Short Communication

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Hepatitis E virus infection in Brazil: results of laboratory-based surveillance from 1998 to 2013

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ABSTRACT

Introduction: Data on hepatitis E virus (HEV) in Brazil are limited. We analyzed 15 years of HEV surveillance data in a major clinical laboratory in São Paulo, Brazil. **Methods:** The seroprevalence of HEV of 2,271 patients subjected to anti-HEV tests from 1998 to 2013 were analyzed. **Results:** HEV seroprevalence was 2.1%, and the anti-HEV IgM positivity rate was 4.9%. Six hepatitis E patients were identified. **Conclusions:** HEV seroprevalence and detection rates appear to have increased in recent years. Hepatitis E should be investigated further and included in the differential diagnosis of hepatitis in Brazil.

Keywords: Hepatitis E virus. Epidemiology. Seroprevalence.

Hepatitis E occurs as both large epidemics and sporadic cases in endemic areas, including genotypes 1, 2, and 4 in Asia and Africa, Mexico and Africa, and Asia, respectively. Meanwhile, sporadic cases of genotype 3 occur in Europe, Japan, and the Americas. Genotypes 1 and 2 are restricted to primates and are transmitted predominantly via the fecal-oral route. Genotypes 3 and 4 infect numerous mammalian species and can be transmitted via the ingestion of raw or undercooked meat from infected animals[1].

Data on hepatitis E virus (HEV) seroprevalence in Brazil are limited. Although this region is classified as moderately endemic for HEV, most available studies are outdated and cannot be compared properly because of their small sample sizes and/or diverse methodology[2]. Moreover, HEV is not routinely investigated in Brazil, even in cases of unexplained liver enzyme elevation or acute hepatitis, and only a few laboratories perform anti-HEV tests. Therefore, the occurrence and characteristics of hepatitis E in Brazil are poorly understood. Thus, the present study reports 15 years of HEV surveillance data, including seroprevalence, from a major clinical laboratory in Brazil.

We retrospectively analyzed all laboratory records of anti-HEV tests performed between January 1998 and December 2013 in a major clinical laboratory in São Paulo, Brazil that covers an area extending from Southern to Northeastern Brazil. The samples originated from patients clinically suspected of being HEV carriers at clinics or hospitals. The study protocol was approved by the appropriate institutional ethics committee (approval numbers: 162/09 and 86730/14).

All serum samples were shipped to the Quest Diagnostics Nichols Institute (San Juan Capistrano, CA, USA) where anti-HEV immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies were tested by enzyme-linked immunosorbent assay (ELISA). Information on age, sex, origin, comorbidities, transplants, and hepatic enzyme and bilirubin test results was collected from medical records.

Descriptive statistics were used to analyze demographic, clinical, and laboratory characteristics as well as anti-HEV seroprevalence. Continuous variables are presented as percentages, medians and ranges, and means and standard deviations (SDs) where appropriate. Categorical variables were analyzed by Pearson's χ^2 test. Linear regression analysis was used to evaluate the trends of anti-HEV positivity with respect to year and age. All data were analyzed by Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS Inc., Chicago, IL, USA). All reported values are two-tailed, and the level of significance was set at $p < 0.05$.

The epidemiological and laboratory data with respect to anti-HEV IgG status are shown in **Table 1**. Between January 1998 and December 2013, 2,271 patients underwent anti-HEV IgG tests. The median age of patients was 37 years (range: 0-94 years old, mean ± SD: 37.8 ± 16.0 years). Moreover, 50.5% were female.

The overall anti-HEV IgG positivity rate was 2.1% (47/2,271), ranging from 0% (0/183) to 8.6% (12/139) annually. Anti-HEV IgG positivity exhibited a significant linear trend

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with year (p = 0.010). The highest frequencies were observed from 2011 to 2013: 5.9% (2/34), 8.6% (12/139), and 6.1% (9/148), respectively. HEV seropositivity was not linearly associated with age; however, it was significantly associated with age group, with the highest frequencies in persons older than 40 years (median age of 47 HEV seropositive patients: 46 years, range: 10-94 years; median age of seronegative patients: 36 years, range: 0-91 years; p < 0.0001). There were no differences in HEV seropositivity with respect to sex, hepatic enzymes, or bilirubin.

The anti-HEV IgM test became available in January 2006, and 552 tests were performed from 2006 to December 2013. The anti-HEV IgM positivity rate was 4.9% (27/552), ranging from 0% (0/47) to 8.8% (3/34) annually. IgM positivity exhibited a linear trend over time (p = 0.016); the highest frequencies were observed from 2011 to 2013: 8.8% (3/34), 5.8% (8/139), and 7.4% (11/148), respectively. Although the IgM positivity rate did not exhibit a linear trend with age, it was significantly associated with age group (p = 0.041); the highest IgM frequencies were observed in people aged 10-19 years (12.5%; 7/56) and 0-9 years (5.3%; 2/38) (median age of 27 HEV IgM-positive patients: 36 years, range: 1-59 years; median age of IgM-negative patients: 36 years, range: 0-94 years. Anti-HEV IgM positivity was not associated with sex, hepatic enzymes, or bilirubin.

