The Prevalence of Hepatitis E Virus Infection in the Adult Turkish Population: A Systematic Review of the Literature and Prevalence Study in Blood Donors in Mersin Province

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ABSTRACT

Background: *The hepatitis E virus (HEV) is an RNA virus that causes acute hepatitis, and can become chronic in immunocompromised patients, though this is rare. The frequency of HEV infection varies, depending on factors such as geographical region, socioeconomic level, and age. Despite limited studies on the adult population in Turkey, there is no current information about HEV frequency in our country. Therefore, we aimed to scrutinize the data found from such studies, in comparison to our own results.*

Methods: *A total of 900 volunteers who applied to donate blood to the University Hospital Blood Center and accepted the use of their data were enrolled in the study. Serum anti-HEV IgG antibody (Ab) was examined by the enzyme-linked immunosorbent assays method. The donors' location, occupation, and animal contact status were determined. In addition, we evaluated the full text and conference papers (in Turkish or English) of Turkey-based HEV seroprevalence studies from 1990-2020, investigating the adult population.*

Results: *The average age of the 900 volunteers in the study was 35.22 ± 9.60 years, of whom 889 (98.7%) were men. Anti-HEV IgG was positive in 12.8% of the serum samples. The average age of the volunteers who were seropositive was 40.40 ± 9.72 years, and 98.2% were men. No association was found between anti-HEV IgG positivity and occupation, place of residence, and contact with animals. An evaluation of the studies conducted in Turkey reveals that the average HEV infection seroprevalence is 9.52% in the healthy population, and the prevalence is increased in the region of Southeastern Anatolia. Patients with acute hepatitis and hemodialysis also had increased rates.*

Conclusion: *The anti-HEV IgG seropositivity rate in healthy blood donors in Mersin province was 12.8%, and was similar to the rates reported earlier in our country. However, this rate, found in a sample of individuals from a healthy society, causes concern about what the frequency may be in sick people. Wide-ranging community screening is needed.*

Keywords: *Hepatitis E virus, anti-HEV IgG, Turkey, Mersin*

INTRODUCTION

Viral hepatitis is a major health problem in Turkey, and the hepatitis E virus (HEV) is one of the main causes of enterally transmitted acute hepatitis.[1] Rarely, it can become chronic in immunosuppressed individuals. In developing countries, transmission is mainly via the fecal–oral route, and drinking water plays a major role.[2] Person-to-person transmission is rare. However, HEV can also be transmitted by blood transfusion, especially in endemic areas.[3,4] Worldwide, an estimated 20 million people develop infections annually, of which 3 million are symptomatic. The number of cases resulting in death is approximately 70 000 per year.[4,5]

In Turkey, sporadic cases of acute hepatitis are generally seen, and no HEV outbreaks have been reported so far. There have been some studies examining the seroprevalence of HEV infection in Turkey. In those studies, different prevalence rates have been reported by geographic regions. Data of HEV infections from the Eastern Mediterranean region, in which our center is also located, are very limited. Therefore, we aimed to conduct a study to evaluate HEV seroprevalence in healthy adult blood donors admitted to our hospital's blood donation center, and to review all results of Turkey-based scientific studies of HEV infection in the adult population.

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MATERIALS AND METHODS

The study included healthy volunteers who applied to our hospital's Blood Center as blood donors. They had no risk factors for parenterally transmitted diseases, tested negative in donor screening tests, and accepted to participate in the study by reading and signing written consent documents. Blood samples of 5 ml were taken from each of these voluntary donors. The blood samples obtained were centrifuged immediately at 5000 rpm for 3 minutes to separate the serum component. Sera collected from the top of the tubes were stored at −80°C until analysis.

The presence of specific IgG class antibodies (Ab) against HEV was investigated with commercially available enzyme-linked immunosorbent assays (ELISA) kits (Euroimmun®, Germany). The study was carried out in line with the manufacturer's recommendations. The volunteers' age, gender, profession, information about their region of residence, and their contact with pets or livestock were recorded.

