Short Communication

Hepatitis A and E virus infections have different epidemiological patterns in Rwanda

Theogene Twagirumugabe[a,*], Fredy Saguti[c], Sylvain Habarurema[b], Jean Bosco Gahutu[a], Tomas Bergström[c], Heléne Norder[c]

[a] School of Medicine and Pharmacy, College of Medicine and Health Sciences, University of Rwanda, P.O. Box 3286 Kigali, Rwanda
[b] Department of Internal Medicine, University Teaching Hospital of Butare, P.O. Box 254 Butare, Rwanda
[c] Department of Microbiology & Clinical Virology, Institute of Biomedicine at Sahlgrenska Academy, University of Gothenburg, Guldhedsgatan 10A, 41346 Göteborg, Sweden

ARTICLE INFO

ABSTRACT

Objectives: To investigate the prevalence of anti-HAV and HEV markers in order to better understand spread of these two viruses among adults in Rwanda.
Methods: Samples from 1045 and 1133 blood donors, healthy adults and liver disease patients were analysed for anti-HAV IgG and HEV markers respectively.
Results: Anti-HAV was present in 96.9% (1013/1045), with proportions of immune persons increasing with age. HEV infection markers were detected in 11.9% (135/1133) without differences between the three categories. Seven persons had low levels of HEV RNA including four blood donors but none of the HEV strains could be sequenced. The highest prevalence of HEV markers was in farmers and persons from the Southern (17.3%) and Western regions (18.6%), which have the national highest density of pigs. This may indicate that pigs constitute an important source of HEV infection for humans in Rwanda.
Conclusion: HAV remains highly endemic in Rwanda, but there may now be a decline of exposure during childhood. HEV is also endemic in Rwanda, but has a moderate spread and may be transmitted by blood transfusion. Based on the geographical and occupational differences in HEV prevalence, a possible zoonotic transmission from pigs should be further explored.

Introduction

Hepatitis E virus is endemic worldwide. There are five genotypes infecting humans (HEV1-4, 7). HEV1 and HEV2 are enterically transmitted and predominate in resource-limited settings of Africa and Asia, causing outbreaks and sporadic self-limiting acute hepatitis but possibly becoming fatal in about 30% of pregnant women infected with HEV1 (Debing et al., 2016). Zoonotic transmission of HEV3 and HEV4 predominate in Europe and China from contaminated pork. HEV3 may cause chronic hepatitis in patients with immune deficiency (Kamar et al., 2008).

HEV3 infections have also been reported in South Africa (Madden et al., 2016) but may be present in other African countries.

Hepatitis A virus (HAV) is highly endemic in Sub-Saharan Africa, and most children get infected at an early age and acquire lifelong immunity. Hygiene and access to clean water may change this epidemiology (Jacobsen and Koopman, 2005).

We conducted this study to evaluate the prevalence of anti-HAV and HEV markers among adult Rwandans. Rwanda is in the East African region where HAV is highly endemic but has limited data on HEV.

Materials and methods

Samples were collected from 720 volunteer blood donors, 246 adult patients diagnosed with acute (jaundice or elevated ALT) or chronic liver disease, cirrhosis, or hepatocarcinoma, and 246 healthy adults. All were recruited from the five provinces of Rwanda (East, West, North, South and Kigali city). The Rwanda National Ethics Committee approved the study

* Corresponding author at: School of Medicine and Pharmacy, University of Rwanda, P.O. Box 3286 Kigali, Rwanda.
E-mail addresses: twagirumugabe@gmail.com (T. Twagirumugabe), fredy.saguti@gu.se (F. Saguti), sylvanio03@gmail.com (S. Habarurema), jbgahutu@yahoo.com (J.B. Gahutu), tomas.bergstrom@microbio.gu.se (T. Bergström), helene.norder@gu.se (H. Norder).

