Changes in acute viral hepatitis epidemiology in the Turkish adult population: A multicenter study

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ABSTRACT

Background/Aims: The present study aimed to determine the changes in the epidemiology of hepatitis in recent years in an adult Turkish population.

Materials and Methods: Overall, 852 patients with acute viral hepatitis from 17 centers were included in this study. Their sociodemographic characteristics, clinical courses, treatments, and laboratory findings were retrospectively analyzed.

Results: The most commonly found microorganisms were the hepatitis B virus (55.2%) and hepatitis A virus (37.6%), and the types of acute viral hepatitis differed significantly according to the age group ($p \leq 0.001$). The most frequently reported symptom was fatigue (73.7%), and the most common complications were cholecystitis (0.4%) and fulminant hepatitis (0.4%). The median hospital stay was 9 days (range 1-373). In total, 40.8% patients with acute hepatitis B virus developed immunity.

Conclusion: In Turkey, there are significantly large adolescent and adult populations susceptible to acute viral hepatitis. Therefore, larger vaccination programs covering these age groups should be implemented.

Keywords: Acute hepatitis, hepatitis A, hepatitis B, hepatitis C, Turkey

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INTRODUCTION

Acute viral hepatitis represents a major public health issue, and the most commonly associated viruses are hepatitis A (HAV), B (HBV), C (HCV), D, and E. Although the clinical signs of acute viral hepatitis can be asymptomatic, this disease may progress to a fulminant or fatal course (1).

In recent years, apparent changes have been reported in both the HAV and HBV epidemiology registries. In Turkey, the HAV morbidity rate decreased from 24.80 to 0.9 of every 100,000 patients between 1970 and 2015, whereas the acute HBV morbidity rate decreased from 4.55 to 2.88 of every 100,000 patients between 1990 and 2015 (2,3). Moreover, the prevalence of HAV infection has declined in several regions of the world, and these changes have manifested as a shift in the HAV exposure age from childhood to adolescence and early adulthood (4). In terms of HBV, the global HBV vaccination protocols conducted in several countries have yielded significant decreases in acute HBV infections during infancy and childhood (5).

In this study, we aimed to assess the epidemiological characteristics and determine the disease course in adult patients with a preliminary diagnosis of acute viral hepatitis in Turkey. Additionally, we aimed to determine the epidemiological changes in hepatitis in the adult Turkish population in recent years.

MATERIALS AND METHODS

This multicenter study was conducted retrospectively. Overall, 17 centers from 10 cities comprising 10 training and research hospitals, five university hospitals, and two state hospitals participated in this study. Each patient's data, including the sociodemographic characteristics, clinical course, treatment, and laboratory findings, were reviewed using hospital records. Those patients were followed-up for acute hepatitis symptoms of infectious diseases, and clinical microbiology clinics and outpatient clinics were included in this study. Pediatric patients and those with missing laboratory data were excluded from this research.

The Declaration of Helsinki and Good Clinical Practice Guidelines were followed during the entire process of enrolling the patients and collecting/analyzing/reporting the data. Informed consent was obtained from all of the patients, and this study was approved by the Local Ethics Committee (09.02.2016/2).

The statistical analysis was performed using SPSS software (IBM Inc.; SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). The descriptive data were expressed in frequencies and percentages for the numeric data and medians (min-max) for the abnormally distributed data. The categorical variables were compared using the Pearson chi-squared test. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Out of 852 patients, the majority were males, the median age was 31 years (range 17-89), and most were in the 21- to 40-years-old age group. The most commonly found microorganisms were HBV and HAV (Table 1). Table 2 shows the distribution of the viral hepatitis microorganisms according to sex, age group, and month. The acute viral hepatitis types were significantly different according to the age group ($p \leq 0.001$). Moreover, the number of patients with HAV and HBV was higher during the autumn season. In addition, 11.6% patients had a concomitant disease, including chronic HCV in 88.8%, cardiovascular disease in 1.9%, chronic HBV in 1.5%, diabetes mellitus in 0.9%, and other diseases in 6.8%. The incidences of acute viral hepatitis in those patients with chronic HCV were HBV in 53.5%, HAV in 39%, HAV+HBV in 1.7%, Epstein-Barr virus (EBV) in 0.5%, and cytomegalovirus (CMV) in 0.1%, whereas 53.8% of the chronic HBV patients had HAV.