SPSS v 21.0 (IBM, USA) was used for statistical analysis. The chi-square test was used for analysis with nonparametric variables and the Student's *t*-test was used for parametric tests, A value of $P > .05$ was considered statistically significant. Permission for the study was obtained from Mersin University Clinical Research Ethics Committee, with the decision dated June 23, 2017 and numbered 2017/188.

HEV seroprevalence studies investigating the adult population in Turkey (full text articles and conference papers, in Turkish or English) were evaluated. The general frequency results were evaluated chronologically by city and region. The risk factors and results in risky populations were evaluated.

RESULTS

A total of 900 volunteers were included in the study. The mean age of the volunteers was 35.22 ± 9.60 years. The ratio of males to females was 889 : 11. The mean age of men was 34.79 ± 9.70 years, and the mean age of women was 42.83 ± 7.69 years. There was a statistically significant difference in age between the 2 groups ($P < .05$). The test for anti-HEV IgG was positive in 12.8% (116/900) of the serum samples obtained from the volunteers. The mean age of those with seropositivity was 40.40 ± 9.72 years. There was no statistical difference between the mean age of volunteers and the positive cases ($P = .282$). In total, 114 of the 116 people who were anti-HEV IgG positive were men. The number of participants residing in the rural areas was 362 (40%), and the number of those residing in the urban areas was 538 (60%). Of those who were positive for anti-HEV IgG, 43.9% (51/116) lived in the rural areas and 56% (65/116) lived in the city. Among all participants, the rate of those with a history of contact with livestock was 5.6%. The rate of those engaged in farming and animal husbandry was 1.89% among anti-HEV IgG-positive donors and 11.95% in the group that was anti-HEV IgG negative, and the difference between the 2 groups was statistically significant ($P < .05$).

A total of 57 studies were analyzed to assess the prevalence of HEV in Turkey: 34 of them constituted screenings of healthy populations, while 23 constituted screenings of at-risk patients.[6-62] The average seroprevalence of HEV infection in the healthy population in Turkey was found to be 9.52%. The details of the study have been provided in Table 1. The regional prevalence was as follows: 5.85% in the Marmara region (8 studies), 4.45% in the Black Sea region (2 studies), 7.45% in Eastern Anatolia (4 studies), 17.15% in Southeastern Anatolia (9 studies), 10.34% in the Aegean region (5 studies), 4.76% in Central Anatolia (5 studies), and 8.15% in the Mediterranean region (6 studies) (Figure 1). In 3 of these studies (6,7,15), the number of cases was between 1300 and 1500, and it was between 100 and 300 in the others. The details of the at-risk population have been provided on Table 2. Most studies were conducted in İstanbul (9 studies), Diyarbakır (9 studies), and Ankara (7 studies).

DISCUSSION

Hepatitis E virus

The hepatitis E virus is the only member of the Orthohepevirus genus in the Hepeviridae family,[5] and has 4 known genotypes.[63] Of these, genotypes 1 and 2 often cause infections in humans and are limited to endemic regions such as Asia, Africa, and Mexico.[64] In contrast, genotypes 3 and 4 are found in a wide range of animal species. Genotype 3 is present worldwide, and infects a variety of hosts such as pigs, wild boars, deer, weasels, and Japanese macaques. Genotype 4 is found particularly in China and Southeast Asia, and infects pigs, wild boars, and sheep.[1] HEV is the only virus with an animal reservoir among the major hepatitis viruses (A, B, C, D, E). Moreover, HEV has also been isolated from soft fruit, rivers, the sea and sea mud, and from animal species such as chickens, rats, rabbits, camels, bats, and shellfish. Phylogenetic studies suggest that the HEV origins found in humans and pigs are similar and the transmission is of zoonotic

Table 1. The Anti-HEV IgG Seroprevalence Studies Performed in Healthy Adults, in Turkey

