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Original Article / Özgün Araştırma

Unveiling the Hepatitis E Seroprevalence: Insights from Dicle University Hospital in Southeastern Turkey

Nida Ozcan[1], **Serkan Kaydas**[1], **Ahmet Kazar**[1], **Hakan Temiz**[1]

1 Dicle University, Faculty of Medicine, Dept.of Medical Microbiology, Diyarbakir, Turkey

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Abstract

Introduction: Hepatitis E virus (HEV) is a substantial concern for public health with varying seroprevalence rates globally. In this study, HEV seroprevalence in patients admitted to Dicle University Hospital, in the southeastern area of Turkey, was investigated.

Methods: The test results for immunoglobulin M type HEV antibodies (Anti-HEV IgM) and immunoglobulin G type HEV antibodies (Anti-HEV IgG) of patients applied to Dicle University Hospital for various reasons between 2017 and 2021 were retrospectively analyzed. The sera samples underwent testing to identify IgG and IgM antibodies using HEV IgG and HEV IgM test kits (Dia-Pro Diagnostic Bioprobes, Milan, Italy) on the Triturus micro-ELISA system (Grifols SA, Barcelona, Spain). The study included both adult and pediatric patients. Statistical analysis was conducted to assess the associations between gender and age groups (pediatric and adult) and HEV seropositivity utilizing the chi-square test at a significance threshold of $p<0.05$.

Results: Among the 4,048 patients tested, 140 adult patients (4.87%) and 10 pediatric patients (0.84%) exhibited Anti-HEV IgM reactivity, with significantly higher rates observed in adults. Similarly, adults exhibited a notably higher Anti-HEV IgG reactivity at 40.5%, in contrast to the 7% observed in children. Gender-based analysis revealed no significant differences in Anti-HEV IgM reactivity among adults, while a potential, though weak, difference in Anti-HEV IgG reactivity was observed, with more reactive cases in males.

Conclusion: Our study sheds light on the noteworthy seroprevalence of HEV among hospital admissions patients in the southeastern region of Turkey, surpassing rates reported in other regions. Further research is needed to understand transmission dynamics.

Keywords: Seroprevalence, Hepatitis E Virus, Epidemiology, Immunoglobulin M, Immunoglobulin G

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Correspondence / Yazışma Adresi: *Nida Ozcan, Dicle University, Faculty of Medicine, Department of Medical Microbiology, Sur/Diyarbakir, Turkey e-mail: nida.ozcan@dicle.edu.tr*

Hepatit E Seroprevalansının Araştırılması: Türkiye'nin Güneydoğusundaki Dicle Üniversitesi Hastane Verileri

Öz

Giriş: Hepatit E virüsü (HEV), küresel olarak değişen seroprevalans oranlarıyla önemli bir halk sağlığı sorunudur. Bu çalışmada Türkiye'nin güneydoğu bölgesindeki Dicle Üniversitesi Hastanesi'ne başvuran hastalarda HEV seroprevalansı araştırıldı.

Yöntemler: Dicle Üniversitesi Hastanesi'ne 2017-2021 yılları arasında çeşitli nedenlerle başvuran hastaların immünglobulin G tipi HEV antikorları (Anti-HEV IgG) ve immünglobulin M tipi HEV antikorları (Anti-HEV IgM) test sonuçları retrospektif olarak incelendi. Serum örnekleri, HEV IgG ve HEV IgM test kitleri (Dia.ProDiagnostic Bioprobes, Milan, İtalya) kullanılarak Anti-HEV IgG ve Anti-HEV IgM varlığı açısından Triturus otomatik ELISA sisteminde (Grifols SA, Barselona, İspanya) çalışıldı. Çalışmaya yetişkin ve pediatrik hastalar dahil edildi, cinsiyet ve yaş grupları (pediatrik ve yetişkin) ile HEV seropozitifliği arasındaki ilişkiler ki-kare yöntemiylep<0,05 anlamlılık düzeyinde test edildi.

Bulgular: Test edilen 4.048 hasta arasında 140 yetişkin hasta (%4,87) ve 10 pediatrik hasta (%0,84) Anti-HEV IgM reaktivitesi sergiledi; yetişkinlerde anlamlı derecede daha yüksek oranlar gözlendi. Benzer şekilde Anti-HEV IgG reaktivitesi yetişkin hastalarda (%40,5) çocuklara (%7) göre anlamlı derecede yüksekti. Cinsiyete dayalı analiz, yetişkinler arasında Anti-HEV IgM reaktivitesinde anlamlı bir fark olmadığını ortaya koyarken, erkeklerde daha reaktif vakalarla birlikte Anti-HEV IgG reaktivitesinde zayıf da olsa potansiyel bir fark gözlemlendi.

