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Hepatitis E Virus in the Countries of the Middle East and North Africa Region: An Awareness of an Infectious Threat to Blood Safety

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Abstract

Introduction: Hepatitis E virus (HEV) is mainly transmitted through contaminated water supplies which make the virus endemic in developing countries including countries of the Middle East and North Africa (MENA) region. Recent reports suggest potential risk of HEV transmission via blood transfusion particularly in endemic areas.

Materials and Methods: Related articles on HEV were collected by searching through the 25 countries of the MENA region using Pubmed and Medline within the past 14 years: January 2000-August 2014.

Results: One hundred articles were extracted, of which 25 were not eligible. The articles discussed the seroprevalence of HEV and HEV markers in 12 countries. Eight articles provided data on HEV in blood donors. The seroprevalence of HEV in the general MENA population ranged from 2.0%-37.5% and was higher in males than in females. Prevalence increased with age, but exposure seems to be in early life.

Discussion: In the MENA region the role of HEV as an infectious threat to blood safety is under-investigated. More data are needed to quantify the risk of transmission and to assess clinical outcomes. This requires, at least, surveillance screening of donors and recipients for HEV markers using sensitive and specific serological tests. At the present time, serious consideration should be given to selective screening for certain groups of patients (e.g. immunocompromised, pregnant women and others) who commonly require blood transfusion and are at high risk of hepatic failure or chronicity from HEV infection.

Keywords: Hepatitis E; HEV; MENA region; Epidemiology; Blood safety; Blood donors

Introduction

Hepatitis E virus (HEV) is a small (27-34 nm); non-enveloped, icosahedral, single stranded RNA virus of approximately 7.2 kb in length. Analysis of its RNA helicase and RNA-dependent RNA polymerase region shows that the virus forms a phylogenetically distinct group that was recently placed into a separate genus, *Hepevirus* in the Hepeviridae family [1,2]. The family contains mammalian HEV and a more distant avian HEV [3]. Phylogenetic analysis of the mammalian isolates showed that there are 4 major genotypes (genotypes 1-4) and several sub genotypes [4]. Each HEV genotype appears to have a specific geographic distribution: Genotypes 1 and 2 are restricted to humans and are mainly responsible for large waterborne epidemics in Asia and Africa [5] while genotypes 3 and 4 are found in human and animal reservoirs (swine, wild boar, deer, mongooses) and are mainly responsible for sporadic cases of HEV in developed countries [6,7]. The incidental discovery of a novel swine virus closely related to human HEV in 1997 [8,9] was extremely important to studying the epidemiology of HEV. In recent years, autochthonous (locally acquired) zoonotic hepatitis E has been found in many developed countries in Europe, New Zealand, North America (all genotype 3) [10-12] and Japan (genotypes 3 and 4) [13]. It is now believed that HEV in developed countries is zoonotic and food-borne, mainly associated with eating uncooked or undercooked meat or viscera of deer, boars and pigs or by exposure to infected animals [14,15]. This route of transmission in the MENA is unlikely since pig farming is prohibited in the Islamic culture, as is the case in most countries of the region. Furthermore, boars and deer hunting are not commonly practiced in MENA. HEV is currently the focus of greater attention worldwide and the number of HEV-related articles has more than doubled in the last 10 years.

Seroprevalence of HEV

Rates of IgG positivity in a certain area are believed to be a reflection of the frequency of HEV infection in that area. However, estimating the burden of HEV infection in a population is not an easy task. The true figure in many developing countries could be much higher than that reported since earlier studies used assays with poor sensitivity [16]. Higher results are expected when more sensitive assays are used [17]. Sera tested in recent IgG immunoassays based on a variety of HEV antigens gave broadly concordant results suggesting that antibodies detected are truly directed at HEV [18].

In endemic areas, such as India and South-East Asia, studies on HEV seroprevalence have shown high frequencies in the general population, ranging from 27%-80% in the general population. In contrast, in non-endemic regions, seroprevalence varies from 2%-8% in Europe, Japan and South America to 18.0%-21.0% in the USA, Russia, UK, Southern France, Hong Kong, Korea, and China. In developing countries, water-borne epidemics of HEV mainly affect

young adults, the clinical attack rate being highest among 15-35 year-old [19] and men are clinically infected 2-5 times more than women in most outbreaks [20]. Asymptomatic infections have been estimated to exceed the number of symptomatic cases by 2-4 times in waterborne outbreaks [21]. Although routine surveillance and reporting of HEV infection is far from universal and sensitive anti-HEV assays are still lacking, it is clear that the majority of disease burden due to HEV is in the low and medium income countries of Asia and Africa [22].

