AKADÉMIAI KIADÓ

Acta Microbiologica et Immunologica Hungarica

70 (2023) 2, 119–125

DOI:
10.1556/030.2023.02010

RESEARCH ARTICLE

High seroprevalence of hepatitis E virus (HEV) in South Transdanubia, Hungary (2010–2022)

BENIGNA BALÁZS, ÁKOS BOROS, PÉTER PANKOVICS and GÁBOR REUTER*

Department of Medical Microbiology and Immunology, Medical School, University of Pécs, Pécs, Hungary

Received: March 10, 2023 • Accepted: April 19, 2023
Published online: May 9, 2023

ABSTRACT

Hepatitis E virus (HEV) is an increasingly recognized etiological agent of acute, chronic and extrahepatic human infections with primarily zoonotic origin in Europe. Limited numbers of comprehensive population-based studies are available related to HEV seroepidemiology, especially from Central Europe.

The aim of this study was to investigate the seroprevalence and trends of total and IgM antibodies against HEV in different age groups in the population of South Transdanubia, Hungary, within a thirteen years long period between the years 2010 and 2022.

We retrospectively analysed the serological test results of HEV total and HEV IgM antibodies carried out by ELISA technique using Dia.Pro (Diagnostic Bioprobes, Italy) kit from serum samples collected from patients with or without hepatitis between January 1, 2010 and December 31, 2022.

The number of tested samples ($\sum$6,996 for total antibody and $\sum$6,582 for IgM) increased during the study period. The average HEV total and the IgM antibody seropositivities were 33% (2,307/6,996 samples) and 9.6% (642/6,582 samples), respectively, in the study population. The HEV total antibody seropositivity varied in different age groups between 3.9% (age group 1–5 years) and 58.6% (86–90 years) and showed an increasing positivity by age. At the age groups >50 years, nearly half (43%) of the population had antibodies against HEV. The HEV IgM positivity had an increasing trend of up to 13.9% in the age group 81–85 years.

High HEV total and IgM antibody seroprevalence were detected in South Transdanubia, Hungary, confirming that this region is highly endemic for HEV infections in Europe.

KEYWORDS

hepatitis E virus, HEV, seroepidemiology, antibody, age group, human, Hungary

INTRODUCTION

Hepatitis E virus (HEV) is a leading cause of acute viral hepatitis and belongs to the genus *Orthohepevirus,* family *Hepeviridae* [1]. Human pathogen HEVs have been classified into 6 genotypes in two species (*Paslahepevirus balayani* and *Rocahepevirus ratti* formerly known as *Orthohepevirus A* and *Orthohepevirus C*, respectively) [1]. Genotypes 1 and 2 in species *Paslahepevirus balayani* circulate in tropical/subtropical countries where faecal-oral and waterborne infections are the main modes of transmission [2, 3]. Genotypes 3 and 4 are dominant in Europe, the USA and Asia and are associated with zoonotic infection from animals (swine, wild boar, roe deer and rabbit) to humans [3]. Human cases of genotype 7 from camels have been also reported [4, 5]. Recently, rat HEV belonging to the species *Rocahepevirus ratti* also poses a risk of zoonotic infections in humans [6, 7]. Transmission of HEV by blood and blood products and from mother to foetus is also possible [8, 9].

Recent studies confirmed that HEV is associated with a wide range of diseases in humans. HEV not only cause acute hepatitis but also play a role in chronic hepatitis among immunocompromised patients [10, 11] and is related to extrahepatic, like neurological (neuralgic

*Corresponding author.
Department of Medical Microbiology and Immunology, Medical School, University of Pécs, H-7624, Szigeti út 12., Pécs, Hungary.
Tel.: +36 (72) 536 252.
E-mail: reuter.gabor@gmail.com

amyotrophy, Guillain-Barré syndrome, myelitis etc.), renal (glomerulonephritis, nephropathy, cryoglobulinemia) and other immune-mediated manifestations [12–14].