Sonuç: Çalışmamız, Türkiye'nin güneydoğu bölgesinde hastaneye başvuran hastalarda HEV seroprevalansının diğer bölgelerde bildirilen oranları geride bırakarak kayda değer olduğunu göstermektedir. Bulaşma dinamiklerini anlamak daha kapsamlı araştırmaları gerektirmektedir.

Anahtar kelimeler: Seroprevalans, Hepatit E Virüsü,Epidemiyoloji, İmmünoglobulin M, İmmünoglobulin G.

INTRODUCTION

Hepatitis E virus (HEV), is a single-stranded RNA virus that lacks an envelope and has a size of approximately 27-34 nm, with an icosahedral structure and positive polarity[1]. HEV ranks as the second most prevalent agent causing hepatitis through fecal-oral transmission, after Hepatitis A virus (HAV). Hepatitis E infections can range from an asymptomatic condition to fulminant disease[2].

In 1983, Balayan and co-authors documented HEV as a non-A, non-B hepatitis agent with fecal-oral transmission[3]. In current taxonomy, HEV is categorized within the Paslahepevirus genus, belonging to the Orthohepevirinae sub-family of the Hepeviridae family. It includes eight separate genotypes under the species Paslahepevirusbalayani, named after the scientist who first described the virus[4]. Responsible for waterborne transmission, genotypes 1 and 2 are limited to humans. On the other hand, genotypes 3 and 4 are prevalent in wild animals and pigs, with the potential to cause zoonotic infections in humans, mainly when they consume contaminated meat products[5].

HEV is responsible for infecting around 20 million individuals globally on an annual basis, with 55,000 deaths attributed to HEV infection[6]. Hepatitis E epidemics are primarily associated with waterborne transmission, particularly in areas with poor sanitation where drinking water is sourced from rivers, lakes, and other natural sources[7]. Soil contaminated with feces has also been reported as a source of transmission, with HEV epidemics occurring after natural disasters like landslides and floods[8].

The prevalence of hepatitis E worldwide is closely associated with economic development and varies significantly based on factors such as

geographic region, socioeconomic status, and age[9-12]. In Turkey, HEV seroprevalence has been reported to range from 0% to 73%, reflecting the diversity of regions and study populations[13]. This study investigates the seroprevalence of HEV in patients admitted to Dicle University Hospital, one of the tertiary care hospitals in the southeastern region of Turkey.

METHODS

The study retrospectively examined the test outcomes of patients who visited Dicle University Hospital for various reasons and were screened for immunoglobulin M type HEV antibodies (Anti-HEV IgM) and immunoglobulin G type HEV antibodies (Anti-HEV IgG) from 2017 to 2021. Both children (aged 0-17) and adults (aged 18 and above) were included. Blood samples were gathered from patients using sterile precautions, permitted to coagulate at room temperature for 15-20 minutes, and subsequently subjected to centrifugation. The acquired serum samples underwent examination for qualitative testing of Anti-HEV IgM and Anti-HEV IgG employing HEV IgM and HEV IgG testing kits (DiaPro Diagnostic Bioprobes, Milan, Italy) on the Triturus automated ELISA system (Grifols SA, Barcelona, Spain). The test outcomes were analyzed following the guidelines provided by the manufacturer. For Anti-HEV IgM, samples with a Sample signal/Cut Off (S/CO) value of < 1 were regarded as non-reactive, value of ≥1.2 were considered reactive, and values between 1 and 1.2 were considered gray zone and retested with a new sample. For Anti-HEV IgG, samples with S/CO values < 0.9 were regarded as non-reactive, values of ≥1.1 S/CO were considered reactive, and values between 0.9 and 1.1 were considered gray zone and retested with a new sample. Each patient contributed a single sample to the study and repeated positivity samples were excluded from analysis.

Statistical Analysis

Categorical variables were displayed as numbers and percentages in the study. Comparisons were conducted between the adult and pediatric age groups, as well as between male and female groups, by the chi-square ($\chi 2$) test, considering statistical significance at a $p < 0.05$ level.

Ethical Approval

The study received ethical authorization from Non-Interventional Clinical Research Ethics Committee of Dicle University Medicine Faculty on January 17, 2023, with approval number 54.

