ORIGINAL ARTICLE

The characteristics of patients with chronic hepatitis B in Turkey

Mustafa Kemal Celen¹, Suda Tekin Koruk², Bilgehan Aygen³, Tuba Dal⁴, Oğuz Karabay⁵, Selma T奥斯⁶, İftihar Koksal⁷, Hüseyin Turgut⁸, Yusuf Onlen⁹, Ismail Balik¹⁰, Necmettin Yıldırım¹¹, Mehmet Sinan Dal¹², Celal Ayaz¹, Fehmi Tabak¹³

¹Dicle University, Faculty of Medicine, Department of Infectious Diseases, Diyarbakir, Turkey, ²Harran University, Faculty of Medicine, Department of Infectious Diseases, Sanliurfa, Turkey, ³Erciyes University, Faculty of Medicine, Department of Infectious Diseases, Kayseri, Turkey, ⁴Dicle University, Faculty of Medicine, Department of Microbiology, Diyarbakir, Turkey, ⁵Dicle University, Faculty of Medicine, Department of Infectious Diseases, Sakarya, Turkey, ⁶Manisa State Hospital, Department of Infectious Diseases, Manisa, Turkey, ⁷Karadeniz Technical University, Faculty of Medicine, Department of Infectious Diseases, Trabzon, Turkey, ⁸Panakkale University, Faculty of Medicine, Department of Infectious Diseases, Denizli, Turkey, ⁹Mustafa Kemal University, Faculty of Medicine, Department of Infectious Diseases, Hatay, Turkey, ¹⁰Ankara University, Faculty of Medicine, Department of Infectious Diseases, Ankara, Turkey, ¹¹State Hospital, Department of Infectious Diseases, Mardin, Turkey, ¹²Dicle University, Faculty of Medicine, Department of Internal Medicine, Diyarbakir, Turkey, ¹³Istanbul University, Faculty of Medicine, Department of Infectious Diseases, Istanbul, Turkey

ABSTRACT

Aim To evaluate the characteristics of patients with hepatitis B virus (HBV) infection and summarize the treatment modalities.

Methods By September 30, 2011 the data of 7871 HBsAg (+) patients were complied and analysed according to demographic and medical records (age, sex, laboratory tests, treatment with antiviral agents) in thirty centres of Turkey.

Results Of the 7871 patients 3078 (39.1%) were females; mean (standard deviation) age was 35 (14) years, 3180 (40.4%) were HBsAg positive (+) after admission to a hospital, 1488 (18.9%) after blood donation and 967 (11.9%) were found during routine screening. The HBV prevalence among relatives of HBsAg (+) patients was 1764 (22.4%), and most frequently infected family members were siblings and mothers, 4961 (63.0%) and 2149 (27.3%), respectively). Anti-HDV was negative in 7407 (94.1%) of patients. Three-fourths of the patients 6383 (81.1%) were HBeAg negative (-). Mean (SD) ALT was 85.8 (266.4) U/L. Majority of patients, 5588 (71.0%) were chronic hepatitis-B patients under treatment, while 2283 (29.0%) were asymptomatic carriers without treatment and only 165 (2.1%) of patients were cirrhotic and 6612 (84.0%) of those were compensated. One-third of the patients 2983 (37.9%) were under a combined treatment, while others were under monotherapy. Lamivudine, entecavir and adefovir were the most frequently used oral therapies, used for 2583 (32.8%), 11.6% and 787 (10.0%) of patients, respectively), while 2975 (37.8%) of patients were under interferon treatment.

Conclusion Hepatitis B is still a problem in our country. First task of the physicians and our state should be to prevent the development and spread of the disease with education and vaccination programs, safe blood transfusions, and control of barbers.