Mode(s) of transmission and endemicity

One of the earliest documented massive outbreaks of infectious hepatitis took place in New Delhi, India in late 1955 where at least 30,000 clinical cases of jaundice were reported with elevated morbidity and mortality in pregnant women [23]. Outbreaks with similar characteristics to the New Delhi outbreak were also documented in Kashmir Valley in 1978 [24] and in Afghanistan in 1983 [25]. All three outbreaks were associated with fecal-contamination of drinking water or flooding. In 1990-1991, the etiological agent of such outbreaks was isolated, partially cloned and was labelled hepatitis E virus [26]. HEV is now considered the leading cause of acute hepatitis worldwide and is considered endemic in developing countries.

Recent reports showed higher HEV seroprevalence in specific groups as paid blood donors and in repeatedly transmitted hemodialysis patients [27,28]. Furthermore, the recent reporting of transmission of HEV through blood transfusion from Saudi Arabia [29], Japan [30] and the UK [31] has led to the suggestion that the parenteral route could be an important route in the transmission of HEV. As early as 1996 we speculated on the possible transmission of HEV by blood transfusion in Saudi Arabia [32]. Since HEV is endemic in developing countries, including countries of the MENA region, the awareness of an infectious threat to blood safety is legitimate. The purpose of this manuscript, therefore, is to review the status of HEV in the MENA region countries and to see whether the transfusion-transmission route has been evaluated.

Materials and Methods

Related articles were collected, by searching through the countries of the MENA region. Over the past 14 years (from January 2000–August 2014); literature was reviewed using countries of the MENA region Pubmed and Medline. The search was conducted using predefined combination of keywords: “hepatitis E virus”, “hepatitis E”, “hepatitis E infection”, “blood donors” in combination with all the names of the countries of the MENA region. The MENA region includes 25 countries (Algeria, Bahrain, Cyprus, Djibouti, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, Turkey, UAE and Yemen) and covers a population of over 380 million people. One hundred articles were reviewed, of which 25 articles were excluded; the excluded papers were written in non-English language or had uninterpretable data (didn’t have seroprevalence data).

Results

HEV seroprevalence (anti-HEV IgG) and HEV markers, across age groups and in different categories of populations in various countries of the MENA region during the past 14 years are shown in Table 1.

There were eight articles published on HEV in blood donors (Table 2) of which only 2 studies performed HEV-RNA testing to see whether or not the donor was viremic at the time of donation. Only one study from Saudi Arabia was a prospective study [76]. Seroprevalence of HEV among the reported blood donors was within the range found in the general population except for one study from Saudi Arabia where 19% of the donors were anti-HEV positive [77].

Anti-HEV in Egypt exceeds 12.5% in children and can reach 84.0% in adults. In Iran, anti-HEV varies from region to another (2%-14%) but it does not exceed 14%. Similarly anti-HEV among Saudis varied from 4.0%-8.0% in the general population and in one study a seroprevalence of 19% was reported among blood donors. Regional variation in anti-HEV seroprevalence was also reported in the Turkish population (2%-13%) and anti-HEV was as high as 35% among agriculture workers. Anti-HEV variation (18%-22%) was reported among Iraqis and a seroprevalence of 11% was reported in Yemen. Molecular studies were not attempted in most of the studies reported. High HEV-RNA positivity was reported in pediatric patients with acute hepatitis in Egypt (23%), in hepatitis outbreaks in Sudan (20%-27%) in patients with chronic hepatitis C in Turkey (55%) and in pregnant women in UAE (30%).

Country	Category/Population studied	Number of participants	Mean age (Age group)	anti-HEV IgG (%)	anti-HEV IgM (%)	HEV RNA (%)	References
Egypt	**Outbreaks**						
	Assiut	235	(2-54)	-	24	-	[33]
	Hepatitis						
	Patients who had a history of jaundice	134	(20-40)	38	-	-	[34]
	Pregnant women with chronic HCV infection	56	32.5 ± 12.3	71	-	-	[35]
	Pregnant women free from chronic HCV infection	60	33.6 ± 7.8	47	-	-	[35]
	Patients with acute on chronic liver disorders	100	46.38 ± 8.87	30	5	13	[36]
	Patients suffering from hepatitis*	50	(1.5-15)	-	-	0.50	[37]