Between Years 1990 and 2000			Between Years 2001and 2010			From 2011 to the Present		
Year-Reference Number	City	Anti-HEV Ig G Frequency (%)	Year-Reference Number	City	Anti-HEV Ig G Frequency (%)	Year-Reference Number	City	Anti-HEV Ig G Frequency (%)
1993-6	İstanbul Aydın Ayvalık Adana Trabzon	5.9	2001-22	İstanbul, blood donors	4	2011-36	Van	4.0
1994-7	Trabzon Diyarbakır	3.0 29	2001-23	Malatya	6.7	2013-37	Denizli	12.4
1994-8	Bursa blood donors	9	2002-24	Ankara	3.8	2013-38	Ankara	4.4
1994-9	İzmir	3.5	2002-25	Mersin blood donors	11.2	2017-39	İzmir	6.6
1995-10, 11	Adana	7.0	2002-26	Ankara	5.3	2020-our study	Mersin blood donors	12.8
1995-12	Malatya	9.3	2003-27	Van	7.5			
1995-13	İstanbul	5.3	2003-28	Erzurum	8.0			
1995-14	Diyarbakır	7.7	2003-29	Erzurum	10.3			
1996-15	Ankara blood donors	7.6	2003-30	Ankara Manisa Diyarbakır	2.7 3.8 11.7			
1996-16	Antalya blood donors	11	2006-31	Gaziantep	15.7			
1996-17	Diyarbakır	34	2006-32	Isparta blood donors	1.0			
1997-18	Diyarbakır	23	2006-33	İstanbul	15.8			
1997-19	Diyarbakır	17.3	2009-34	Edirne	2.4			
1998-20	İstanbul	4.4	2010-35	İstanbul	0.0			
1999-21	Denizli	25.4						
		Average 12.65			Average 6.86			Average 8.04

Average of Turkey 9.52%

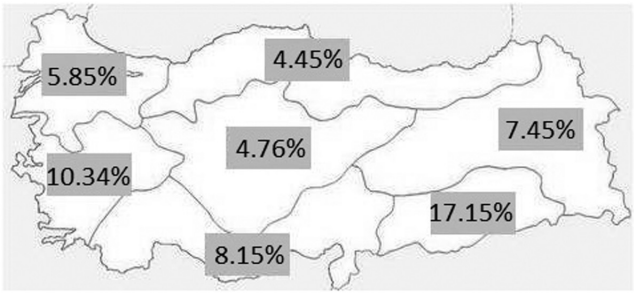

Figure 1. Anti-HEV IgG rates by regions.

origin.[65] This theory has been supported by strong studies in Japan in which humans were infected by uncooked pork and venison.[66] Genotypes 3 and 4 are more common in industrialized countries and are observed as zoonotic infections. In Turkey, genotypes 1 and 2 are prevalent.[67]

Table 2. The Anti-HEV IgG Seroprevalence Studies Performed in the Population At-risk, in Turkey

Year, Reference Number	City	Anti-HEV IgG Frequency (%)
In patients with acute hepatitis		
1993-40	İstanbul	11
1994-41	Diyarbakır	73.3
1995-42	Diyarbakır	19.5
2003-43	Gaziantep	11.2 (8.8% IgM positive)
2005-44	Antalya	2.3%
In patients with chronic hepatitis		
2007-45	Gaziantep	13.7 in patients with CHB 54 in patients with CHC
In patients with cryptogenic cirrhosis		
2019-46	İstanbul	25.7 (HEV-RNA positivity 8.6%)
In hemodialysis patients		
1996-47	Samsun	13.9
1996-48	Ankara	12.3
1996-49	Antalya	13.4
1999-50	Denizli	10.4
2001-51	Ankara	16
2007-52	Afyon	10.7
2009-53	Hatay	20.6
2017-54	Kırıkkale	42
In pregnant women		
2001-55	Van	3.7
2003-28	Erzurum	8
2004-56	Afyon	12.6
2006-57	Aydın	7
2010-35	İstanbul	1.3