Key words: hepadnaviridae infections, prevalence, blood donor
INTRODUCTION

Hepatitis B virus (HBV) infection is a major cause of morbidity and mortality worldwide (1,2). The World Health Organisation (WHO) has reported that ~2000 million people worldwide have been infected with Hepatitis B virus and that 350 million of these are chronically infected. The World Health Organisation estimated that 65 million of chronically infected patients will die from liver disease due to their HBV infection (1,2).

Hepatitis B virus is transmitted by percutaneous or permcusal exposure to infected blood or body fluids and its incubation period ranges from 40 to 160 days. Acute HBV infections are generally asymptomatic (1). In adults, ~30% will present with jaundice and hepatitis and 0.1–0.5% develop fulminant liver failure. During acute infection, hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) can be detected in the serum. There are high levels of IgM antibodies to the viral core antigen (IgM anti-HBc) in acute period (1-4). A successful host immune response to the virus leads first to clearance of HBeAg and subsequent clearance of HBsAg (1-4). The appearance of antibodies to HBsAg demonstrates recovery from acute infection (1-4). The persistence of HBsAg for >6 months from its first detection defined as chronic hepatitis B (CHB) infection. The likelihood of developing CHB varies according to the age at which the infection is acquired, the risk being lowest in adults (<5%) and greatest in neonates born to HBeAg positive mothers (~90%) (1-4).

The prevalence of HBV infection varies geographically. Areas are divided into three groups in the world as follows: areas of high (>8%), intermediate (2–8%) and low (<2%) endemicity (1,2). Overall, 45% of the global population live in areas of high prevalence (4). In low prevalence areas (etc. Northern Europe and North America), HBV infection is primarily acquired in adult age group through sexual contact or injecting drug use. However, in areas of high endemicity, it is most commonly acquired perinatally or in early childhood (1,2).

Turkey is an intermediate endemic area. According to our knowledge our study is of the largest scale including 7871 patients with HBV. With this multi-centre study we aimed to evaluate the characteristics of patients with hepatitis B virus infection and summarize the treatment modalities. We believe that our country and the world literature will acquire important data with this study.

PATIENTS AND METHODS

Participants

A total of 7871 patients who were HbsAg positive or HBV positive were included in this multi-centre study. Mean age of the patients was 35 (standard deviation 14) years; 3078 (39.1%) were females; and 4793 (60.9%) were males. The data of the patients including demographic and medical records (age, sex, laboratory tests, treatment with antiviral agents) were collected from seven regions (30 centres) of Turkey including Marmara, Aegean, Black Sea, Central Anatolia and Mediterranean, Eastern and South-eastern Anatolia. All participants gave their written informed consents. The study conformed to the standards set by the latest revision of the Declaration of Helsinki and was approved by the Ethical Committee of the School of Medicine, Diyarbakir, Turkey.

Laboratory methods

In this study the Hepatitis B surface antigen (HBsAg), Anti-HBs, Hepatitis B envelope antigen (HBeAg), Anti-HBe, Anti-HBc and HBV DNA were investigated by using enzyme-linked immunosorbent assay (ELISA) method (Abbott GmbH Co & KG, Abbott Laboratories, Chicago, IL, USA). The patients were further investigated for the results of liver function tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gama-glutamyl transpeptidase (GGT), and alkaline phosphatase (AP) levels by using standard radioimmunoassay (RIA) kits (BioSource Europe S.A., Belgium). Laboratory results of patients were recorded.

Statistical methods

All patients were included in the Hepatitis Information Network, Turkey (Turk-Hep-Net) patient monitoring program. Turk-Hep-Net project is a centralized online patient registry program and includes real-life cohort of HBV patients and is supported by Viral Hepatitis Society of Turkey. Thirty centres specialized in viral hepatitis have access to the system. By September 30, 2011, the data of HBsAg positive (+) patients were complied and analysed. Two-sided statistical tests were used in this study. A p value of 0.05 or less was considered significant.
RESULTS

Of 7871 patients the vast majority were from South-eastern Anatolia, 2361 (30%) the Aegean region 1480 (18.8) ranked second (Table 1). The mean (standard deviation) age was 35 (14) years; the mean age of patients form South-eastern Anatolia was significantly lower than the others (p<0.001) (Table 1). A total of 3078 (39.1%) patients were females (Table 2).