Of the 47 anti-HEV IgG-positive patients, 28 (59.6%) were evaluated from 2006 to 2013 and therefore also have anti-HEV IgM results. Six (1.1%) patients exhibited both IgM and IgG positivity and were considered acute hepatitis E cases **(Table 2)**. Because of the retrospective nature of this study, we could only further investigate case no. 2, in which HEV ribonucleic acid (RNA) was detected (genotype 3b, Brazil h4, GenBank accession number: KF152884) with a viral load of 4.5 $\log_{10}$ copies/mL. Examination of viral RNA extracted from paraffin-embedded formalin-fixed liver tissue (RNeasy FFPE kit; Qiagen, Germany) from 3 years prior showed the presence of HEV sharing >99% homology with the sequence found in the serum sample from 2013, thus indicating chronic hepatitis E infection (KM502569). The patient was treated with ribavirin for 10 months, and her HEV RNA load became undetectable (<100 copies/L) in August 2013[3].

Studies conducted on blood donors in Brazil from 1997 to 2006 report the prevalence of anti-HEV IgG to be

TABLE 1 - Epidemiological and laboratory data of samples according to anti-HEV IgG status in Brazil (1998–2013).

Variable	Anti-HEV IgG positive			Anti-HEV IgG negative	
	n	%	p	n	%
Age group (years)					
0-19	3	1.1	0.008*	265	98.9
20-39	12	1.2		966	98.8
40-59	26	3.4		736	96.6
60-94	6	2.9		200	97.1
Sex					
female	20	1.7	0.273	1126	98.3
male	27	2.4		1097	97.6
AST					
elevated	4	1.7	0.877	229	98.3
normal	8	1.6		504	98.4
ALT					
elevated	8	2.1	0.441	378	97.9
normal	6	1.4		430	98.6
GGT					
elevated	4	1.7	0.714	227	98.3
normal	6	1.4		432	98.6
Bilirubin					
elevated	2	2.0	0.916	98	98.0
normal	7	2.2		315	97.8

HEV: hepatitis E virus; **IgG:** immunoglobulin G; **AST:** aspartate aminotransferase; **ALT:** alanine aminotransferase; **GGT:** gamma-glutamyl transpeptidase; Reference values: AST ≤ 31U/L in females and ≤ 37U/L in males; ALT ≤ 31U/L in females and ≤ 41U/L in males; GGT 8 to 41U/L in females and 12 to 73IU/L in males; Bilirubin 0.2 to 1.1mg/dL. *p < 0.05 with Pearson's χ^2 test.

TABLE 2 - Clinical and laboratory data of patients with hepatitis E in Brazil (1998-2013).

Case number	Year	Age (y)	Sex	Transplant (organ)	AST (U/L)	ALT (U/L)	Origin	Comorbidities
1	2007	45	Male	No	30	27	*	Chronic colitis
2	2012	13	Female	Liver	199	163	Hospital	ACR
3	2012	41	Male	No	NA	NA	Hospital	CHB
4	2013	52	Male	Liver	17	16	Hospital	None
5	2013	59	Female	No	NA	NA	*	†
6	2013	44	Female	No	23	41	Hospital	None

AST: aspartate aminotransferase; **ALT:** alanine aminotransferase; **ACR:** acute cellular rejection; **NA:** not available; **CHB:** chronic hepatitis B. *Samples sent from other laboratories for confirmation. †This patient had positive anti-HEV IgM and IgG results in October 2013 and again in February 2014.

2.0-4.3%[4]. A 2002 study on laboratory patients reports a 2.4% seroprevalence[5]. In the present study, the anti-HEV IgG positivity was ranged 0-3.6% from 1998 to 2006, reaching 8.6% in 2012.

Solid organ transplant recipients are more susceptible to hepatitis E infection and even chronic hepatitis E[6]. Our previous study of 192 renal transplant patients in São Paulo, Brazil identified 20 (10%) patients positive for HEV RNA and 28 (15%) positive for anti-HEV IgG antibodies[7]. The HEV strains were genotype 3; further investigation of 3 patients suggested chronic hepatitis E, although the retrospective study design precluded follow-up[8].

It should be noted that the present data did not come from an established systematic program of epidemiologic surveillance in Brazil. Therefore, the actual prevalence of hepatitis E may differ. Hence, future epidemiological studies must include the general population to accurately characterize HEV in Brazil.

In summary, the present study provides valuable insights into the detection and seroprevalence of hepatitis E in Brazil. HEV seroprevalence and detection rates appear to have increased in recent years. Cases have occurred in both immunocompetent and immunocompromised patients. Therefore, hepatitis E should be investigated further and included in the differential diagnosis of suspected hepatitis in Brazil.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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