(RNEC 024/2014). Demographic data were collected in a questionnaire after informed consents were obtained. Samples were analysed in the Laboratory of Clinical Virology of Sahlgrenska Academy, Gothenburg in Sweden for anti-HAV IgG on Architect *i*4000SR (Abbott Park, IL, USA) and for anti-HEV IgG and IgM by the HEV IgM/HEV IgG test (DiaPro, Milan, Italy). Samples with anti-HEV IgG titres >1.7 samples OD/cut-off OD (S/CO) were considered as positive (Norder et al., 2016). All samples with titres >1S/CO and samples from all 15 patients with acute liver disease were analysed for anti-HEV IgM and for HEV RNA by PCR as previously described (Norder et al., 2016).

Results

Only 1045 samples could be analysed for anti-HAV and 1133 for anti-HEV IgG including 966 for both. Anti-HAV IgG was found in 1013 (96.9%) persons, and more often in older participants (Table 1).

Table 1
Prevalence of anti-HAV IgG and HEV markers according to different categories of study participants.

Variable		Anti-HAV			HEV markers									
					Blood donors		Healthy		Liver patients		Total			
		N tested	Pos; n (%)	P value	N tested	Pos; n (%)	N tested	Pos; n (%)	N tested	Pos; n (%)	N tested	Pos; n (%)	P value	
Age group	18–20 years	63	59 (93.6)	Ref	56	7 (12.5)	1	0 (0)	2	0 (0)	59	7 (11.9)	Ref	
	21–25 years	218	205 (94)	0.910	173	16 (9.2)	20	0 (0)	18	2 (11.1)	211	18 (8.5)	0.437	
	26–30 years	168	163 (97)	0.249	119	16 (13.4)	27	1 (3.7)	23	2 (8.7)	169	19 (11.2)	0.897	
	31–35 years	192	186 (97)	0.262	149	9 (6)	29	8 (27.6)	22	4 (18.2)	200	21 (10.5)	0.767	
	36–40 years	113	111 (98.2)	0.132	75	14 (18.7)	17	0 (0)	25	5 (20)	117	19 (16.2)	0.442	
	41–45 years	74	73 (98.6)	0.158	41	6 (14.6)	21	7 (33.3)	19	3 (15.8)	81	16 (23.5)	0.218	
	46–50 years	53	53 (100)	0.997	18	2 (11.1)	20	2 (10)	18	2 (11.1)	56	6 (11.4)	0.846	
	51–55 years	40	39 (97.5)	0.392	8	1 (12.5)	19	0 (0)	26	3 (11.5)	53	4 (7.5)	0.447	
	56–60 years	31	31 (100)	0.998	3	1 (33.3)	27	5 (18.5)	12	3 (25)	42	9 (21.4)	0.200	
	61–65 years	25	25 (100)	0.998	-	-	18	0 (0)	21	1 (4.8)	39	1 (2.6)	0.134	
	66–70 years	22	22 (100)	0.998	-	-	10	0 (0)	27	4 (14.8)	37	4 (10.8)	0.875	
	71–75 years	25	25 (100)	0.998	-	-	22	4 (18.2)	16	2 (12.5)	38	6 (15.8)	0.581	
	> 76 years	21	21 (100)	0.998	-	-	15	4 (26.7)	16	1 (6.3)	31	5 (16.1)	0.573	
Sex	Female	294	284 (96.6)	Ref	118	7 (5.9)	125	15 (12)	125	15 (12)	368	37 (10.1)	Ref	
	Male	751	729 (97.1)	0.691	524	65 (12.4)	121	16 (13.2)	120	17 (14.2)	765	98 (12.8)	0.183	
Residence	Kigali city	188	181 (96.3)	Ref	60	3 (5)	63	5 (7.9)	64	3 (4.7)	187	11 (5.9)	Ref	
	Rural provinces	857	832 (97.1)	0.562	582	69 (11.9)	183	26 (14.2)	181	29 (16)	946	124 (13.1)	0.007	
	East	219	217 (99.1)	0.076	138	5 (3.6)	31	2 (6.4)	31	4 (12.9)	200	11 (5.5)	0.913	
	North	165	159 (96.4)	0.957	150	15 (10)	21	0 (0)	19	0 (0)	190	15 (7.9)	0.239	
	South	373	362 (97.1)	0.628	250	39 (15.6)	90	19 (21.1)	87	16 (18.4)	427	74 (17.3)	<0.001	
	West	100	94 (94.0)	0.380	44	10 (22.7)	41	5 (12.2)	44	9 (20.5)	129	24 (18.6)	0.008	
Occupation	Farmers	497	487 (98.0)	Ref	338	45 (13.3)	114	21 (18.4)	119	20 (16.8)	571	86 (15.1)	Ref	
	Others	548	526 (96.0)	0.066	307	27 (8.8)	122	10 (8.2)	126	12 (9.5)	562	49 (8.7)	0.001	
Total		**1045**	**1013 (96.9)**		**642**	**72 (11.2)**	**246**	**31 (12.6)**	**245**	**32 (13.1)**	**1133**	**135 (11.9)**	**>0.440**[a]	