Table 1. Distribution of hepatitis B patients according to the regions of Turkey and the mean age

<table>
<thead>
<tr>
<th>Regions of Turkey</th>
<th>No (%) of patients</th>
<th>Mean (standard deviation) age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southeastern Anatolia</td>
<td>2361 (30)</td>
<td>26.2±11.3</td>
</tr>
<tr>
<td>Aegean</td>
<td>1480 (18.8)</td>
<td>38.1±15.2</td>
</tr>
<tr>
<td>Central Anatolia</td>
<td>1390 (17.6)</td>
<td>33.1±10.4</td>
</tr>
<tr>
<td>Marmara</td>
<td>1189 (15.1)</td>
<td>39.4±14.9</td>
</tr>
<tr>
<td>Black Sea</td>
<td>752 (9.6)</td>
<td>38.7±15.2</td>
</tr>
<tr>
<td>Eastern</td>
<td>389 (4.9)</td>
<td>27.1±10.8</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>310 (4)</td>
<td>39.3±8.9</td>
</tr>
<tr>
<td>Total</td>
<td>7871</td>
<td>35 (14)</td>
</tr>
</tbody>
</table>

Among patients, 3180 (40.4%) were HBsAg positive (+) after admission to a hospital, 1488 (18.9%) after blood donation and 967 (11.9%) were found during routine screening.

The HBV prevalence of HBsAg (+) patients among relatives was 1764 (22.4%), and most frequently infected family members were siblings, 1111 (63.0%), and mothers, 482 (27.3%). Anti-HDV was negative in 7407 (94.1%) patients (Table 2). Three-fourths of the patients, 6383 (81.1%) were HBeAg negative (-) (Table 2). Mean (SD) ALT was 85.8 (266.4) U/L. Majority of patients, 5588 (71.0%), had chronic hepatitis-B under treatment (Table 2), while 2283 (29.0%) were asymptomatic carriers without treatment (Table 2), only 165 (2.1%) patients were cirrhotic (Table 2) and 139 (84.0%) of those were compensated. One-third of the patients, 2983 (37.9%), were under the combined treatment, while others were under monotherapy. Lamivudine, entecavir and adefovir were the most frequently used oral therapies, used for 2583 (32.8%), 11.6% and 787 (10.0%) of patients, respectively, while 2975 (37.8%) of patients were under interferon treatment.

DISCUSSION

Turkey is an intermediate endemic area (2%-8%) for HBV infection (5,6,7). However, some regions of Turkey are high endemic area. In Eastern Anatolia, HBsAg prevalence was found to be 9.8% (8). In our study the vast majority of patients were from South-Eastern Anatolia (30%) where most of the population live in rural areas and the Aegean region (18.8%) (near the Aegean Sea) where higher HBV prevalence may be caused by high population migrants from South-East of Turkey.

In our study mean age of overall patients was consistent with other findings in the world and Turkey (5,9,10). In a study from Turkey, the mean age of 35±11 years among patients with HBV was found (9) as well as age-specific prevalence also varied greatly between the lowest prevalence in the age group of 0-14 years and the highest, in 25-34 years age group (5). On the other hand mean age of patients form South-Eastern Anatolia was significantly lower than in other regions probably as a consequence of frequent placental transition of infection from mothers. Moreover, we found that the frequently infected family members were siblings and mothers, and accordingly mother to-child transmission probably was the main route of HBV transmission.