CHB: Chronic Hepatitis B, CHC: Chronic Hepatitis C

Infection with HEV was first documented in 1955, during an epidemic in New Delhi, India.[68] This was a massive epidemic of acute viral hepatitis, affecting about 29 000 people. However, the virus was first described by Balayan et al. in 1983. They reported the virus by experimentally inducing the disease by injecting virus-like particles obtained from the stool of non-A and non-B hepatitis patients into Cynomolgus monkeys, after the water-borne acute hepatitis epidemic (year 1980) in New Delhi and Kashmir.[69] Later, in 1991, sequence analysis of the entire genome of the virus was performed by Tam et al and named as HEV.[70]

HEV almost always causes acute hepatitis. However, chronic HEV infections have been reported in organ transplant recipients, those with HIV infection, or in immunocompromised patients undergoing chemotherapy.[1] Although the contamination is mainly fecal–oral, it has been reported as a case report that it may cause acute hepatitis E in an immunocompetent patient by transfusion of blood products containing HEV RNA.[3,4] The most severe disease course is seen in pregnant women infected with HEV genotype 1. Maternal, fetal, and neonatal morbidity and mortality rates are high.[71]

HEV is one of the most common causes of acute viral hepatitis in tropical and subtropical countries. In the past, its prevalence was thought to be limited to developing countries, but recently, there has been increasing information showing a wider distribution of geographic regions and hosts. Contrary to popular belief, seroprevalence is quite high in developed countries. HEV is detected less frequently than HAV, as it is less resistant to the external environment. Men are more commonly affected than women.[72] Unlike hepatitis A and other enteric viruses, human-to-human transmission of HEV is rare.

Prevalence of HEV Infection in Healthy Individuals in Turkey

According to studies related to anti-HEV positivity in Turkey, there is considerable regional variation in HEV infection seroprevalence. According to studies conducted in Turkey considered in chronological order within the 10-year period: in the early 1990s, when HEV Ab could be detected for the first time, Thomas et al. reported the rate of anti-HEV Ab positivity as 5.9%, based on serum

samples collected from 5 regions of Turkey (Istanbul, Aydın, Ayvalık, Adana, and Trabzon).[6] They claimed that the frequency increased in those infected with HCV, that being in Adana was a risk factor, and that the frequency increased with age. The details of the following studies are given in Table 1.[7-39]

In studies conducted between 1990 and 2000, the average seroprevalence of HEV infection was found to be 12.6% in the healthy population, and 6.8% in studies conducted between 2001 and 2010. In studies conducted in the last decade, it was found to be 8.04%. In total, according to studies conducted in Turkey, we found that HEV infection prevalence of 9.52% (Table 1).

The highest prevalence rate was in Southeastern Turkey (Figure 1).

In our study, the seroprevalence rate is similar to those in other studies that have reported results of a similar healthy population in Turkey. The highest rates are reported from Diyarbakır.[7,17-19] As the average age of the population increases, the frequency of HEV infection inc reases.[6,24,30,33,37,38,61] Age in the third-fourth decades and older was determined as an independent risk factor for HEV seropositivity. Seroprevalence was found between 0.3% and 6.6% in studies conducted in the pediatric age group, which was significantly lower than our result.[73]

Prevalence of HEV Infection in At-Risk Communities in Turkey

The results of the seroprevalence studies that included pregnant women, patients with acute hepatitis, patients with chronic hepatitis, patients with cryptogenic cirrhosis, and patients of hemodialysis have been provided in detail in Table 2. We determined the average frequency of HEV infection rate to be 17.41% in hemodialysis patients and 6.52% in pregnant women.

Other Risky Groups

Aksu et al. also found the prevalence rate of 7% in Behçet's patients in İzmir, in 1999.[58] The frequency had been determined as 34.8% among agricultural workers in Diyarbakır, in 2003,[59] and 9.0% among garbage workers in İzmir, in 2004.[60] Anti-HEV IgG positivity was detected in 7.2% of hospital cleaning personnel in Çanakkale, in 2020, while anti-HEV IgM positivity and HEV RNA positivity were not detected.[61] In one study on HEV seropositivity in animal workers in Erzurum, in 2016, the frequency was 35.9%; and the highest rate among livestock was found in poultry. There was no seropositivity among veterinarians.[62]

