anti-hepatitis A virus (HAV), immunoglobulin G (IgG)] positivity. Of the 374 patients, 70 siblings had a history of chronic HBV infection. Siblings of 32 (25.6%) girls and 38 (15.3%) boys had a history of chronic HBV infection. The frequency of chronic HBV infection seen in the siblings of females with chronic HBV infection was determined to be significantly higher than that in male patients. There was no significant difference between the two genders with respect to HBV-DNA positivity (Table 2).

Chronic active HBV infection was present in 147 (39.3%) of 374 patients. In all patients, the infection was of maternal origin. Treatment with tenofovir disoproxil fumarate was started in 61 cases, lamivudine in 54, interferon alpha (IFN-α) in 53, and entecavir in 10. The treatments administered to patients diagnosed with chronic active HBV infection are shown in Figure 1.

Table 1. Comparisons of demographic and laboratory data of cases according to gender			
	Male, n=249 (66.6%)	**Female, n=125 (33.4%)**	**p-value**
	Median (range)	**Median (range)**	
Age (years)	12.0 (1.0-18.0)	11.0 (1.5-17.0)	0.944
ALT (U/L)	45.0 (10.0-3559.0)	42.0 (7.0-1698.0)	0.710
AST (U/L)	41.0 (11.0-3560.0)	41.0 (2.0-1934.0)	0.754
HbsAg (+)	480.0 (17.0-14600.0)	387.0 (13.0-5416.0)	0.692
HbeAg (+)	234.0 (0.0-18100.0)	259.0 (0.0-3977.0)	0.684
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HbsAg: Hepatitis B surface antigen, HbeAg: Hepatitis B e antigen			

Table 2. Comparisons of some clinical characteristics of cases according to gender			
	Male, n=249 (66.6%)	**Female, n=125 (33.4%)**	**p-value**
Pathology	**n (%)**	**n (%)**	
Normal (biopsy not performed)	150 (60.2)	77 (61.6)	0.823
Active hepatitis B (biopsy performed)	99 (39.8)	48 (38.4)	
Inflammation			
Biopsy not performed	152 (61.0)	77 (61.6)	0.917
Biopsy performed (inflammation)	97 (39.0)	48 (38.4)	
Sibling history of chronic HBV			
Absent	211 (84.7)	93 (74.4)	0.017
Present	38 (15.3)	32 (25.6)	
Anti-HAV IgG (+)			
Absent	181 (72.7)	81 (64.8)	0.121
Present	68 (27.3)	44 (35.2)	
HBV-DNA			
Negative	76 (30.5)	39 (31.2)	0.906
Positive	173 (69.5)	86 (68.8)	
HAV: Hepatitis A virus, HBV: Hepatitis B virus, IgG: Immunoglobulin G			

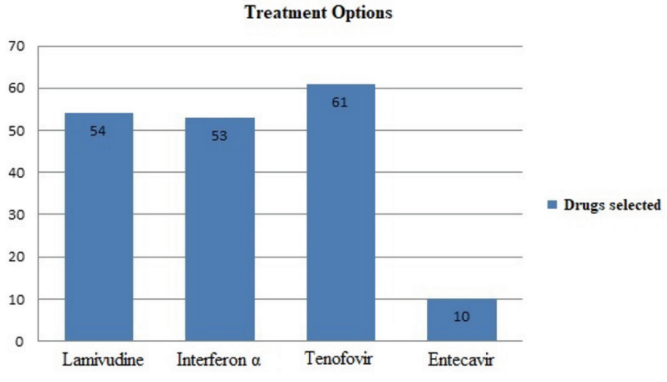

Figure 1. Treatments received by the patients followed up with a diagnosis of chronic active HBV infection
HBV: Hepatitis B virus

The frequency of active chronic HBV infection was statistically significantly higher in children born in or after 2006 than in other age groups. The frequency of inflammation was also significantly higher in those born in or after 2006. The rate of anti-hepatitis A virus (HAV) IgG positivity was determined to be significantly higher in children born between 2003 and 2006 than in other age groups (Table 3).

Discussion

Chronic HBV infection continues to be an important health problem worldwide. Previous studies have reported that chronic HBV infection occurs more often in male children than in females (7,8). The male/female ratio of the patients included in this study was 2:1.