We thought that prevalence of HBV in blood donors was probably higher in our country because some of the blood donors might have occult hepatitis B (absence of HBsAg, low viral replication) (11,12). In the current study, anti-HDV was positive in 5.9% of patients. The prevalence of HDV is relatively low in the Northern Europe and North America, where HDV infection is confined to intravenous drug users (13). HDV infection appears to be higher in Eastern Europe, South America, Mediterranean countries and the western regions of Asia than in the rest of world (13). Due to HBV vaccination and screening donor sera for HBsAg the prevalence of HDV decreased in the western countries, recently (10). The prevalence of HDV in HBsAg-positive patients in Pakistan was extremely high, 58.6% (14), 9.3% and 12.7% in patients infected with HBV and chronic hepatitis B, respectively (15), as well as in the United Kingdom, 8.5% among HBV-infected adult patients.
In a Turkish study, HDV prevalence was 45.5% among the patients with chronic HBV (13). We thought that because of social and cultural development of our country and vaccinations, the prevalence of the virus reduced.

HBeAg is one of the serum markers for HBV infection and correlates with high virus infectivity (17). A WHO study reported that HBeAg seroprevalence across the WHO sub-regions varied between 0%-72.8 (18). Demirtürk et al. found that 8% of the HBsAg-positive group were seropositive for HBeAg and the patient infected with a mutant virus did not express HBeAg. They suggested that infection with mutant HBV strains was associated with a negative response to treatment (19). Bozdayi et al. also reported that the HBeAg-negative phenotype in Turkish patients with chronic hepatitis was associated with precore mutations (20). Thus, some studies also showed that the Mediterranean area and Middle East and Asian countries had the highest proportions worldwide of HBeAg-negative chronic HBsAg carriers (21,22).

18.9% of our patients were HBeAg (+). This ratio was consistent with literature and it was higher in an earlier Turkish study. The ratio of precore mutations in general population of Turkey is unknown, so large scale studies in our country are needed.

Being male may be a risk for HBV infection (23-27). Risk factors for Hepatitis B such as multiple partnership, intravenous drug usage, having shave in barbers, traveling, etc. are more common in male population. This may explain the higher rate of HBsAg positivity in males.

An elevated ALT level indicates active liver inflammation and is a predicting marker of disease progression. Mean ALT level of our study was consistent with the literature (28).

Agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of HBV are interferons or nucleoside or nucleotide analogs (lamivudine, adefovir, entecavir, tenofovir, and telbivudine). Of our patients 63.1% were under monotherapy and lamivudine, which is a synthetic nucleoside analogue, was the most frequently used drug. Duration of the treatment with lamivudine is quite long, and resistance is a significant problem. The most frequent mutation is the tyrosine-methionine-aspartate-aspartate (YMDD) mutation of the HBV polymerase gene (29,30). The frequency of mutation increases proportionally with the duration of lamivudine treatment, and the five-year post-treatment frequency is about 65%-70% (31,32). Otherwise, lamivudine resistance might also be seen in nucleoside naive chronic hepatitis B patients or inactive HBsAg carriers due to structural changes in the DNA polymerase enzyme gene (33,34). In a Turkish study, lamivudine resistance was 10.7% in chronic hepatitis B patients and of those 4% had primary, and 53.1% had secondary resistance to lamivudine (29). In fact, the main targets of anti-HBV therapy are to prevent the development of progressive liver disease, cirrhosis, liver failure, hepatocellular carcinoma and mortality. The authors recommended the usage of more potent agents, treatment change in patients in whom the disease progressed during the treatment, and combined antiviral agents (29). We should apply these recommendations in the patients of Turkey.

In conclusion, our results may be beneficial in the prevention of HBV infection and in the management of patients with HBV. First task of the physicians and our state should be to prevent the development and spread of the disease. People must be educated on this issue, the living conditions of families should be improved, safe blood transfusions should be made, barbers should be inspected by the government. Further, frequency of HBV may be reduced at the society by implementation of vaccination practices proposed by the Health Ministry of Turkey. The possibility of resistance development in patients receiving monotherapy should be kept in mind, if necessary combination therapy should be started.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.


27. Donovan, B. Sexually transmissible diseases other than HIV. Lancet 2004; 363:545-56.