HEV infections have worldwide distribution. Seroprevalence studies demonstrate various levels of anti-HEV total antibodies in populations in different countries and different locations within countries [15, 16]. In Europe, there were HEV seroprevalence studies among healthy blood donors [17], organ transplant recipients and other immunocompromised patients, patients with inflammatory bowel disease [18], refugees [19] and patients with liver symptoms [20] but there is a limited number of a comprehensive study about the prevalence of HEV in the general populations. In studies from Albania, the Czech Republic and Greece [21–23] reported the lowest (<10%) and France, the Netherlands and Poland [16, 17, 24–26] reported the highest (>20% and reaching 86.4% in Ariége in Southwest France) average HEV seroprevalence in Europe. These studies found that HEV seroprevalence is increasing with age [15–17, 23, 27].

In Hungary, limited and controversial data is available on HEV seroprevalence in humans. In 2007, HEV IgG seroprevalence of 6.1% was reported among 264 patients with acute hepatitis in Southwest Hungary [28]. In 2018, a European study classified Hungary as a country with low (under 5%) HEV seroprevalence [29]; however, a recent report shows 31% HEV seropositivity among patients with acute hepatitis in Southeast Hungary [30]. At the same time, based on molecular epidemiological studies HEV is thought to be endemic, food-borne zoonosis in this country [11, 31].

In this study, the age-specific rates and trends of HEV immunity in Southwest Hungary (South Transdanubia) were reviewed between 2010 and 2022.

MATERIALS AND METHODS

Collection of specimens

The seroepidemiological analysis is based on a retrospective analyses of the serological laboratory results of the HEV total antibodies and HEV IgM antibody tests, respectively, between January 1, 2010 and December 31, 2022. Blood samples were originally sent by physicians (university/county hospitals and general practitioners) from patients with a history of hepatitis or without hepatitis for routine clinical HEV serological testing to the Laboratory of Virology, Department of Medical Microbiology and Immunology, University of Pécs (Pécs, Hungary) covering a population of ∑894,000 persons (9.1% of the total population of Hungary in 2017) in three counties (Baranya, Somogy and Tolna) in the region South Transdanubia, Southwest Hungary (Fig. 1). South Transdanubia represents one of the seven regions in Hungary. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The health data collection authorisation number is: KK/208-1/2023 (University of Pécs).

Serological methods

Serum samples were tested by ELISA method using the HEV Ab (version Ultra, Dia.Pro Diagnostic Bioprobes, Sesto San Giovanni, Italy) and HEV IgM (Dia.Pro Diagnostic Bioprobes, Sesto San Giovanni, Italy) test kits according to the manufacturer's instructions. Based on the available information the HEV Ab (HEV total antibody) and HEV IgM ELISA test plates are coated with specific synthetic HEV-ORF2 capsid protein antigen encoding conservative and

Fig. 1. Schematic map of Hungary with counties ($N = 19$) and the capital Budapest. The study area (South Transdanubia) is indicated with a dark coloured background and the names of the three counties

immunodominant determinant of genotypes 1–4 HEVs. These assays are allowing the qualitative detection of total anti-HEV antibodies (IgG, IgM, and IgA together) and IgM separately (in case of IgM assay) in human serum and plasma samples [https://www.diapro.it/products/hev-ab-version-ultra-elisa/, 32]. According to the manufacturer's validation criteria the sample is positive for HEV total and HEV IgM antibodies if the optical density (OD) was equal or higher than 1.1 compared to the OD/cut-off ratio. A positive test result for HEV IgM may indicate an acute (recent) HEV infection, while a positive result for HEV total antibody may indicate a previous infection [33].

Statistical analyses

The selection of the 5-year age groups was made using MedBakter program (Prolab Kft.). Statistical analyses were performed using IBM SPSS Statistics software V024 (Chicago, IL, US) and Microsoft Excel 2013 (Redmon, WA, US). We used regression analysis. $p < 0.05$ was considered significant. Age group 91–95 years was excluded from statistical analyses because of the low sample size ($N = \sum 8$).

RESULTS

A total of 6,996 and 6,582 serum samples were tested for HEV total and HEV IgM antibodies, respectively, between 2010 and 2022. The yearly distribution of the samples had an increasing trend; however, there was a decline in 2020 and 2021. Figure 2 represents the total numbers of HEV total antibody and IgM antibody tests and the positive test results per years (Fig. 2).

Most of the specimens (54.7% tested for HEV total antibody and 54.3% tested for HEV IgM antibody) was originated from age groups between 40 and 70 years (Fig. 2). The fewest samples collected from the age groups under 10 (less than 2% by age groups) and over 80 (less than 2% by age groups). The highest percentage (9.9% for both HEV total and for HEV IgM antibodies) of samples were collected from the age group 61–65 years. Figure 3 shows the distribution of specimens tested for HEV total and HEV IgM antibodies by age groups (Fig. 3).