RESULTS

Anti-HEV IgM tests were performed on a total of 4,048 patients (2,870 adults, 1,178 children). Anti-HEV IgM reactivity was detected in 140 (4.87%) of adult patients and 10 (0.84%) of pediatric patients. The distribution of Anti-HEV IgM reactivity in adult and pediatric patients is shown in Table I. Anti-HEV IgM reactivity exhibited a significant difference between adult and pediatric patients (χ^2= 37.998, p<0.05), with higher levels observed in adults.

Table I: Anti-HEV IgM reactivity in adult and pediatric patients

Adult / Child Status	Anti-HEV IgMn (%)			X^2	P
	Reactive	Non-reactive	Total		
Adult	140 (4.9)	2730 (95.1)	2870 (100)	37.998	0.001
Child	10 (0.8)	1168 (99.2)	1178 (100)		
Total	**150 (3.7)**	**3898 (96.3)**	4048 (100)		

Anti-HEV IgM: Immunoglobulin M type Hepatitis E Virus antibodies

Anti-HEV IgG tests were performed on 4,215 patients (2,988 adults, 1,227 children). Anti-HEV IgG reactivity was detected in 1,212 (40.5%) adult patients and 86 (7%) children. Anti-HEV IgG reactivity in adult patients was significantly higher than in children ($\chi 2$= 459.496, p<0.05) (Table II).

Table II: Anti-HEV IgG reactivity in adult and pediatric patients

Adult / Child Status	Anti-HEV IgG n (%)			X^2	P
	Reactive	Non-reactive	Total		
Adult	1212 (40.6)	1776 (59.4)	2988(100)	459.496	<0.001
Child	86 (7)	1141(93)	1227(100)		
Total	**1298 (30.8)**	**2917 (69.2)**	4215 (100)		

Anti-HEV IgG: Immunoglobulin G type Hepatitis E Virus antibodies

When examining the association between Anti-HEV IgM reactivity and gender in adult patients, reactivity was observed in 4.5% of female patients (66/1,458) and 5.2% of male patients (74/1,412). Anti-HEV IgM reactivity in adult patients was not significantly associated with gender (χ^2= 0.788, p>0.05) (Table III). The distribution of Anti-HEV IgM reactivity over the years was determined as follows: 33 (22%) in 2017, 30 (20%) in 2018, 37 (24.7%) in 2019, 2 (1.3%) in 2020, and 48 (32%) in 2021. Due to the COVID-19 pandemic restrictions, the number of reactive cases was notably low from the latter months of 2019 until the middle of 2021. The highest reactivity was observed in the spring months with 13, 11, and 17 patients in 2017, 2018, and 2019, respectively.

Table III: Association between gender and anti-HEV IgM reactivity in adult patients

Gender	Anti-HEV IgM n (%)			X^2	p
	Reactive	Non-reactive	Total		
Female	66 (4.5)	1392 (95.5)	1458 (100)	0.788	0.375
Male	74 (5.2)	1338 (94.8)	1412 (100)		
Total	**140 (4.9)**	**2730 (95.1)**	**2870 (100)**		

Anti-HEV IgM: Immunoglobulin M type Hepatitis E Virus antibodies

Among adult female patients, 38% (585/1,508) had Anti-HEV IgG seropositivity, while among male patients, 42% (627/1,480) had Anti-HEV IgG seropositivity (Table IV). The higher number of reactive individuals in males and a p-value below 0.05 suggest a potential difference in Anti-HEV IgG reactivity based on gender. However, the p-value close to 0.05 indicates that this relationship is weak and would require further investigation.

Table IV: Association between gender and anti-HEV IgG reactivity in adult patients

Gender	Anti-HEV IgGn (%)			X^2	p
	Reactive	Non-reactive	Total		
Female	585 (38.8)	923 (61.2)	1508 (100)	3.952	0.047
Male	627 (42.4)	853 (57.6)	1480 (100)		
Total	**1212 (40.6)**	**1776 (59.4)**	2988 (100)		

Anti-HEV IgG: Immunoglobulin G type Hepatitis E Virus antibodies

Of the 1212 adult patients tested reactive for Anti HEV-IgG, 591 (48.8%) were from the gastroenterology department, 53 (4.4%) from the infectious diseases department, and 184 (15.2%) from other internal medicine clinics. Anti HEV-IgG reactivity was relatively lower in surgical clinics, with 134 (11%) cases detected in the Organ Transplantation clinic, 25 (2%) in the Ophthalmology clinic, 10 (0.8%) in the

Obstetrics and Gynecology clinic, and 115 (9.5%) in other surgical clinics. Seropositivity data for pregnant women could not be obtained as they seek care in clinics other than Obstetrics and Gynecology, such as Infectious Diseases clinics. Furthermore, among the pediatric patients who tested positive for Anti HEV-IgG, 47 (54.6%) were identified among patients from the pediatric hematology clinic.