The potential transmission routes were as follows: consumption of suspicious food (9.3%), contact with contaminated blood and body fluids (6.3%), daily contact with an individual with chronic hepatitis (3.2%), daily contact with an individual with acute viral hepatitis (2.6%), travel history (1.2%), penetrating/perforating injuries (0.8%), suspicious sexual intercourse (0.1%), and recent surgery (0.1%). The main reasons for admission were suspicious symptoms (94.8%), investigation for another disease (2.7%), check-up because of a relative with hepatitis (1.4%), following blood donation (0.1%), and check-up after suspicious sexual contact (0.1%).

The most common symptom in those patients with acute viral hepatitis was fatigue, whereas the most common sign was scleral icterus (Table 3). Overall, 84.2% patients were monitored in the hospitals; of these, 0.4% were monitored in the intensive care unit, and 0.4% were transferred to a transplantation center. Those factors affecting the decision to follow the patient in an inpatient or outpatient setting included the type of hepatitis ($p=0.02$), urine color ($p=0.001$), fever ($p=0.045$), scleral color ($p=0.025$), mental status ($p=0.03$), loss of appetite ($p=0.019$), muscle pain ($p=0.009$), headache ($p=0.029$), dizziness ($p=0.048$), vomiting ($p<0.001$), and the presence of concomitant disease ($p<0.001$).

Table 1. Sociodemographic characteristics and diagnoses of the patients (n=852)

	n	%
Sex		
Male	516	60.6
Female	336	39.4
Age (Median [min-max] years)	31 (17-89)	
Age groups (years)		
<20	41	4.8
21-30	350	41.1
31-40	260	30.5
41-50	84	9.9
51-60	52	6.1
61-70	27	3.2
>71	38	4.5
Occupation		
Self-employed	91	10.7
Civil servant	85	10
Student	84	9.9
Housewife	82	9.6
Worker	46	5.4
Unemployed	10	1.2
Retired	9	1.1
Farmer	3	0.4
Health care employee	2	0.2
Unknown	440	51.6
Comorbid disease		
Yes	99	11.6
No	413	48.5
Unknown	340	39.9
Type of follow-up		
Outpatient	135	15.8
Inpatient	717	84.2
Type of hepatitis		
HBV	470	55.2
HAV	320	37.6
HAV+HBV	15	1.8
HCV	10	1.2
Other hepatotropic viruses	6	0.7
Non-infectious causes	2	0.2
Unknown	29	3.4

HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus

Other hepatotropic viruses: Epstein-Barr virus=4; cytomegalovirus=1; varicella zoster virus=1

The length of the hospital stay was calculated for 685 patients, and the median duration was 9 days (1-373) days. During the follow-up, 8 patients developed complications: cholecystitis in 3 (0.4%), fulminant hepatitis in 3 (0.4%), encephalopathy in 1 (0.1%), and brain edema in 1 (0.1%). Fulminant hepatitis only developed in those cases with acute HBV (0.4%). Of the hospitalized patients, 70.1% were given a variety of therapies consisting of fluid replacement (85.4%), lactulose (45%), diet (36.6%), vitamin K (31.6%), paracetamol (8.5%), steroids (7.5%), oral antiviral therapy (4.2%), and fresh frozen plasma (4%), with some patients receiving more than one therapy. Bed rest was recommended for 64.4% of the outpatients and 96.9% of the inpatients.