Over the study period, the seropositivity of HEV total antibody increased significantly between 2010 and 2015 ($p < 0.001$) reaching 36.3% (Fig. 4). Between 2015 and 2022

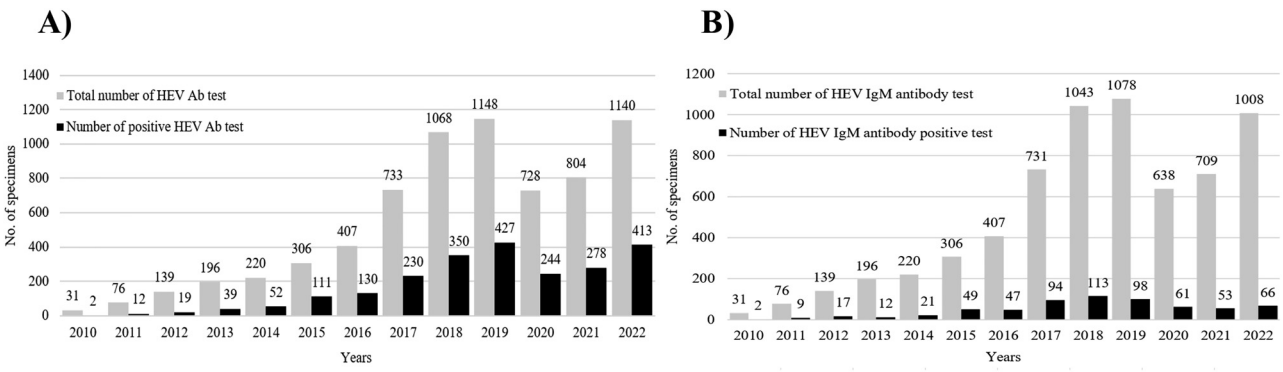

Fig. 2. A) Yearly distribution of serum samples ($N = 6{,}996$) tested for hepatitis E virus (HEV) total antibodies in South Transdanubia, Hungary, between 2010 and 2022. Grey and black columns represent the total numbers of the tested and HEV antibody-positive specimens, respectively. B) Yearly distribution of serum samples ($N = 6{,}582$) tested for HEV IgM in South Transdanubia, Hungary, between 2010 and 2022. Grey and black columns represent the total numbers of the tested and HEV IgM antibody-positive specimens, respectively

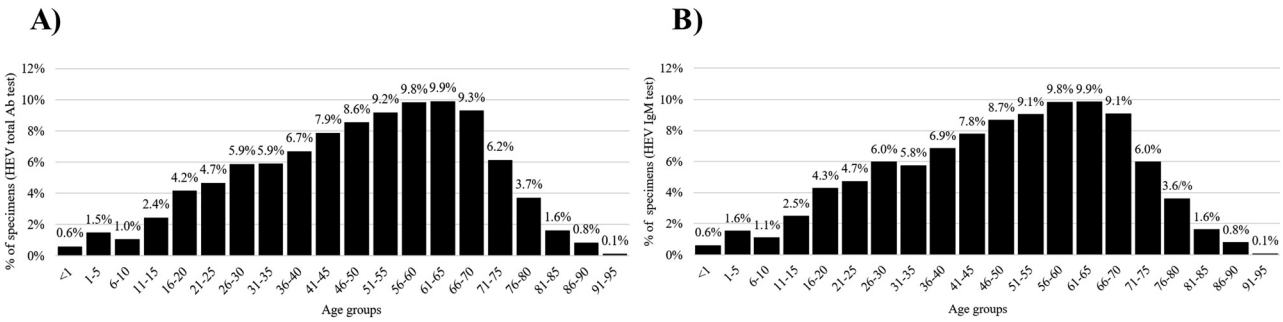

Fig. 3. A) Distribution of specimens ($N = 6{,}996$) tested for HEV antibody in percentage by age groups in years. B) Distribution of specimens ($N = 6{,}582$) tested for HEV IgM in percentage by age groups in years

