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## SEROPREVALENCE FOR HEPATITIS E VIRUS (HEV) INFECTION AMONG VOLUNTEER BLOOD DONORS OF THE REGIONAL BLOOD BANK OF LONDRINA, STATE OF PARANÁ, BRAZIL

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### SUMMARY

A cross-sectional study was carried out among 996 volunteer blood donors enrolled from May 1999 to December 1999 to determine the seroprevalence of hepatitis E virus (HEV) infection among volunteer blood donors of the Regional Blood Bank of Londrina, State of Paraná, Brazil, and to evaluate whether the rate of seroprevalence of IgG anti-HEV antibodies is associated with sociodemographic variables and with seropositivity for hepatitis A virus (HAV) infection. All participants answered the questionnaire regarding the sociodemographic characteristics. Serum samples were tested for IgG antibodies to HEV (anti-HEV) by an enzyme linked immunoassay (ELISA). All serum samples positive for anti-HEV IgG and 237 serum samples negative for anti-HEV were also assayed for IgG anti-HAV antibodies by ELISA. Anti-HEV IgG was confirmed in 23/996 samples, resulting in a seroprevalence of 2.3% for HEV infection, similar to previous results obtained in developed countries. No significant association was found between the presence of anti-HEV IgG antibodies and the sociodemographic variables including gender, age, educational level, rural or urban areas, source of water, and sewer system ( $p > 0.05$ ). Also, no association with seropositivity for anti-HAV IgG antibodies was observed ( $p > 0.05$ ). Although this study revealed a low seroprevalence of HEV infection in the population evaluated, the results showed that this virus is circulating among the population from Londrina, South Brazil, and point out the need of further studies to define the clinical and epidemiological importance of HEV infection and to identify additional risk factors involved in the epidemiology and pathogenesis of this infection in this population.

**KEYWORDS:** Hepatitis E virus; Hepatitis A virus; Epidemiology; Seropositivity; Blood donors.

### INTRODUCTION

Epidemic jaundice has been recognized from the time of Hippocrates over 2000 years ago. However, it was only between 1965 and 1990 that the various human hepatitis viruses, their syndromes and their role in hepatic oncogenesis were determined, leading to the expansion of their nomenclature from A to E. It has been estimated that between four and 19% of patients with sporadic, community-acquired acute hepatitis have no detectable viral agent<sup>22</sup>.

Hepatitis E virus (HEV) is considered a major etiological agent of enterically transmitted viral hepatitis in several developing countries<sup>25</sup>. The infection has been shown to occur in both epidemic and sporadic forms and to be primarily associated with ingestion of fecally contaminated drinking water<sup>31</sup>.

HEV infection is quite common in some world areas such as India, Africa and Southeast Asia, where it can represent the main cause of acute hepatitis<sup>27</sup>. In India, this infection is the main cause of sporadic cases of non-A, non-B and non-C hepatitis<sup>18</sup>. Outbreaks of HEV infection have been reported from Central Asia, Southeast Asia, the

Middle East, Northern Africa, Sub-Saharan Africa, and Mexico<sup>31</sup>. In the Xinjiang area of China, 119,280 cases of HEV infection were notified in the epidemic of 1986 to 1988<sup>19</sup>.

In addition, epidemiological investigation in non-endemic areas has shown a low, but constant presence of anti-HEV antibodies (about 1.2%) in normal human populations<sup>27,31</sup>. In Brazil, outbreaks of hepatitis E have never been reported, although some authors have demonstrated the evidence of anti-HEV antibodies in some population groups<sup>12,24,27,31</sup>. The seroprevalence of anti-HEV IgG among normal Brazilian populations was reviewed<sup>8</sup> and reported a positivity of 6.1% among gold miners, 3.3% in the general population, 2.0-7.5% among blood donors, 1.0% among pregnant women, and 4.5% in children, with no difference among regions. The review also showed that the prevalence of anti-HEV varies widely in populations considered to be at risk. Among patients with acute non-A, non-B, non-C hepatitis, the prevalence was 2.1% in the Southeast, 29% in the Northeast, 10.6% among relative of acute non-A, non-B, non-C hepatitis patients in the Amazon basin, 12% among acute sporadic non-A non-B hepatitis patients in the Northeast, 25 to 38% among patients co-infected with acute hepatitis A in the Northeast, 14 to 18% among prostitutes and

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women considered at risk for human immunodeficiency virus type 1 (HIV-1) in the Southeast, and 12% among intravenous drug users in the Southeast<sup>8</sup>. In the State of Paraná, South Brazil, no studies of the HEV infection have been reported.