The mean age of children with chronic HBV infection has been reported to be 8, 9, and 15 years according to various sources of reference (7,8,9). The data of the current study were consistent with the literature in this respect.

Screening of family members was performed for the current study cases followed up because of chronic HBV infection. Cases with HBV infection determined in a family member were followed up, and family members with no immunity against HBV infection were administered three doses of HBV vaccine in accordance with the immune schedule.

Of all the cases in this study, 41.4% were born between 1998 and 2003, 13.6% between 2003 and 2006, and 7.5% were born after 2006. In the national vaccination program, the first dose of HBV vaccine was administered at birth in 2003. Accordingly, there was a significant decrease in chronic HBV infection after 2003. This can be attributed to the inclusion of the HBV vaccine in the national

Table 3. Characteristics of cases with HBV infection according to date of birth

	Born before 1998 n=140 (37.4%)	Born 1998-2003 n=155 (41.4%)	Born 2003-2006 n=51 (13.6%)	Born in or after 2006 n=28 (7.5%)	p-value
Pathology					
Normal	79 (56.4)	99 (63.9)	37 (72.5)	12 (42.9)	0.036
Active hepatitis	61 (43.6)		14 (27.5)	16 (57.1)	
Inflammation (biopsy)					
Absent	81 (57.9)	99 (63.9)	37 (72.5)	12 (42.9)	0.049
Present	59 (42.1)	56 (36.1)	14 (27.5)	16 (57.1)	
Anti-HAV IgG					
Negative	111 (79.3)	107 (69.0)	27 (52.9)	17 (60.7)	0.003
Positive	29 (25.9)	48 (31.0)	24 (47.1)	11 (39.3)	
Sibling history of chronic HBV					
Absent	116 (82.9)	124 (80.0)	40 (78.4)	24 (85.7)	0.794
Present	24 (17.1)	31 (20.0)	11 (21.6)	4 (14.3)	

HBV: Hepatitis B virus, HAV: Hepatitis A virus, IgG: Immunoglobulin G

vaccination program from 2003 (10). The decrease in the number of cases in this study after 2003 demonstrates that HBV infection was prevented to a large extent due to effective vaccination. Families stated that all children born after 2003 were vaccinated against HBV during the newborn period. On the other hand, they said that only 15 of the families had their children administered Hepatitis B immunoglobulin (HBIg) during the newborn period. It was determined that HBIg was administered to these 15 children in State or University hospitals. Similarly, all babies born to HBsAg-positive mothers were also vaccinated against HBV in private health institutions. However, it was observed that these babies were referred to other health institutions (State or University Hospitals) for HBIg application. Despite the administration of the hepatitis B virus vaccine and HBIg, perinatal transmission can be observed at a rate of at least 10% (11). The most important reasons for this may include transplacental and intrauterine infection or insufficiency of vaccination and immune prophylaxis (12). According to health statistics in Türkiye, with a decrease over time, the frequency of acute HBV infection seen in children below the age of 5 years fell to 0.09 per 100,000 in 2022 (13). In 2021 in Türkiye, the coverage of three doses of HBV vaccine reached 95% (14). The data of the current study and other studies show that the application of HBV vaccine in Türkiye is effective for the eradication of HBV infection.

HBV infection is most often spread from HBsAg-positive mothers during childbirth (7,9,15). All the cases in the current study were found to have contracted HBV infection perinatally, which was consistent with the literature.

In 70% of the current study cases, there was a sibling history of chronic HBV infection. The frequency of chronic HBV infection seen in the siblings of females with chronic HBV infection was determined to be significantly higher than that in male patients. Female children with chronic HBV infection may marry and become pregnant later in life. Therefore, infected female children must be closely followed up, and it is extremely important to determine the stage of chronic HBV infection, especially during pregnancy. The initiation of treatment in pregnant patients with chronic active HBV infection and immediate HBV and HBIg vaccination of the infant can prevent the spread of the infection (16).

Chronic active HBV infection was present in 147 (39.3%) patients in the current study. Of these patients, 26 developed chronic HBV infection during follow-up in a previously immunotolerant stage. Of the total cases, 227 (60.7%) were chronic inactive HBV carriers. Although 47 cases were at the immunotolerant stage on first presentation, they were observed to develop as chronic inactive HBV carriers during follow-up. According to these data, the inactive carrier form is the most common form of chronic HBV infection (8,9).