	Symptomatic acute hepatitis patients	235	(1-65)	-	16	-	[38]
	Asymptomatic contacts	200	-	-	7	-	[38]
	Acute viral hepatitis patients ₸	287	-	-	20	0.69	[39]
	Patients with elevated liver enzymes	214	42.2 ± 8.6	-	2	0	[40]
	Children with sporadic acute hepatitis	162	7.0 ± 2.0	39	2	-	[41]
	Healthy controls	13	7.5 ± 1.5	0	0		[41]
	Inpatients with clinical acute viral hepatitis	200	20.2 ± 14.2 (4-65)	-	13	-	[42]
	Pediatric patients with acute hepatitis	64	(6-12)	13	17	23	[43]
	Healthy children	16	(6-12)	13	0	0	[43]
	Patients with ALT levels that were least twice the normal level	47	(2-77)	85	2	0	[44]
	HCV Cases	321	(25-47)	56	-	-	[45]
	non-HCV (controls)	475	(14-30)	51	-	-	[45]
	Others						
	Mothers	29	-	31	-	-	[46]
	◊Wastewater treatment plants workers	43	47.1 ± 3.7	51	-	-	[47]
	Comparison group	43	48.2 ± 2.4	30	-	-	[47]
	◊Workers in wastewater treatment plants	205	(20-40)	51	-	-	[48]
		-	(41-50)	43	-	-	[48]
		-	(51-60)	46	-	-	[48]
	Aborted women	-	-	22	3	16	[49]
	Villagers	919	(5-75)	4	-	-	[50]
	Pregnant women	2428	(16-48)	84	-	-	[51]
	Communities in the Nile Delta and Upper Egypt	10,026	(0->75)	68	-	-	[52]
	Patients admitted to Children's Hospital	68	(6-12)	3	41	6	[53]
Iran	**Hemodialysis**						
	◊Hemodialysis patients	80	55.69 ± 14.70 (26-80)	6	-	-	[54]
	Healthy individuals (Control)	276	51.73 ± 15.10 (24-77)	3	-	-	[54]
	◊Kidney transplant patients	-	-	30	-	-	[55]
	◊Hemodialysis patients	324	53.5 ± 15.1	7	-	-	[56]
	Others						
	Pregnant women	136	(14-39)	4	-	-	[57]

	General population of Mashhad, north east of Iran	1582	29.06 ± 18.513 (<5 - ≥ 65)	14	-	-	[58]
	HIV-infected patients	100	(34-43)	10	0	0	[59]
	Population based (Tehran)	551	41.28 ± 16.96 (1-83)	9	-	-	[60]
	Active health centers in Khorramabad (Western Iran)	400	36 (>20)	8	-	-	[61]
	Community based (Sari district)	1080	(2-25)	2	-	-	[62]
	Population-based (Isfahan Province)	816	(6- ≥ 50)	4	-		[63]
	Population-based (Nahavand)	1824	34.7 ± 19.5 (6->70)	9	-	-	[64]
Iraq	**Outbreak**						
	Al-Sadr city, Baghdad	270	-	21	-	-	[65]
	Al-Sadr city, Baghdad	268	(<10->40)	-	38	-	[66]
	Hepatitis						
	Patients with suspected acute viral hepatitis	2,692	(<5->45)	-	2	-	[67]
	Others						
	Thai Troops Deployed with U.N. Peacekeeping Forces in Iraq	869	(21-55)	21	2	-	[68]
	Refugee Kurds from Iraq	637	24 ± 8.4 (0.5-55)	18	-	-	[69]
Israel	**Others**						
	Travelers returning from tropical countries	4,970	37 ± 14.2	0.38	-	-	[70]
	Backpackers to Tropical Countries	105	22.3 ± 2.5 (<32)	0	-	-	[71]
Saudi Arabia	**Hepatitis**						
	Patients with acute viral hepatitis	246	(<10->21)	-	13	-	[72]
	Hemodialysis						
	◊Hemodialysis patients	83	39.0 ± 17.8 (7-82)	7	5	-	[73]
	Healthy controls	400	40.3 ± 18.5 (10-78)	11	0.30	-	[73]
	Patients from clinics	64	42.5 ± 19.1 (6-75)	13	2	-	[73]
	Patients admitted to wards	113	49.8 ± 20.2 (14-95)	11	0	-	[73]
	Others						
	◊Multiple transfused patients (retrospective)	145	30.7 ± 17.3 (4-75)	6	9	6	[74]
	Healthy controls (retrospective)	250	27.1 ± 20.4 (2-76)	4	0.80	0.80	[74]
	Transfused patients (prospective)	25	31.5 ± 16.4	12	4	-	[74]
	Untransfused patients (prospective)	25	29.5 ± 15.9	8	0	-	[74]
Sudan	**Outbreaks**						
	Darfur, Sudan Cases	75	(0- >45)	3	97	-	[75]