Of the patients, 40.8% were discharged with recovery, and 38.8% were discharged with a stable status to return for a scheduled follow-up visit. Overall, 7 patients were transferred to other centers for liver transplantation, whereas 3 patients underwent liver transplantations in the centers in which they were treated. The long-term follow-up showed that 52.6% patients with acute HBV developed immunity, 4.9% had isolated hepatitis B core antibody immunoglobulin G positivity, 3.4% had chronic active hepatitis B, and 3% had hepatitis B surface antigen positivity. In addition, HCV RNA negativity was detected during the long-term follow-up of 2 patients with acute HCV.

DISCUSSION

The results of this retrospective multicenter study investigating acute viral hepatitis cases in Turkey showed that the most common causative microorganism was HBV. HAV infections are common during childhood in the majority of Asian, African, and Latin American countries, whereas the prevalence has shifted toward adult age groups in other countries (4). In different regions of Turkey, the HAV seroprevalence varies between 61% and 94.2% and increases with age (6-10). Tekin et al. (11) found that HAV was most commonly seen in individuals aged 15-30 years in southeastern Turkey. Erturk et al. (6) reported that in the adult population, the anti-HAV immunoglobulin M positivity prevalence rate is 1.2% at an age range of 17-29 years old. The high rate of acute viral hepatitis caused by HAV seen in this study may be because of the evaluation of a high number of cases from various regions.

Since 2005 in Turkey, a dramatic decline has been noted in acute HBV cases in patients younger than 15 years, whereas acute HBV has continued to be relatively common among people >15 years (5). In addition, HBV vaccines

Table 2. Distribution of viral hepatitis agents (n=821)

		HBV	HAV	HCV	HAV+HBV	Other hepatotropic viruses	p
Sex	Male	295	185	5	10	4	0.600
	Female	175	135	5	5	2	
Age group (years)							<0.001
	<20	4	30	0	0	1	
	21-30	139	191	2	7	3	
	31-40	169	82	2	5	1	
	41-50	71	9	0	2	0	
	51-60	41	3	2	1	1	
	61-70	21	0	3	0	0	
	71<	25	5	1	0	0	
Months							0.061
	January	43	30	1	1	0	
	February	28	24	1	2	0	
	March	33	25	1	1	3	
	April	42	26	1	0	0	
	May	42	22	2	3	1	
	June	39	14	1	0	0	
	July	36	13	0	4	0	
	August	28	19	0	1	0	
	September	52	33	0	1	0	
	October	40	29	1	1	1	
	November	43	47	2	1	1	
	December	44	38	0	0	0	

HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus;

Other hepatotropic viruses: Epstein-Barr virus, cytomegalovirus, varicella zoster virus

administered during childhood still provide protection in 81.8% of individuals 15 years after the vaccination (12). More than one-half of the acute viral hepatitis patients included in this study were infected with HBV, and a majority of them were within the 20- to 40-years-old age group. This indicates that the population that lived through childhood before the inclusion of the HBV vaccine into the national vaccination program is now under a higher risk.

In the overall European population, anti-HCV positivity varies between 0.4% and 5.2% depending on the country (13). In Turkey, the rate of anti-HCV positivity is 1.12% among all age groups, but it increases with age, reaching 2.1% at ages >50 years (14). Therefore, being 50 years or older in Turkey is an important predictive factor for anti-HCV positivity (15). The anti-HCV positivity among blood donors significantly increased in 10 years (16). Based on our study results, the prevalence of HCV is consistent with the HCV epidemiological data in Turkey.

The most common cause of this disease is viral hepatitis developing into fulminant hepatitis; among these cases, the most frequently seen microorganisms are HAV in children and HBV in adults (17). Fulminant hepatitis develops at a prevalence rate of 0.1% to 0.4% in acute HBV cases (18). However, the complication rate among the cases included in this study was lower. In addition, fulminant hepatitis was rare and was seen most often in acute HBV patients.

Following acute HBV infections, 77.7% of Turkish patients develop immunity (19), but this figure was reported as 85% in the United Kingdom (20). The lower rate of immunity after an acute HBV infection found in this study may be because of shorter follow-up periods for certain patients. As demonstrated in the present study, a majority of the patients with acute HCV developed chronic disease (20).