DISCUSSION

Hepatitis E infection is a matter of great public health importance, particularly in the developing world. HEV is responsible for outbreaks in developing countries, including India, China, Myanmar, Indonesia and Chad, whereas in developed countries, it presents as sporadic cases[5,6]. While in highly endemic countries such as China and India, the seroprevalence of Hepatitis E virus (HEV) exceeds 25% in the general population, this rate is approximately 2% in Europe and approximately 3% in the United States[14]. Although the current study did not cover the general population and was conducted among hospital admissions patients, a considerable HEV seropositivity rate underscored the endemic status of HEV in our area.

The seroprevalence of HEV in different regions varies widely and is influenced by several factors, including sanitation, hygiene, climate, water quality, and food safety. In a 1992 study investigating the epidemiology of HEV in Turkey, anti-HEV antibodies were examined in a sample of 300 individuals randomly selected from five distinct regions of Turkey, namely the Aegean, southwest, northwest, northeast, and southeast. The study identified several factors that independently predicted anti-HEV seropositivity. These factors encompassed individuals aged 25 or older, those with an education level below elementary, and individuals living in the warmest region, specifically the southeast[15]. Consistent with this study, our study showed high seroprevalence in a very hot province and revealed a significantly higher Anti-HEV IgM and Anti-HEV IgG reactivity in adult patients compared to pediatric patients. This observation may be attributedto a higher probability of HEV exposure in adults over time.

The seroprevalence of HEV has been reported at varying rates according to regions, age groups, and the populations studied.In a study conducted at Çanakkale Onsekiz Mart University, located in the northwest region of Turkey, involving 180 hospital workers aged between 17 and 73 years old (90 of whom were cleaning staff, and 90 were administrative personnel), 13 participants (7.2%) exhibited Anti-HEV IgG reactivity. In the same study, it was reported that HEV seropositivity was significantly higher in employees aged 45 and older, those with more than five children, and those residing in households with fewer than two rooms[16]. In a study carried out at Ankara University between 2000-2001, which included 1046 patients aged 15-75 with no acute hepatitis symptoms, total (IgG+IgM) HEV antibody positivity was investigated, and seropositivity was found in 40 patients (3.8%), with the highest seropositivity reported among those aged 30-60[17]. Although the seropositivity rate was low in these studies, the high positivity rate after the third decade is consistent with our study. In our study, although it is not clear whether the patients had hepatitis symptoms or not, the fact that most of the seropositive patients were from the gastroenterology clinic suggests that they may have hepatitis-related findings. This may explain the high HEV seropositivity in our study.

In 2002, in Erzurum, HEV IgG levels were examined in 340 individuals aged 0-73 with different socioeconomic levels, and HEV seropositivity was found to be 10.3%. The population included in the study was compared in terms of gender, age below and above 20, and low and high socioeconomic status, and no

significant differences were found. Although seropositivity was found to be two times higher in individuals over 20 years old, it was not statistically significant[18]. In Malatya, blood samples were obtained from 600 individuals with different age groups and socioeconomic levels. HEV seropositivity was documented as 6.7% in those with a high socioeconomic level, 13% in those with a low socioeconomic level, and 9.8% overall[19]. In İzmir, in 2012, 18 out of 270 adult patients who presented to the hospital for various reasons were reported to have Anti-HEV IgG positivity (6.7%), and 2 had Anti-HEV IgM positivity (0.7%). The study reported that 39% of the HEV seropositive patients were from the infectious diseases clinic, 33% from the general surgery clinic, and 17% from the gastroenterology clinics[20]. In our study, approximately half (48.8%) of the HEV seropositive adult patients were those who presented to the gastroenterology clinic.

The highest seropositivity among pediatric patients in our study being among patients in the hematology clinic suggests that there may be different sources of infection. Indeed, HEV seropositivity was recorded as 29.9% in Aktaş et al.'s study conducted in 1999 in Erzurum among 87 individuals working in Atatürk University Faculty of Dentistry[21]. Furthermore, in a study including hemodialysis patients, a group that frequently undergoes blood transfusions, Uçar et al. reported a HEV seroprevalence of 20.6%[22].