	Darfur, Sudan Controls	143	(0->45)	26	34	-	[75]
	Darfur, Sudan	20	(15-44)	90	95	20	[76]
	Darfur, Sudan ₸	84	-	100	100	27	[77]
	Hepatitis						
	Pregnant women with features of acute viral hepatitis	16	26.8 ± 7.1	-	50	-	[78]
	Patients with fulminant hepatic failure	37	38 (19-75)	-	5	-	[79]
Tunisia	**Others**						
	◊Polytransfused patients	107	-	29	-	-	[80]
	Control group	160	-	10	-	-	[80]
	Pregnant women	404	30.08 ± 5.95 (17-52)	12	0	-	[81]
	Population-based study	1505	20.71 ± 1.96 (16-25)	4	-	-	[82]
Turkey	**Hepatitis**						
	Patients with chronic hepatitis B	190	42.2 ± 9.1 (19–66)	14	8	15	[83]
	Patients with chronic hepatitis C	174	47.2 ± 6.2 (21–72)	54	6	55	[83]
	Control group	178	37.2 ± 8.8 (18–55)	16	7	-	[83]
	Hemodialysis						
	◊Hemodialysis patients	92	55 ± 11 (22-71)	21	-	-	[84]
	Others						
	Primary school children	185	(7-14)	12	-	-	[85]
	Primary school children	515	9.6 ± 0.1 (6-13)	2	-	-	[86]
	Community-based study	582	(>15)	2	-	-	[87]
	Children after an earthquake	589	11.5 ± 5.4 (0.5-17)	0.30			[88]
	Pregnant women	386	24.28 ± 4.56	7	-	-	[89]
	Children after an earthquake in Duzce	383	8.8 ± 4.0 (2-15)	5	-	-	[90]
	Children after an earthquake in Golyaka	93	8.8 ± 3.0 (2-15)	17	-	-	[90]
	Healthy children	210	9.37 ± 7.31 (1-18)	6	-	-	[91]
	Pregnant women	245	26.3 ± 7.6 (17-41)	13	0	-	[92]
	Control	76	27.5 ± 3.4 (19-42)	12	0	-	[92]
	◊Agricultural workers	46	27.6 (15->40)	35	-	-	[93]
	Control group	45	28.5 (15->40)	4	-	-	[93]
	Children	340	(5-16)	9	7	-	[94]
	Patients with no acute hepatitis signs and symptoms	1046	32.3 (15-75)	4	-	-	[95]
	Pediatric age groups	338	-	0.89	-	-	[96]
	Children	909	(0.5-15)	2	-	-	[97]

	Refugee Kurds from Turkey	368	24 ± 9.1 (0.8-50)	10	-	-	[69]
UAE	**Hepatitis**						
	Acute hepatitis patients	122	29.2 ± 10.56 (14- 64)	-	40	-	[98]
	Others						
	Pregnant women	469	-	-	20	30	[99]
Yemen	**Others**						
	Attendants of polyclinics	356	18.2 ± 19.4 (0-79)	11	-	-	[100]

HEV genotypes reported: *G3 ∓ G1

◊Populations that may be at risk due to potential blood route of HEV exposition.

All percentages were rounded if>1%.

Table 1: Hepatitis E virus (HEV) markers in different categories of populations in the middle east and north africa (MENA) countries.

Country	Number of participants	Mean age (Age group)	anti-HEV IgG (%)	anti-HEV IgM (%)	HEV RNA (%)	References
Egypt	760	23.8 ± 5.3	-	0.45	0.26	[101]
Iran	52	(34–44)	12	0	-	[59]
	530	36.3 ± 11.7 (18->50)	14	-	-	[102]
	400	33.3 (18-60)	12	-	-	[103]
	399	31.4 ± 9.8	8	-	-	[104]
Saudi Arabia	900	30 ± 7.8 (18-66)	19	4	-	[105]
	107	-	10	3	4	[74]
Tunisia	687	32.6 ± 8.6	5	-	-	[106]

Table 2: Hepatitis E virus (HEV) markers among blood donors in the middle east and north africa (MENA) countries.