The group with the lowest number of cases in the current study was children born in or after 2006. The frequency of chronic active HBV infection in this group was significantly higher than that in the other age groups (p=0.036). Despite the administration of HBV vaccine and HBIg as prophylaxis in the neonatal period, perinatal infection can be seen at a rate of 10% (11). Infants who have received the HBV vaccine and HBIg are diagnosed with chronic HBV infection in a later period because of deficiencies experienced during follow-up. Following the administration of the HBV vaccine and HBIg to infants born to mothers with chronic HBV infection, the infants should be screened again when they are 9-15 months old (17).

Hepatitis A virus infection in individuals with chronic HBV infection may cause superinfection. High morbidity and mortality can be encountered in these cases (18). All the cases in the current study were examined with respect to immunity against HAV infection. For those with a low anti-HAV IgG level, two doses of hepatitis A vaccine were recommended. The rate of anti-HAV IgG positivity was determined to be significantly higher in children born between 2003 and 2006 compared with the other age groups (p=0.003). The HAV vaccine was added to the national vaccination program in Türkiye on November 15, 2012. The free-of-charge HAV vaccination of children with chronic HBV infection since that date has contributed to immunity against HAV infection in that age group.

It is recommended that liver biopsy be performed before starting treatment for chronic HBV infection (19). Liver biopsy is required according to the Social Security Healthcare Practices

Communique (20). In the current study, liver biopsy was performed in 99 (39.8%) of 249 male patients and 48 (38.4%) of 125 female patients. According to the pathology results, there was no statistically significant difference between the genders (p=0.823).

For treating chronic HBV infection in children, oral antivirals (lamivudine, adefovir dipivoxil, tenofovir disoproxil fumarate and entecavir), IFN-α, and pegylated IFN-α-2A are used starting from the age of 2 years (21). Drug treatment was initiated for 125 of the 147 patients with chronic HBV infection in the current study. Treatment with tenofovir disoproxil fumarate was started in 61 cases, lamivudine in 54, IFN-α in 53, and entecavir in 10. Side effects such as fever, headache, and abdominal pain were observed in patients using IFN-α similar to those reported in the literature (21). Before IFN-α treatment was administered, acetaminophen was administered to the children as an antipyretic. The treatment of the children who were started on IFN-α was continued with lamivudine. Lamivudine is used safely in children and adults. The most common side effects are pancreatitis, peripheral neuropathy, neutropenia, and fatigue (21). Drug resistance may develop during lamivudine treatment; resistance was observed in five cases in the present study. In children who developed resistance, lamivudine was discontinued and tenofovir disoproxil fumarate was started. No side effects were observed due to tenofovir disoproxil fumarate treatment. For 21 patients who did not attend regular follow-up appointments, treatment could not be started. It was seen that the patients who were followed up in the Adult Gastroenterology Clinic after turning 18 years old had been started on entecavir treatment. No entecavir-related side effects were observed in any patient. The development of resistance to entecavir is very rare (21). The drugs used in this study were consistent with those reported in the literature (22,23).

A significant decrease in chronic HBV infection was determined in children born after 2003. This decrease suggests that it could be due to the routine HBV vaccination of every newborn infant and the administration of HBIg to infants born to HBsAg-positive mothers. It also suggests that increased awareness of HBV infection over the years has been helpful in preventing this infection.

Study Limitations

The main limitation of this study was that the majority of patients lived outside Elazığ's city and could not regularly attend follow-up appointments.

Conclusion

Recent studies in Türkiye for protection against HBV infection have been extremely effective. With regular follow-up of children with chronic HBV infection, morbidity and mortality can be reduced. Family members of these children must be screened for HBV infection, and with the vaccination of family members with no immunity to HBV infection, the spread can be prevented.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Fırat University Faculty of Medicine (approval number: 11/03, date:10/08/2023).

Informed Consent: Retrospectively study.

Authorship Contributions

Surgical and Medical Practices: U.D., Y.D., Concept: U.D., Y.D., M.H., Design: U.D., Y.D., M.H., Data Collection or Processing: U.D., Y.D., A.M.K., Ş.A., F.K., M.H., Analysis or Interpretation: U.D., A.M.K., Ş.A., F.K., M.H., Literature Search: U.D., Y.D., M.H., Writing: U.D., Y.D., M.H.,

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare no financial support.

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