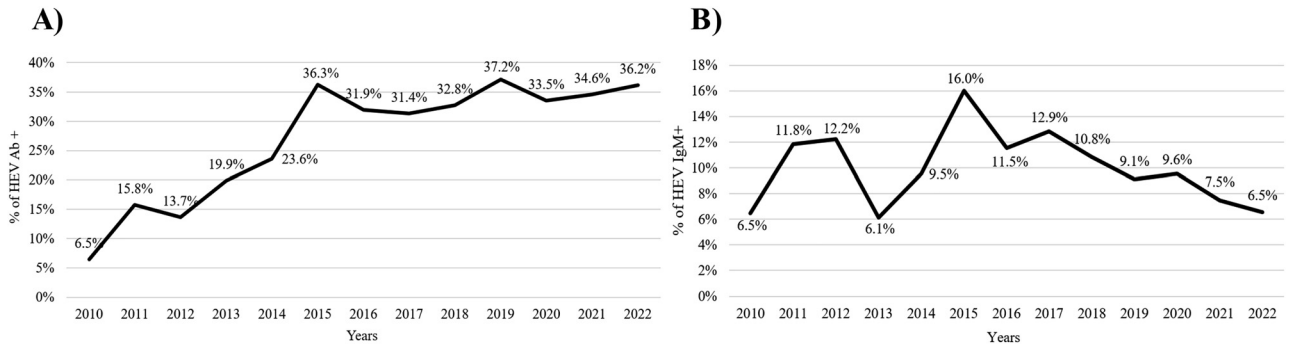

Fig. 4. A) Percentage (%) of HEV total antibody positivity (HEV Ab +) of tested samples by year between 2010 and 2022. B) Percentage (%) of HEV IgM positivity (HEV IgM +) of tested samples by year between 2010 and 2022

it varied between 31.4% (2017) and 37.2% (2019) without further significant increase ($p > 0.05$). The average seropositivity rate was 33% (2,307 HEV total antibody positive specimens from 6,996 tests). Figure 4A shows the yearly distribution of HEV total antibody seropositivity in percentage in detailed (Fig. 4A).

The HEV total antibody seropositivities varied in the different age groups between 3.9% in the age group 1–5 years and 58.6% in the age group 86–90 years (Fig. 5). Seropositivity increases continuously with age ($p < 0.001$). It varies between 40% and 50% between the age group 51–55 and the age group 81–85, respectively. The average HEV total antibody seropositivity (33%) was crossed by the age group 46–50 years. Figure 5A represents the percentages of HEV total antibody seropositivity by age groups in detailed (Fig. 5A).

The yearly distribution of HEV IgM positive specimens varied between 6.1% (2013) and 16% (2015) with an average of 9.6% (642 HEV IgM antibody positive specimens from 6,582 tests) during the study period. The trend increased between 2010 and 2012 (from 6.5% to 12.2%) followed by a decrease in 2013 to 6.1% which was the lowest percentage. There was a peak (16%) in 2015. The change of trend was not significant during the whole study period ($p > 0.05$); however, there was a significant decrease from 12.9% to 6.5% between 2017 and 2022 ($p < 0.001$). Figure 4B represents the HEV IgM seropositivities by years in detailed (Fig. 4B).

The HEV IgM seropositivity varied between 0% in the age groups less than 5 years and 13.9% in the age group 81–85 years and increases with age ($p < 0.001$) (Fig. 5B). The average HEV IgM seropositivity was 9.6%. Between age groups 51–55 and 81–85 the HEV IgM seropositivities were more than 10% in all age groups. Figure 5B shows the percentages of HEV IgM positivities by age groups in detailed (Fig. 5B).

DISCUSSION

The number of currently available HEV seroprevalence studies in the general population is not sufficient for a comprehensive and comparative analysis to draw further conclusions in Europe, furthermore, limited and controversial data is available on HEV seroprevalence in Hungary, too. In this study, the seroprevalence of human HEV infections was investigated using total antibody and IgM ELISA assays in more than 6,500 specimens collected from the population of South Transdanubia, Hungary, between the years of 2010 and 2022. The difference in the numbers of total and IgM antibody tests can be explained by the test