HEV infection usually presents an acute and benign clinical course and does not provoke chronic infection. However, among all the responsible hepatitis viruses, HEV is associated with the largest number of fulminant hepatitis cases (3.0%) in the general population, and up to 20% in pregnant women<sup>7</sup>.

Hepatitis A virus (HAV) is an extremely stable virus which is spread by the fecal-oral route, either directly from person to person or by contaminated food or water, with the prevalence being closely correlated with the degree of environmental sanitation and the prevailing socioeconomic and hygienic conditions<sup>33</sup>. Considering that the HEV and HAV infections share the same transmission routes, it is possible that the local seroprevalence of both infections may also be similar. However, few studies have examined the epidemiology of the association between HEV and HAV infections.

The aim of this study was to determine the seroprevalence of HEV infection among volunteer blood donors of the Regional Blood Bank of Londrina, State of Paraná, Brazil, and to evaluate whether the rate of seroprevalence of anti-HEV IgG antibodies is associated with the sociodemographic characteristics and the seropositivity for HAV infection. These data can contribute to define the epidemiological importance of the HEV infection in this district and to elaborate rational clinical and epidemiological strategies in the investigation of cases classified as non-A, non-B, and non-C hepatitis.

## MATERIALS AND METHODS

A cross-sectional study was carried out to determine the seroprevalence of HEV infection among volunteer blood donors of the Blood Bank of the University Hospital, Londrina, State of Paraná, South Brazil. The protocol was approved by the institutional Research Ethics Committee of Londrina State University. The individuals were invited to participate and informed in detail about the research, and voluntary written consent was obtained from the subjects enrolled.

*Study population:* The convenience sample consisted of individuals consecutively recruited during the period from May 1999 to December 1999. For the population of 250,000 adults aged 18 to 60 years living in district of Londrina, with an estimated prevalence of seropositivity for HEV infection of 0.025 (with an error margin of 0.01), the calculated sample size was of 933 individuals, with a confidence interval (CI) of 95%. In order to decrease the margin of error, 996 blood donors were evaluated. A questionnaire was applied to the participants to obtain information about sociodemographic data including gender, age, educational level, place of residence (rural or urban area), source of water, and the sanitary conditions of their homes (sewer or pit), in order to evaluate possible risk factors for HEV infection. On the basis of the standard clinical screening of the blood donors, all individuals enrolled in this study were also questioned about a past clinical history of symptomatic hepatitis.

The results obtained for the blood donors with positive anti-HEV

IgG were compared with those obtained for blood donors with negative anti-HEV IgG.

*Serological assays for anti-HEV IgG and anti-HAV IgG:* All serum samples were stored at -20 °C until used. Serum samples were tested for specific anti-HEV IgG antibodies by enzyme linked immunosorbent assay (ELISA), according to the method described elsewhere<sup>32</sup> using commercially available reagents (HEV EIA, ABBOTT Laboratories, IL, USA). According to the manufacturer, this assay presents 98.5% sensitivity and 99.5% specificity. The results were scored as positive or negative according to standard procedures recommended by the manufacturers. The individuals were considered to be seropositive when they showed two repeated positive reactions. Positive and negative controls were included in all the ELISA microplates assayed. All serum samples from blood donors positive for anti-HEV IgG and 237 samples from blood donors negative for anti-HEV IgG were also assayed for anti-HAV IgG antibodies by ELISA, as described elsewhere<sup>11</sup>, using commercially available products (ABBOTT Laboratories, HAV EIA). According to the manufacturer, the assay presents 99.0% sensitivity and 99.5% specificity.

*Statistical analysis:* A database was set up using the EPI INFO software version 6.04d<sup>10</sup>. Descriptive statistical analysis was used to calculate the mean, median, standard deviation (SD), and percentage of the sociodemographic variables of the blood donors, and 95% confidence intervals (95% CI) of the proportion of seropositivity for anti-HEV IgG and anti-HAV IgG antibodies and the variables evaluated. The statistical analysis was performed using the Chi-square ( $\chi^2$ ) and Exact Fisher tests. The level of significance adopted for all tests was 5% ( $p < 0.05$ ).