[a] No significant difference of prevalence between blood donors and healthy adults (p = 0.564) and liver disease patients (p = 0.445).

Table 2
Distribution of participants with anti-HEV IgM and/or HEV RNA according to different characteristics.

Variable		Anti-HEV IgG positive						Anti-HEV IgG borderline					
		Liver disease patients			Blood donors and Healthy			Liver disease patients			Blood donors and Healthy		
		N	Anti-HEV IgM+	HEV RNA+	N	Anti-HEV IgM+	HEV RNA+	N	Anti-HEV IgM+	HEV RNA +	N	Anti-HEV IgM+	HEV RNA+
Age group	18–20 years	–	–	–	7	0	–	–	–	–	3	0	–
	21–25 years	2	1	–	16	0	–	1	0	–	12	0	–
	26–30 years	2	0	–	15	0	1	–	–	–	10	1	1
	31–35 years	4	0	–	16[b]	1	–	2	0	–	15	0	–
	36–40 years	5	1	1[a]	12	2	–	–	–	–	5	2	–
	41–45 years	2	0	–	11	2	–	2	0	1	2	1	1
	46–50 years	2	0	–	4	0	–	2	0	–	2	0	–
	51–55 years	3	0	1	–	–	–	–	–	–	3	0	1
	56–60 years	3	0	–	6	0	–	1	0	–	–	–	–
	61–65 years	1	0	–	–	–	–	2	0	–	–	–	–
	66–70 years	4	0	–	–	–	–	1	0	–	–	–	–
	71–75 years	2	0	–	3	0	–	–	–	–	2	1	–
	> 76 years	1	1	–	4	0	–	–	–	–	–	–	–
Sex	Female	15	0	–	20[b]	3	–	6	0	–	7	1	–
	Male	16	3	2	74	2	–	5	0	–	47	4	3
Residence	Kigali city	3	0	–	8	0	–	1	0	–	6	0	–
	Rural provinces	28	3	2	86[b]	5	1	10	0	–	48	5	3
Occupation	Farmers	19	3	2	59[b]	4	1	6	0	–	29	4	2
	Others	12	0	–	35	1	–	5	0	–	25	1	1
Total		31	3	2	94[b]	5	1	11	0	1	54	5	3

[a] Anti-HEV IgM positive.
[b] We did not have enough serum sample to run the anti-HEV IgM in one sample.

For anti-HEV IgG, 126 (11.1%) were reactive (median: 3.82 S/CO; range: 1.717–9.393) and 65 (5.7%) had borderline values (1-1.7S/CO). New HEV infections comprised eight persons with anti-HEV IgM among 125 (6.4%) with anti-HEV IgG, five (7.7%) in 65 with borderline values (Table 2) (median anti-HHEV IgM: 1.396 S/CO; range: 1.054–5.749) and seven with HEV RNA (Ct values: 30.26–41.45) including only one yielding anti-HEV IgM. All were all from persons living in rural provinces (5 in South, 1 in North and 1 from East). Three were patients with acute liver disease (ALT: 41–187 IU/L) and four were blood donors (Table 2). None of these strains could be sequenced.