To the best of our knowledge, this is the largest study evaluating acute viral hepatitis cases among the adult popula-

Table 3. Distribution of the patients' symptoms and signs (%)*

Symptoms	HBV	HAV	HCV	HAV+HBV	Other viruses	p	All Patients
Fatigue	76	79.1	30	53.3	83.3	0.002	73.7
Nausea	68.1	74.4	20	66.7	33.3	0.002	67.4
Loss of appetite	66	64.4	30	33.3	83.3	0.030	62.3
Vomiting	39.6	52.2	20	40	0	0.001	42.6
Abdominal pain	33.2	31.6	20	33.3	66.7	0.544	31.7
Joint pain	16	15.9	0	40	66.7	<0.001	16.1
Flu-like symptoms	12.1	20.9	20	6.7	66.7	<0.001	15.4
Fever	9.4	22.2	10	26.7	50	<0.001	14.4
Muscle pain	11.1	17.5	20	13.3	83.3	<0.001	13.8
Headache	7.2	13.8	70	20	83.3	<0.001	10.1
Constipation	10.6	7.8	10	6.7	0	0.432	9.3
Itching	9.8	8.8	0	20	0	0.448	9
Dizziness	7.9	6.3	10	13.3	66.7	<0.001	7.5
Diarrhea	5.5	8.4	0	13.3	33.3	0.066	6.7
Signs							
Consciousness					0.942		
Open	92.8	93.8	80	93.3	100		92.8
Confusion	1.2	2.3	0	0	0		1.6
Precoma	0.2	0	0	0	0		0.1
Sclera color					0.720		
Normal	18.7	22.5	20	20	33.3		20.1
Subicteric	17.2	16.9	30	13.3	0		16.7
Icteric	57.9	56.9	30	60	66.7		57.6
Body temperature					0.699		
Normal	76	71.3	70	86.7	83.3		73.7
High	11.7	15.6	10	6.7	16.7		13.7
Urine color					0.011		
Normal	25.1	31.3	70	13.3	33.3		28.1
Dark	57.4	57.5	10	73.3	50		57
Stool color					0.018		
Normal	58.5	70.3	80	60	83.3		64.7
Acholic	14.9	7.5	0	20	0		11.4
Flapping tremor					0.743		
No	73.8	78.4	80	73.3	83.3		76.4
Mild	1.9	0.9	0	6.7	0		1.5
Severe	0.9	1.6	0	0	0		1.1
Line test					0.092		
Normal	61.3	65.6	60	60	33.3		63.8
Mild impairment	1.1	1.6	0	13.3	0		1.4
Severe impairment	0.6	0.9	0	0	0		0.7
Skin color					-		
Icteric	4.9	5.3	0	0	0		4.7

*Patients with missing signs and symptoms are not shown.

HAV: hepatitis A virus, HBV: hepatitis B virus, HCV: hepatitis C virus;

Other viruses: Epstein-Barr virus, cytomegalovirus, varicella zoster virus

tion in Turkey. We believe that the present study is valuable, because it demonstrated the changes in the epidemiology of HAV and HBV in Turkey and presented the current data on the clinical status and prognosis of the disease in this age group. However, this study did have some limitations. For example, the prodromal period, duration of findings and symptoms were not available for evaluation because of the retrospective design of this study. Therefore, further prospective studies are required to demonstrate these findings.

In conclusion, acute viral hepatitis has no specific treatment; therefore, prevention methods are more important than treatment. Our study results showed that significant populations of susceptible adolescents and adults have developed in Turkey, highlighting the need for more extensive vaccination programs in these age groups. Vaccinations during childhood may help eliminate certain preventable diseases, such as HBV and HAV, from communities in the long term; however, the current immunization programs should also strive to cover susceptible adults.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bozyaka Training and Research Hospital (Decision Date: February 9, 2016; Decision No: 2).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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