## RESULTS

The age of the volunteer blood donors ranged from 18 to 60 years (mean: 29.9  $\pm$  9.8 years; median: 26.9 years) and 605 (60.7%) were males. Table 1 shows that 23 blood donors showed positive anti-HEV IgG antibodies, corresponding to an overall seroprevalence rate of 2.3% (95% CI = 1.5 - 3.5). The sociodemographic characteristics of the blood donors enrolled according to seropositivity for anti-HEV IgG are shown in Table 2. No association was observed ( $p > 0.05$ ) between seropositivity and the variables evaluated including gender, age ( $\leq 35$  years old and  $> 35$  years old), educational level (incomplete elementary school and  $\geq$  elementary school), origin (urban or rural area), source of water (public or other) and sewer (public service or pit). Most subjects lived under adequate sanitary housing conditions in view of the high

**Table 1**

Distribution of the results of anti-hepatitis virus E antibodies (anti-HEV) IgG in serum samples from volunteer blood donors of the Regional Blood Bank of Londrina, Paraná, Brazil

ANTI-HEV IgG *	Number	%	CI† (95%)
Positive	23	2.3	1.5 – 3.5
Negative	973	97.7	96.5 – 98.5
Total	996	100.0	

\* Anti-hepatitis virus E IgG antibodies evaluated by enzyme immunoassay (ELISA); †: confidence interval.

rate of presence of a sewage system (73.2%) and public water (98.6%). All the 23 (100.0%) subjects with positive results for anti-HEV IgG and 959 (98.6%) with negative results had public piped water available. Therefore, there was no statistically significant difference in anti-HEV prevalence when the presence of a sewage system and the source of water were taken into consideration.

The results obtained from the 23 blood donors with positive anti-HEV IgG were compared with those obtained from 237 blood donors with negative anti-HEV IgG. Among the 260 serum samples assayed for anti-HAV IgG, 211 were positive for anti-HAV IgG, corresponding to a seropositivity of 81.1%. Among the positive samples for anti-HEV IgG, 19 (82.6%) were also positive for anti-HAV IgG. Regarding the samples that were negative for anti-HEV IgG, 192 (81.0%) were also positive for anti-HAV IgG. No association between the two rates of seropositivity (anti-HEV and anti-HAV) was observed ( $p = 1,000$ ), as shown in Table 3.

## DISCUSSION

Viral hepatitis is considered to be a worldwide public health problem, representing a significant cause of morbidity and mortality. On most occasions, the etiologic agent of the infection is not defined, generating problems in the handling of those cases and in the decision about the most adequate prophylactic measures.

The areas of the world with a high incidence of HEV infection are mainly developing countries, mainly in Asia and in Africa. In Brazil, different patterns of hepatitis virus distribution are found throughout the country. Outbreaks of HEV infection have not yet been described. However, the possibility of the occurrence of such outbreaks exists since in our country there are great social differences and sanitary conditions are quite precarious in many areas. Besides, the disease surveillance is deficient in the country as a whole, with the consequent serious problem of undernotification of cases.

**Table 2**

Sociodemographic characteristics of 996 volunteer blood donors of the Regional Blood Bank of Londrina, Paraná, Brazil, distributed according to seropositivity for anti-hepatitis virus E (anti-HEV IgG) antibodies

Characteristic	Anti-HEV positive n (%)	Anti-HEV negative n (%)	Total n (%)	p value
<b>Gender</b>				
Male	15 (65.2)	590 (60.6)	605 (60.7)	0.8190* NS
Female	8 (34.8)	383 (39.4)	391 (39.3)	
<b>Age (years)</b>				
≤ 35	17 (73.9)	692 (71.1)	709 (71.2)	0.9526* NS
> 35	6 (26.1)	281 (28.9)	287 (28.8)	
<b>Place of residence</b>				
Rural area	2 (8.7)	58 (6.0)	60 (6.0)	0.6442† NS
Urban area	21 (91.3)	915 (94.0)	936 (94.0)	
<b>Education</b>				
Elementary school	5 (21.7)	175 (18.0)	180 (18.1)	0.5886† NS
≥ Elementary school	18 (78.3)	798 (82.0)	816 (81.9)	
<b>Source of water</b>				
Public	23 (100.0)	959 (98.6)	982 (98.6)	1.000† NS
Other (mine, shaft)	0 (0.0)	14 (1.4)	14 (1.4)	
<b>Sanitary conditions</b>				
Sewer	14 (60.9)	715 (73.5)	729 (73.2)	0.2660* NS
Pit (closed and open)	9 (39.1)	258 (26.5)	267 (26.8)	

\* Chi-square test ( $\chi^2$ ); † Exact Fisher Test; n: number of samples; NS: not significant.