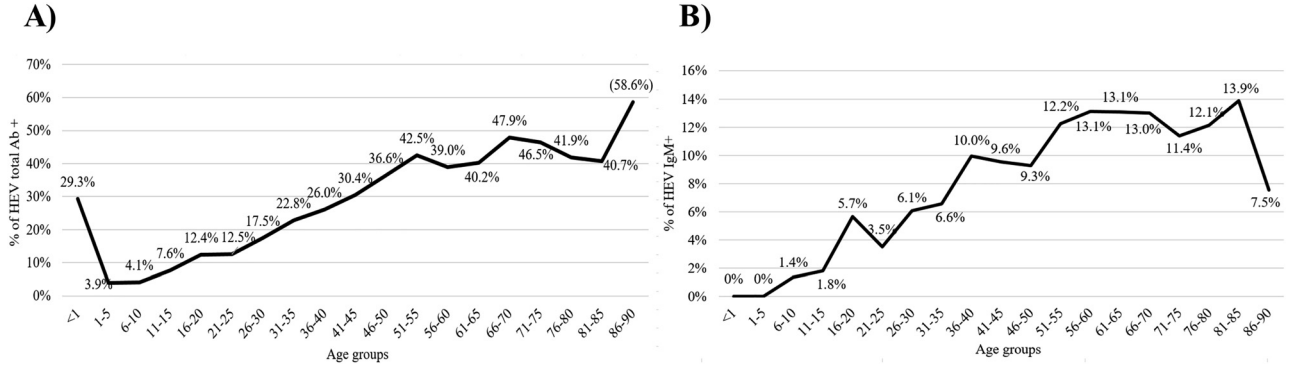

Fig. 5. A) Percentage (%) of HEV total antibody positive results by age groups in years. B) Percentage (%) of HEV IgM positive results by age groups in years. Each age group covers 5 years from 1 to 90 years. The sample size was low ($N = \sum 8$) in age-groups 91–95, therefore, this data is not included in the figure

requests of clinicians. The number of HEV specimens were continuously increased from the start of our study until 2019, interrupted by a sharp decline in 2020/2021 because of the ongoing SARS-CoV-2 pandemic. Following the end of emergency, the upward trend has reversed by 2022. The overall increasing trend in testing suggests that more and more clinicians are recognising the importance of HEV and requests more tests.

The seroprevalence of HEV total antibodies increases with age similar as found in other studies [15–17, 23, 26]. The lowest seroprevalence was observed in children similar as found in other studies [26]. The relatively high HEV total antibody seroprevalence (29.3%) in age group <1 year could be explained partially by the presence of maternal antibodies in the tested samples. The seroprevalence of HEV antibodies did not disappear completely in any age group and remains higher in children, adolescents and young adults than in similar age groups in other studies [26]. The observed 33% average HEV total antibody seropositivity of the overall population and the 40–50% seropositivity in the population over age of 50 in South Transdanubia could be considered as very high values compared to the international data [26, 29]. Based on these observations the investigated regions and therefore Hungary could belong to countries with high HEV seroprevalence such as Poland, Netherlands and France [17, 24, 25]. According to an international study [29], comparing European countries, Hungary estimated as low HEV seroprevalence. However, our study in concordance with the study from the Southern Great Plain region, Southeast Hungary [30] – two of the seven regions in Hungary with available HEV seroprevalence data – debates this.

The average HEV IgM seropositivity was found to be 9.6% in the investigated population and growing with age. The HEV IgM seropositivity sharply increased near to 10% in age group 36–40 years, and consistently above 10% from 50 years of age reaching the peak of 13.9% in age group 81–85 years. This finding could be a result of more testing because of symptomatic acute HEV infection may manifest more frequently in older population [3, 13] leading to better diagnosis in these groups than others. In addition, the higher total HEV antibody prevalence among older age groups together with IgM antibody prevalence also suggest, that majority of acute infection actually occur in elderlies. On the other hand, HEV IgM positivity shows a decreasing trend in the last five years almost halved by 2022 compared to 2017 including the years of the SARS-CoV-2 pandemic. We should notice, that our results about HEV total antibodies were similar as in Southeast Hungary [30] but we found nearly twofold (9.6% versus 5.1%) IgM seropositivity. This can be explained by different study designs (only symptomatic acute hepatitis versus all cases of HEV-positive tests). The high total antibody seroprevalence of HEV including the high HEV IgM seroprevalence in the population in South Transdanubia means a common circulation and endemic infection of HEV.