A significantly higher prevalence of HEV markers among farmers and persons from Southern and Western provinces than other parts was found (Table 1).

Discussion

In this study, a high prevalence of anti-HAV IgG in Rwandans was found, as could be expected. However, increasing proportions of young adults who had not been exposed to HAV were identified. This may indicate a decreasing exposure in childhood owing to improved hygiene and access to clean water (Jacobsen and Koopman, 2005). Since there is no vaccination against HAV in Rwanda, regular surveillance will be needed to detect a shift of HAV epidemiology in a timely manner.

Despite HEV1 outbreaks reported in zones neighbouring Rwanda (Hakim et al., 2017), the prevalence for HEV markers was rather moderate. It was comparable in all age groups investigated and this may indicate a recent introduction of HEV into Rwanda. The findings of highest prevalence among persons from the Southern and Western provinces of Rwanda, which have the highest density of pig breeding (http://harvestchoice.org/sites/default/files/downloads/publications/Rwanda_2008.pdf) may support this recent introduction by pigs imported from Europe (Mbuza et al., 2016). Zoonotic HEV3 strains might then have been introduced into Rwanda as well since cases of HEV3 infections have been reported among humans and imported pigs in Sub-Saharan Africa (Kaba et al., 2010, Madden et al., 2016) but further research is needed to isolate circulating strains. We could not molecularly characterize HEV strains in this study, probably because of low levels of HEV RNA or genetically divergent HEV strains that could not be amplified with primers used.

Identification of current HEV infection among blood donors raises a concern for blood-borne transmission of HEV in this region, as it is now in several European countries (Dreier et al., 2018).

In conclusion, HAV remains highly endemic in Rwanda with a possible decrease of exposure, which may in the future lead to clinically overt infections at older patient ages as in Europe (Gassowski et al., 2018). HEV shows a moderate endemicity and a possible zoonotic transmission from pigs.

Conflict of interest

None.

References

Debing Y, Moradpour D, Neyts J, Gouttenoire J. Update on hepatitis E virology: implications for clinical practice. J Hepatol 2016;65(1):200–12.

Dreier J, Knabbe C, Vollmer T. Transfusion-transmitted hepatitis E: NAT screening of blood donations and infectious dose. Front Med (Lausanne) 2018;5:5.

Gassowski M, Michaelis K, Wenzel JJ, Faber M, Figoni J, Mouna L, et al. Two concurrent outbreaks of hepatitis A highlight the risk of infection for non-immune travellers to Morocco, January to June 2018. Euro Surveill 2018;23(27).

Hakim MS, Wang W, Bramer WM, Geng J, Huang F, de Man RA, et al. The global burden of hepatitis E outbreaks: a systematic review. Liver Int 2017;37(1):19–31.

Jacobsen KH, Koopman JS. The effects of socioeconomic development on worldwide hepatitis A virus seroprevalence patterns. Int J Epidemiol 2005;34(3):600–9.

Kaba M, Colson P, Musongela JP, Tshilolo L, Davoust B. Detection of hepatitis E virus of genotype 3 in a farm pig in Kinshasa (Democratic Republic of the Congo). Infect Genet Evol 2010;10(1):154–7.

Kamar S, Selves J, Mansuy JM, Ouezzani L, Peron JM, Guitard J, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. N Engl J Med 2008;358:811–7.

Madden RG, Wallace S, Sonderup M, Korsman S, Chivese T, Gavine B, et al. Hepatitis E virus: Western Cape, South Africa. World J Gastroenterol 2016;22(44):9853–9.

Mbuza F, Majyambere D, Ayabagabo JDD, Dutuze MF. Inventory of pig production systems in Rwanda. Int J Livestock Prod 2016;7(7):41–7.

Norder H, Karlsson M, Mellgren A, Konar J, Sandberg E, Lasson A, et al. Diagnostic performance of five assays for anti-hepatitis E virus IgG and IgM in a large cohort study. J Clin Microbiol 2016;54(3):549–55.