**Table 3**

Seropositivity for anti-hepatitis A virus (anti-HAV) IgG antibodies obtained for volunteer blood donors of the Regional Blood Center of Londrina, Paraná, Brazil, distributed according to the seropositivity for anti-hepatitis E virus (anti-HEV) IgG antibodies

Serologic result	Anti-HEV*Positive n (%)	Anti-HEV*Negative n (%)	Total n (%)	CI‡ (95%)
Anti-HAV† positive	19 (82.6)	192 (81.0)	211 (81.1)	75.75-85.61
Anti-HAV† negative	4 (17.4)	45 (19.0)	49 (18.8)	14.39-24.25
Total	23 (100.0)	237 (100.0)	260 (100.0)	

\*: Anti-hepatitis E virus IgG antibodies evaluated by enzyme immunoassay (ELISA); †: Anti-hepatitis A virus IgG antibodies evaluated by enzyme immunoassay (ELISA); Exact Fisher Test:  $p = 1.000$  (not significant); ‡CI: confidence interval.

According to the Municipal Health System, in the district of Londrina, State of Paraná, in the year of 1999, it was not possible to identify the etiologic agent in 6% of the total of cases of viral hepatitis and those cases were classified as non-A, non-B, and non-C hepatitis infections (personal communication). On this basis, it is possible that some of those cases might have been HEV infection.

The 2.3% seroprevalence of anti-HEV IgG obtained among volunteer blood donors residing in the district of Londrina enrolled in this study is similar to that reported in other recently reviewed Brazilian studies<sup>8</sup>. In the city of São Paulo, State of São Paulo, a previous investigation detected a seroprevalence of 1.68% for anti-HEV IgG antibodies in the general population<sup>12</sup>. In another study carried out in Campinas, State of São Paulo, the seroprevalence was 3.0% among blood donors from that municipal district<sup>13</sup>. In Salvador (State of Bahia), the seroprevalence of anti-HEV IgG antibodies among blood donors was 2.0%<sup>24</sup>. In Rio de Janeiro (State of Rio de Janeiro), a retrospective study conducted on selected populations revealed a 4.3% of prevalence of anti-HEV IgG among the different groups and among blood donors<sup>31</sup>. In a study carried out in riverine communities from the Western Region of the Brazilian Amazon Basin, the overall prevalence observed (4.0%) was considered to be low<sup>25</sup>.

As mentioned previously, the main route of transmission of HEV infection is the fecal-oral one, which is also the route of transmission of HAV infection, whose prevalence is associated with the quality of the individuals' life including housing, drinking water, and sewer service<sup>5</sup>. HAV infection is highly prevalent in Brazil, as demonstrated in a study carried out in the city of São Paulo, State of São Paulo, on individuals ranging in age from 16 to 30 years, in which the prevalence of anti-HAV was 91.9% among individuals of middle socioeconomic condition and 100% among those of low socioeconomic condition<sup>23</sup>.

Regarding the similarity of the transmission mechanisms, there is a trend to evaluate the association between these two infections (HAV and HEV infections). A study carried out in Israel on hemophiliac patients detected a strong association between the viruses<sup>6</sup>. In Brazil, the same association was found in a study carried out in Salvador, State of Bahia, and the authors concluded that similarities exist between the epidemiology of the two infections, and that individuals exposed to HAV have a higher probability to be also exposed to HEV<sup>24</sup>.

In the present study, no association was found between these two infections, a result similar to that reported in a study that evaluated the prevalence of these viruses in the general population of the city of São Paulo, State of São Paulo<sup>12</sup>. Also, no association was found in the urban population of Burundi, Africa, and the authors concluded that, although the two viruses are transmitted by the fecal-oral route, the epidemic models of the two infections are different<sup>3</sup>. HEV infection has a few distinct epidemiological features that differentiate it from HAV infection. Unlike HAV infection, HEV infection appears to affect mainly young adults, which is unusual for a virus transmitted via the fecal-oral route. Also unusual is that secondary cases of HEV infection are much less frequent than HAV infection, and finally a major difference is the high mortality rate observed among pregnant women infected with HEV<sup>31</sup>.

In California (USA), a group of candidates to blood donors was

evaluated and the results did not show an association between those infections and the authors concluded that, possibly, different patterns of transmission of the two viruses may exist and the risk factors for HEV infection in the sporadic cases that occur in non-endemic areas have not been defined<sup>20</sup>.

Similarly, in this study, since the association of the type of water consumed, including the use of untreated water, with the seroprevalence of IgG anti-HEV antibodies was not demonstrated, other possible transmission routes should be suggested.