Seroprevalence of HEV total antibody in the study area shows increasing trend while HEV IgM shows a slowly decreasing trend following a peak in 2015 during the study period. Increasing HEV total antibody prevalence can be related to the combination of wider recognition of HEV infections among clinicians, the increasing and specific testing requests and improved laboratory capacity of HEV [11, 30]. In addition, previous studies confirmed the high RT-PCR positivity of genotype 3 HEV strains in domestic pigs (30.8%–39%), and wild animals such as roe deer (34.4%) and wild boar (12.2%) in Hungary [31, 34]. These domestic and wild animals and the Hungarian pork-related traditions (e.g. backyard pig farming, homemade pork butchering) and (e.g. pork based) dietary habits could be the main, food-borne source of the genotype 3, subgenotypes 3 a/c/e/f/i human HEV infections in Hungary [11, 30, 31]. While the frequent HEV infections among pigs and other frequently consumed animals can explain the higher seroprevalence among humans, further studies are needed to investigate (confirm or exclude) the full spectrum of causes of the high HEV seroprevalence and transmission modes (e.g. risk of blood transfusion) in the country.

This study has some limitations: The study represents only a regional situation of HEV seroepidemiology and not covered the whole country which probably differs from region to region. Dia.Pro ELISA kit used in this study might be less sensitive compared to other ELISAs [15]. While it could detect antibodies against HEV genotypes 1–4 of species *Paslahepevirus balayani* the whole spectrum of HEV variants (genotypes, subgenotypes and serotypes) covered by the kit is unknown [https://www.diapro.it/products/hev-ab-version-ultra-elisa/, 32]. False negative results and – in consequence - a possible higher HEV seropositivity are just as possible [15] as false positive ELISA results, the latter are not investigated in all cases by further confirmatory tests (see strengths below).

This study also has some strengths: High number of persons ($N > 6{,}500$) were tested and analysed who were in contact with the healthcare system without exclusions on symptoms, underlying conditions or age which can better represent the general population and the disease spectrum (asymptomatic infection, acute hepatitis, chronic hepatitis, extrahepatic infection etc.) of HEV. This seroepidemiological study partially covered the molecular epidemiological (confirmatory) study conducted on the same cases and specimens from 2014 to 2017 [11]. This study fills a gap about HEV seroprevalence in a barely studied European area in Central Europe that put South Transdanubia into the high HEV seroprevalence area.

During the completion of the study we recognized that there is no easy-to-use, simple and informative international classification scheme for the endemicity levels of HEV seroprevalence. Horn et al. [29] categorised HEV seroprevalence as low (<5%), intermediate (5–10%) and high (>10%). Capai et al. [26] established simple three categories: high, intermediate and low risk for industrialized countries. Other studies made free ranges of HEV seroprevalence for comparison of countries without exact definitions [15, 16]. In comparison, hepatitis A virus (HAV) is well classified based on IgG seroprevalence in different age groups. Countries have been classified as high, intermediate, and low

Table 1. Proposed classification scheme for the endemicity levels for HEV seroprevalence in different populations. Countries/regions/populations have been classified as high, intermediate, and low HEV endemicity, defined as the population HEV antibody immunity level in percentage (%) by two age groups (<30 years and >60 years)

	HEV endemicity level based on the HEV antibody positivity in percentage (%)		
Age of years	High	Intermediate	Low
<30	≥10%	5–10%	<5%
>60	≥40%	25–40%	<25%

HAV endemicity, defined as ≥90% of the population being immune by age of 10 years, ≥50% by the age of 15 years, and ≥50% by the age of 30 years, respectively [35]. Similar age-related classification scheme of HEV is considerable to better comparing the HEV seroprevalence in different geographical locations. Taking into account the worldwide HEV seroprevalence in children, adults and the elderly, we recommend the following three categories: Countries/regions have been classified as high, intermediate, and low HEV endemicity, defined as ≥10% or ≥40% of the population immune by ages of <30 or >60 years, 5–10% or 25–40% by the ages of <30 or >60 years, and <5% or <25% by the age of <30 or >60 years (Table 1.), respectively. However, further comprehensive age cohorts in different geographic locations can refine the HEV seroepidemiological categories.

In summary, according to our 13-year-long study high average and age-related seroprevalence of HEV infection was detected increasing with age. South Transdanubia in Hungary has one of the highest HEV seroprevalence rates in Europe.