Research conducted on anti-HEV positivity in our country has indicated that seroprevalence rates of HEV differ according to regional factors and the characteristics of the sample cohorts. In a 2002 study carried out by Yazgı et al. in Erzurum, it was found that 9% of pregnant women and 8% of the control group, composed of women aged 20 to 41, exhibited anti-HEV IgG positivity[23]. According to a study by Cesur et al. in Ankara between 2000-2001, HEV seropositivity was detected in 40 out of 1046 individuals aged 15-75 (3.8%)[17]. When Eker et al. examined blood samples from 582 individuals aged 15 and above in Edirne, they found anti-HEV IgG positivity to be 2.4%[24]. In a study conducted in Gaziantep in 2000 among 489 patients with symptoms of viral hepatitis, HEV IgG was found to be 11.2%, and HEV IgM was found to be 8.8%. The study reported that seropositivity was most common in the 15-44 age group, with no significant difference between genders[25]. The seropositivity rates in our study were higher compared to the results from Gaziantep and Erzurum, which were the closest to our study data[23,25], but significantly higher than the rates reported from western regions of the country[17,24].

There are studies covering different groups investigating HEV seropositivity in Diyarbakir, which is located in the southeastern region of Turkey. Olcay et al.conducted a study in the year 2000, where they compared different age groups and genders within a randomly selected sample of 910 individuals, they also compared three different regions, namely Ankara (located in the Central Anatolia region), Manisa (situated in the western region), and Diyarbakir.They reported a HEV seroprevalence of 6.3% in the total of the three provinces, while in Ankara it was 2.7%, in Manisa it was 3.8%, and in Diyarbakir, it was notably higher at 11.7%. They pointed out that the prevalence they discovered in Diyarbakir was substantially higher than that in the other regions[26]. In another study conducted in Diyarbakir, Ceylan et al. in 2003 found HEV seroprevalence to be 34.8% among 46 agricultural workers and 4.4% in the control group (45 individuals). The study reported that HEV seropositivity was highest in the 20-34 age group[27].

Furthermore, Ozbek et al. reported an Anti-HEV IgG reactivity of 25.9% in 158 patients of reproductive age with various complaints in Diyarbakir[28].

The seropositivity rates in our study were found to be higher than in other regions of our country. The results obtained in study are most resembling to those found in Erzurum among dental faculty employees (29%) and in Hatay among hemodialysis patients (20%)[22,23]. The HEV seroprevalence we detected is also similar to the rates previously reported among patients and agricultural workers in our province[27,28]. However, the rates in our study are notably higher than the seroprevalence rates in Olcay et al.'s study in the general population (11.7%) and in Ceylan et al.'s control group (4.4%)[26,27]. It is assumed that this difference may be attributed to the variation in the selected samples. Beskisiz et al. conducted an investigation into HEV seropositivity and established risk determinants for HEV infection among adult viral hepatitis patients. The study's results revealed that 56.4% of the entire patient population (578 out of 1025) had Anti-HEV IgG seropositivity, consistent with our own findings. Their results also indicated that advanced age, rural background, limited education, history of animal interaction and the presence of other hepatitis viruses were found to be significant risk factors for HEV seropositivity[29].

It should be recognized that this study has a few shortcomings, such as its retrospective nature and the lack of detailed information on the presence of hepatitis symptoms, additional diseases, occupational information, and the history of animal contacts. A comprehensive epidemiological investigation, including risk factor analysis and genotyping of HEV strains, would provide valuable insights into the dynamics of HEV transmission in this region.

CONCLUSION

This study provides insight into the seroprevalence of HEV in patients visiting Dicle University Hospital. The results suggest that HEV exposure is relatively common in this region, with a higher prevalence in adults compared to children. Additional studies are necessary to expand our knowledge of the factors that contribute to HEV transmission. Public health interventions, such as improved sanitation and food safety measures, may be necessary to reduce the burden of HEV infection in this region.

Ethics Committee Approval: The study received ethical authorization from Non-Interventional Clinical Research Ethics Committee of Dicle University Medicine Faculty on January 17, 2023, with approval number 54. Since the study was retrospective, it was not necessary to obtain informed consent from the patients.

Conflict of Interest: No conflicts of interest were disclosed by the authors.

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