Discussion

In recent years, studies from developed countries have shown asymptomatic viremia (HEV-RNA) in blood donors which is suggestive of ongoing subclinical infection [107-109]. The presence of HEV RNA is in the serum of healthy donors indicates that there is a potential risk of transmission of HEV through blood and indeed transmission of HEV by transfusion has been reported on several occasions from Europe and Japan [110-114]. The first molecularly confirmed case of transfusion-transmitted HEV was reported in 2004 from Japan [112]. Other cases have been confirmed in Sweden, Germany and the United States [107,108], in the United Kingdom [110] and in France [111]; to mention only few. Recent articles have already reviewed the risk of HEV infection by blood donation from developed countries. The incidence of HEV in the blood donor population in developed countries however, is unclear and is likely underestimated and this could be possibly due to several factors including: 1) The lack of well-validated assays; 2) The asymptomatic nature of HEV infection among adults; 3) The lack of testing; 4) and finally the underreporting of HEV disease in all countries.

On the other hand, in endemic countries including countries of the MENA region, the impact of HEV transmission through blood transfusion has rarely been evaluated. The possibility of transmission through blood transfusion was based mainly on retrospective evaluation in transfusion recipients [115,116] and that multi transfused had significantly higher prevalence of markers for acute HEV (anti-IgM and HEV-RNA) as compared to controls [117-119]. In the MENA region, out of the 75 published articles that showed interpretable data during the past 14 years, only 8 articles provided data on HEV in blood donors: Seven of the articles reported on the seroprevalence of HEV in blood donors and only one study was prospective. Anti-HEV (IgG) in blood donors ranged from 5.4% among Tunisians to over 50% among Egyptians. In one study from Saudi Arabia, anti-HEV (IgG) in blood donors was as high as 19.0% (105). It is interesting to note that the blood donors in this Saudi study were from one location (Makkah) where the majority of the people drank well-water [105]. Moreover, 4.3% of the blood donors tested was anti-HEV (IgM) positive implicating HEV as a potential transfusion risk. In the prospective study from Saudi Arabia [74] HEV infection developed in 3 of 22 susceptible patients following blood transfusion. The infections were traced to infected donor samples (HEV-RNA-positive) and occurred within the incubation period of HEV infection. Thus asymptomatic viremia may occur in healthy adults in endemic areas and viremia and fecal shedding have been reported in symptom-free carriers. The available but scanty data therefore, show that the disease burden of HEV infection in blood donors in countries which experience outbreaks of HEV infection is grossly under-investigated. This fact, in addition to the high endemicity of HEV in developing

countries, and the risk of transmission of HEV by transfusion documented in some developed countries lead to the emerging awareness of infectious threat to blood safety in developing countries.

As for the seroprevalence of HEV in the MENA region, published data during the past 14 years confirm the endemicity of HEV in all 12 MENA countries studied but data on the remaining 13 countries are still lacking. Except for Egypt where anti-HEV reaches 100% in certain populations, the seroprevalence of HEV in the general population ranges from 2.3%-37.5% and is higher in males than in females. Prevalence increased with age, but exposure seems to be in early life in Egypt as high prevalence was detected in young children. This increase in percentage of anti-HEV with age could be consistent with cumulative exposure to infection over time [120].

It must be emphasized however that our study suffers serious limitations. The major limitation is in the methodology of the reported studies where the selection of patients and the assays used were very different. Moreover, earlier assays used were less sensitive than the recent ones [121] which cast some doubt on the frequencies reported as underestimated and hence not representative. In addition, data on HEV on the remaining 13 countries of the MENA region are still missing. Furthermore, only three studies reported on HEV genotypes. In Egypt, genotype 1 [39] and genotype 3 [37] were found among hepatitis patients. In Sudan, genotype 3 was detected during an outbreak in Darfur [77]. More research is needed to identify the predominant genotype(s) in the various countries and even in the various populations of the MENA region.

It can be concluded that more extensive investigations are required to determine the disease burden of HEV infection in blood donors in developing countries. This will include exploring epidemiological, virological and cultural data in evaluating the potential risk of HEV infection via blood transfusion in these counties. National surveillance screening of donors and recipients for markers of recent HEV infection is of utmost importance. The reliability of the data depends on the reliability of the tests employed. IgM antibodies to HEV are present for several weeks following acute HEV infection [122] indicating that perhaps screening for HEV IgM class antibodies could be a marker for detecting active HEV infection. No infectivity data however, are available for IgM-positive donations. HEV-RNA on the other hand does not persist for long, becoming undetectable in blood three weeks after the onset of symptoms [123].

Although screening for HEV in blood donors is still not a universal requirement, selective screening is to be recommended in certain circumstances. Recent evidence shows that HEV infection can take a severe or even fatal course resulting in liver failure in immunocompromised, pregnant women or patients with chronic liver disease [122-126]. Since these patients often require blood transfusion, it is prudent them that screening for HEV-RNA or at least for anti-HEV IgM in donated blood for these patients should be implemented as soon as possible.

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