Conflict of interest: Authors declare that they have no conflict of interest.

ACKNOWLEDGEMENTS

The authors would like to thank the virology laboratory workers (Gertrúd Domonkos, Zsoltné Garamvölgyi, Éva Lovas and Csilla Wéber) for accurately conducting HEV serological tests related to this study. The study was supported by a grant from National Research, Development and Innovation Office (NKFI, FK134311).

REFERENCES

1. Purdy MA, Drexler JF, Xiang JM, Norder H, Okamoto H, Wim H, et al. ICTV virus taxonomy profile: *Hepeviridae*. J Gen Virol 2022; 103(9): 001778.
2. Balayan MS, Andjaparidze AG, Savin SS, Ketiladze ES, Braginsky DM, Suvinov AP, et al. Evidence for a virus in Non-A, Non-B hepatitis transmitted via the fecal-oral route. Intervirology 1983; 20(1): 23–31.
3. Khuroo MS, Khuroo MS. Hepatitis E: an emerging global disease - from discovery towards control and cure. J Viral Hepat 2016; 23(2): 68–79.
4. Woo PC, Lau SK, Teng JL, Tsang AK, Joseph M, Wong EY, et al. New hepatitis E virus genotype in camels, the Middle East. Emerg Infect Dis 2014; 20(6): 1044–8.
5. Woo PC, Lau SK, Teng JL, Cao KY, Wernery U, Schountz T, et al. New hepatitis E virus genotype in bactrian camels, Xinjiang, China, 2013. Emerg Infect Dis 2016; 22(12): 2219–21.
6. Sridhar S, Yip CCY, Wu S, Chew NFS, Leung KH, Chan JFW, et al. Transmission of rat hepatitis E virus infection to humans in Hong Kong: a clinical and epidemiological analysis. Hepatology 2021; 73(1): 10–22.
7. Reuter G, Boros Á, Pankovics P. Review of hepatitis E virus in rats: evident risk of species *Orthohepevirus C* to human zoonotic infection and disease. Viruses 2020; 12(10): 1148.
8. Hewitt PE, Ijaz S, Brailsford SR, Brett R, Dicks S, Haywood B, et al. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet 2014; 384(9956): 1766–73.
9. Khuroo MS, Kamili S, Khuroo MS. Clinical course and duration of viremia in vertically transmitted hepatitis E virus (HEV) infection in babies born to HEV-infected mothers. J Viral Hepat 2009; 16(7): 519–23.
10. Kamar N, Selves J, Mansuy JM, Ouezzani L, Péron JM, Guitard J, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. N Engl J Med 2008; 358(8): 811–7.
11. Pankovics P, Némethy O, Boros Á, Pár G, Szakály P, Reuter G. Four-year long (2014–2017) clinical and laboratory surveillance of hepatitis E virus infections using combined antibody, molecular, antigen and avidity detection methods: increasing incidence and chronic HEV case in Hungary. J Clin Virol 2020; 124: 104284.
12. Pischke S, Hartl J, Pas SD, Lohse AW, Jacobs BC, Van der Eijk AA. Hepatitis E virus: infection beyond the liver? J Hepatol 2017; 66(5): 1082–95.
13. Aslan AT, Balaban HY. Hepatitis E virus: epidemiology, diagnosis, clinical manifestations, and treatment. World J Gastroenterol 2020; 26(37): 5543–60.
14. Fousekis FS, Mitselos IV, Christodolou JK. Extrahepatic manifestations of hepatitis E virus: an overview. Clin Mol Hepatol 2020; 26(1): 16–23.
15. Hartl J, Otto B, Madden RG, Webb G, Woolson KL, Kriston L, et al. Hepatitis E seroprevalence in Europe: a meta-analysis. Viruses 2016; 8(8): 211.
16. Wilhelm B, Waddell L, Greig J, Young I. Systematic review and meta-analysis of the seroprevalence of hepatitis E virus in the general population across non-endemic countries. PLoS One 2019; 14(6): e0216826.
17. Grabarczyk P, Sulkowska E, Gdowska J, Kopacz A, Liszewski G, Kubicka-Russel D, et al. Molecular and serological infection marker screening in blood donors indicates high endemicity of hepatitis E virus in Poland. Transfusion 2018; 58(5): 1245–53.
18. Grigas J, Montoya M, Simkute E, Buitkus M, Zagrabskaire R, Pautienius A, et al. Molecular characterization and seroprevalence of hepatitis E virus in inflammatory bowel disease patients and solid organ transplant recipients. Viruses 2021; 13(4): 670.