In studies conducted in groups at risk, the highest seroprevalence rate was 73.3% in those with acute hepatitis, in Diyarbakır, in 1994,[41] followed by 42% in a study conducted with hemodialysis patients.[53] Patients with chronic renal failure had been given multiple blood transfusions, suggesting that other transmission routes may be effective.[3,4,62,73-75] Frequency is higher than in the general population among those working in farms and animal husbandry,[59,62] and those with chronic blood-borne infections as such HBV and HCV.[6,45] However, some studies show no association with HCV.[50,52] Studies in the literature also suggest that contact with wild animals and working in animal husbandry increase the risk of HEV infection.[1,76] Interestingly, in our study, the frequency of anti-HEV IgG positivity was found to be lower in volunteers engaged in agriculture and animal husbandry or breeding pets. There was no relationship found in our study between seropositivity prevalence and living in either an urban or a rural area.

There are some studies suggesting that HEV infection is more common in the lower socioeconomic groups of the society and is inversely related to education.[61,73] The relationship between seropositivity and having more than 5 siblings and less than 2 rooms in the house was found to be statistically significant ($P < .005$); seropositivity was as high as 18% in the group with a poor socioeconomic status.[61] An infectious disease that is basically transmitted by the fecal–oral route can be expected to be seen more frequently in these groups than in the others, due to poor sanitation conditions. In studies examining the relations with HAV based on the similar transmission routes, it has been reported that the seroprevalence of hepatitis A is 40-70% under the age of 10, and reaches 90% above the age of 15 in our country.[20,39,42,77] In the study in which the frequency of anti-HEV IgG was found to be 11.2% in Mersin, the rate of anti-HAV IgG was 91.4%.[25] Although the transmission routes are similar, it is seen that HAV is more common in the society compared to HEV, and that the HAV infection rate is high especially at younger ages, whereas the age of HEV infection shifts from childhood to adolescence and later. This may be due to the change in the antigenic structure of the virus over time or the lack of complete immunity after infection.

The wide range of results in HEV seroprevalence studies may be due to regional differences in the study groups, as well as the differences in sensitivity between different

microbiological kits used in anti-HEV antibody screening. These commercial kits are ELISA, the Western blot technique, and kits using recombinant antigens or synthetic peptides expressed from the viral genomes ORF-2 and ORF-3, or both. Enzyme immune assay is a diagnostic method that is easy to apply in practice.[78,79] Tests determining antigen-specific antibodies belonging to a single HEV genotype may be insufficient to determine all HEV genotypes. In addition, the duration of the IgG anti-HEV response is not exactly known, and it can be detected up to 14 years after acute infection.

The major limitation of our study was that it included only the healthy blood donor population, and was not representative of the entire population of the city. Our aim in the beginning of the study was to conduct a society-based study to exemplify the city of Mersin. However, in the following denial of permission to conduct such a study by the central healthcare authorities, we were constrained to conduct the study on healthy blood donors only. Another limitation of our study was the gender-specific male dominance; this was probably because most of the blood donors were men. In the literature, there is no difference between the 2 genders, except that HEV infection is more severe in pregnant women.[12,17,19,33]. On the other hand, there is a study showing that it is more common in men.[39]

In previous studies performed among blood donors in Turkey, the average HEV seroprevalence was found to be 7.3%.[8,15,16,22,25,32] We detected 12.8% anti-HEV IgG positivity in this group, like the 11.2% rate found in Mersin in 2002.[25] In worldwide publications on blood donors, the overall rates of anti-HEV IgG reactivity among blood donors in Europe ranged from 4.7-52.5%, in Australia 6.0%, in central Asia 14.3-21.48%, and in the United States 16.0%.[80]

In conclusion, the anti-HEV IgG seropositivity rate in healthy blood donors in Mersin province was 12.8%, and was similar to the rates reported earlier in Turkey. However, this rate, found in a healthy sample of the society, causes concern about what the frequency may be in sick people. Wide-ranging community screening is needed.

Ethics Committee Approval: Mersin University Ethical Committee for Clinical Researh, date: 22 June 2017, number:2017/188.

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

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