HEV infection, unlike HAV infection, presents a very low rate of inter-human transmission, as demonstrated by several authors<sup>1,3,15,26,28,30</sup>. According to these authors, this route of transmission of HEV infection should not be the only one responsible for the sporadic cases that occur in non-endemic areas. Other transmission mechanisms, not yet clarified, may play an important role in the epidemiology of HEV infection in these areas.

According to some authors, HEV infection could be classified as a zoonosis because some animals may act as reservoirs of the virus, a fact justifying the circulation of the virus in non-endemic areas<sup>4,9,14,16,17,26</sup>. Occasionally, HEV may infect humans through direct contact with domestic or farm animals or with contaminated water supplies<sup>25</sup>.

The analysis of the genome of the HEV isolated from swine and from individuals with HEV infection suggests that these animals can serve as a reservoir of the virus<sup>21</sup>. The existence of cross-infection with HEV between humans and swine is a possibility that cannot be ruled out<sup>36</sup>. The high prevalence of HEV antibodies among apparently healthy humans (20.0%) and farm pigs (72.0%) in Bali, Indonesia, whose population is mostly Hindu and has a habit of consuming pork, indicates that HEV infection may occur as a zoonosis<sup>35</sup>.

In a study, related by authors as the first report that showed evidences of HEV circulation in Brazilian animal species and pig handlers, was detected the seroprevalences of HEV infection in cows (1.42%), dogs (6.97%), chickens (20%), swines (24.3%) and rodents (50.0%), as well in pig handlers (6.3%)<sup>34</sup>. The recognition of swine HEV infection in pigs in many countries of the world led these authors to investigate a larger sample of pigs of same Brazilian region that demonstrated a total seroprevalence of 63.6%. However, as the seroprevalence reached 97.3% of animals older than 25 weeks, the authors concluded that swine HEV infection seems to be almost universal within this Brazilian pig population<sup>34</sup>.

The true participation of the animals in the transmission of HEV is still unclear, with many points that still require elucidation. Similarly, the true meaning of the seroprevalence of the anti-HEV IgG antibodies detected in the present study it is still to be defined.

Taken together, although showing a low prevalence of HEV infection among blood donors, the results obtained in the present study demonstrate that HEV circulates in the district of Londrina. However, further studies are necessary to define the clinical and epidemiologic importance of the HEV infection in this area and to identify additional risk factors involved in the epidemiology and pathogenesis of HEV infection. The results obtained open the possibility of other routes of

spreading different from that previously recognized ones such as fecal-oral contamination, mainly the possible participation of animals in the transmission of HEV.

## RESUMO

### Soroprevalência da infecção pelo vírus da hepatite E (VHE) em candidatos a doadores de sangue voluntários do Hemocentro Regional de Londrina, Londrina, Estado do Paraná, Brasil

Os objetivos do estudo foram determinar a soroprevalência da infecção pelo vírus da hepatite E (VHE) em candidatos a doadores de sangue voluntários do Hemocentro Regional de Londrina, Paraná, e avaliar se essa soroprevalência está associada com variáveis socio-demográficas e com o índice de soropositividade para hepatite por vírus A (VHA). Foi realizado estudo transversal para determinar a taxa de soroprevalência da infecção pelo VHE em 996 candidatos a doadores de sangue. Todos os participantes responderam um questionário sobre características sociodemográficas. A pesquisa de anticorpos específicos IgG anti-VHE foi realizada por método de enzima-imunoensaio (ELISA). Todas as amostras soropositivas para IgG anti-VHE e 237 amostras soronegativas para IgG anti-VHE foram submetidas também à pesquisa de IgG anti-VHA por ELISA. Entre as 996 amostras de soro analisadas, anticorpos IgG anti-VHE foram detectados em 23 amostras, resultando em uma soroprevalência de 2,3% (IC 95%: 1,5 - 3,5), semelhante aos resultados de estudos realizados em países desenvolvidos. Não houve associação entre o índice de soropositividade de IgG anti-VHE e as variáveis sociodemográficas (sexo, idade, escolaridade, procedência, fonte de água e origem dos dejetos); também não se detectou associação entre soropositividade para IgG anti-VHE com soropositividade para IgG anti-VHA. Os resultados obtidos sugerem que, embora tenha se observado uma baixa prevalência da infecção pelo VHE na população analisada, verificou-se que existe circulação do VHE no município de Londrina e que estudos posteriores são necessários para definir a importância clínica e epidemiológica da infecção pelo VHE nesse município bem como identificar outros possíveis fatores de risco envolvidos na epidemiologia da infecção pelo VHE.

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