19. Dalekos GN, Zervou E, Elisaf M, Germanos N, Galanakis E, Bourantas K, et al. Antibodies to hepatitis E virus among several populations in Greece: increased prevalence in an hemodialysis unit. Transfusion 1998; 38(6): 589–95.
20. Bruni R, Villano U, Equestre M, Chionne P, Madonna E, Trandeva-Bankova D, et al. Hepatitis E virus genotypes and subgenotypes causing acute hepatitis, Bulgaria, 2013–2015. PLoS One 2018; 13: e0198045.
21. Adhami JE, Angoni R. Hepatitis E virus infection in Albania. Sante 2001; 11(1): 13–5.
22. Nemecek V, Butovicova P, Maly M, Dite P, Vertatova M, Vodickova I, et al. The prevalence of antibodies against hepatitis E virus in the Czech Republic: serological survey. Epidemiol Mikrobiol Imunol 2017; 66(1): 3–7 (Czech).
23. Mrzljak A, Dinjar-Kujundzic P, Jemersic L, Prpic J, Barbic L, Savic V, et al. Epidemiology of hepatitis E in South-East Europe in the "One health" concept. World J Gastroenterol 2019; 25(25): 3168–82.
24. Mansuy JM, Gallian P, Dimeglio C, Saune K, Arnaud C, Pelletier B, et al. A nationwide survey of hepatitis e viral infection in French blood donors. Hepatology 2016; 63(4): 1145–54.
25. Hogema BM, Molier M, Slot E, Zaaijer HL. Past and present of hepatitis E in The Netherlands. Transfusion 2014; 54(12): 3092–6.
26. Capai L, Falchi A, Charrel R. Meta-analysis of human IgG anti-HEV seroprevalence in industrialized countries and a review of literature. Viruses 2019; 11(1): 84.
27. Faber M, Willrich N, Schemmerer M, Rauh C, Kuhnert R, Stark K, et al. Hepatitis E virus seroprevalence, seroincidence and seroreversion in the German adult population. J Viral Hepat 2018; 25(6): 752–8.
28. Haagsman A, Reuter G, Duizer E, Nagy Gy, Herremans T, Koopmans M, et al. Seroepidemiology of hepatitis E virus in patients with non-A, non-B, non-C hepatitis in Hungary. J Med Virol 2007; 79(7): 927–30.
29. Horn J, Hoodgarzadeh M, Klett-Tammen CJ, Mikolajczyk RT, Krause G, Ott JJ. Epidemiologic estimates of hepatitis E virus infection in European countries. J Infect 2018; 77(6): 544–52.
30. Ulbert ÁB, Bukva M, Magyari A, Túri Z, Hajdú E, Burián K, et al. Characteristics of hepatitis E viral infections in Hungary. J Clin Virol 2022; 155: 105250.
31. Reuter G, Fodor D, Forgách P, Kátai A, Szucs G. Characterization and zoonotic potential of endemic hepatitis E virus (HEV) strains in humans and animals in Hungary. J Clin Virol 2009; 44(4): 277–81.
32. Pas SD, Streefkerk RH, Pronk M, de Man RA, Beersma MF, Osterhaus AD, et al. Diagnostic performance of selected commercial HEV IgM and IgG ELISAs for immunocompromised and immunocompetent patients. J Clin Virol 2013; 58(4): 629–34.
33. Zhao Ch, Wang Y. Laboratory diagnosis of HEV infection Adv Exp Med Biol 2016; 948: 191–209.
34. Forgách P, Nowotny N, Erdélyi K, Boncz A, Zentai J, Szucs Gy, et al. Detection of hepatitis E virus in samples of animal origin collected in Hungary. Vet Microbiol 2010; 143(2–4): 106–16.
35. Itani T, Jacobsen KH, Nguyen T, Wiktor SZ. A new method for imputing country-level estimates of hepatitis A virus endemicity levels in the Eastern Mediterranean region. Vaccine 2014; 32(46): 6067–74.