

# Hepatitis E virus seroprevalence in haemodialysis patients in Zanjan province, Islamic Republic of Iran

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معدّل الانتشار المصلي لفيروس التهاب الكبد "E" بين مرضى الديال في زنجان، في جمهورية إيران الإسلامية  
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**الخلاصة:** إن فيروس التهاب الكبد "E" هو الأكثر شيوعاً بين أسباب التهاب الكبد الحاد بين البالغين في المناطق الموطونة به في آسيا. وقد أجرى الباحثون هذه الدراسة الوصفية المستعرضة لقياس أضرار فيروس التهاب الكبد "E" لدى المرضى المحوّلين إلى مركزين للديال في مدينة زنجان في جمهورية إيران الإسلامية، وشملت الدراسة 93 مريضاً بالفشل الكلوي المزمن، بعمر وسطي 57.0 عاماً (الانحراف المعياري 18.5)، فوجدوا أن أضرار فيروس التهاب الكبد اليائي إيجابية في 25 مريضاً (26.9%). ولم يكن هناك ارتباط يُعتدُّ به إحصائياً بين العدوى بفيروس التهاب الكبد اليائي وبين الجنس أو العمر أو المستوى التعليمي أو مكان الإقامة أو مصدر المياه. وكان معدل إيجابية فيروس التهاب الكبد اليائي أعلى لدى المرضى الذين أمضوا فترة تزيد على العام الواحد في الديال (31.3%) مما لدى المرضى الذين أمضوا فترة عام أو أقل في الديال (15.4%)؛ إلا أن ذلك لم يكن له اعتداد إحصائي. ولم يكن لدى أحد من المرضى عدوى مزمنة بالتهاب الكبد سي أو بفيروس الإيدز، وكان اثنان منهم يعانون من العدوى بالتهاب الكبد (بي) أو اليائي المزمن. ونظراً لارتفاع معدلات انتشار فيروس التهاب الكبد اليائي بين مرضى الديال في زنجان فإن الحاجة ماسة إلى المزيد من الاهتمام بالسعات الوبائية لفيروس التهاب الكبد اليائي ومكافحته والوقاية منه مع التدريب على ذلك في غرب جمهورية إيران الإسلامية، وربما في البلدان المجاورة.

**ABSTRACT** Hepatitis E virus (HEV) infection is the most common form of acute hepatitis in adults in endemic regions of Asia. In a descriptive, cross-sectional study, anti-HEV antibody was measured in patients referred to the 2 haemodialysis centres in Zanjan city, Islamic Republic of Iran. Among 93 patients with chronic renal failure, mean age 57.0 (SD 18.5) years, antibodies against HEV were positive in 25 (26.9%) patients. HEV infection was not significantly associated with sex, age, educational level, residence or water source. The rate of HEV positivity was higher in patients with > 1 than ≤ 1 year of haemodialysis (31.3% versus 15.4%) but this was not statistically significant. None of the patients had chronic hepatitis C or HIV infection, and only 2 were suffering from chronic hepatitis B infection. Given the high prevalence of HEV in haemodialysis patients in Zanjan, more attention is needed towards HEV epidemiology, control, prevention and training in the west of the Islamic Republic of Iran and possibly neighbouring countries.

## Séroprévalence du virus de l'hépatite E chez des patients hémodialysés dans la province de Zanjan (République islamique d'Iran)

**RÉSUMÉ** L'infection par le virus de l'hépatite E (VHE) représente la forme la plus fréquente de l'hépatite aiguë chez l'adulte dans les régions endémiques d'Asie. Dans une étude descriptive transversale, les anticorps anti-VHE ont été mesurés chez des patients orientés vers deux centres d'hémodialyse de la ville de Zanjan (République islamique d'Iran). Sur 93 patients atteints d'une insuffisance rénale chronique, âgés en moyenne de 57,0 ans (ET 18,5), 25 patients (26,9 %) étaient positifs pour les anticorps anti-VHE. L'infection par le VHE n'était pas significativement associée au sexe, à l'âge, au niveau d'études, au lieu de résidence ni à une source d'eau. Le taux de positivité pour le virus de l'hépatite E était supérieur chez les patients sous hémodialyse depuis plus d'un an, par rapport à ceux traités depuis un an ou moins (31,3 % contre 15,4 %), mais la différence n'était pas statistiquement significative. Aucun des patients n'était infecté par le virus de l'hépatite C chronique ou le VIH, et seulement deux patients souffraient d'une infection chronique par le virus de l'hépatite B. Étant donné la forte prévalence du VHE chez les patients hémodialysés à Zanjan, une attention accrue est requise vis-à-vis de l'épidémiologie du VHE, de la lutte, de la prévention mais aussi de la formation en la matière dans l'ouest de la République islamique d'Iran, voire éventuellement dans les pays voisins.

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## Introduction

Hepatitis E is a self-limiting acute hepatitis caused by hepatitis E virus (HEV), which can occur both in sporadic or epidemics forms [1]. In terms of clinical symptoms, hepatitis E cannot be differentiated from other viral hepatitis cases. The spectrum of symptoms ranges from asymptomatic to fulminate disease; most patients suffer from pain, abdominal tenderness, nausea, vomiting and fever. Hepatitis E does not become chronic and often shows no recurrence. The most important complication is a severe fulminate and fetal hepatitis in pregnant women and people with chronic liver disease [2]. While in the industrialized countries, including the United States, HEV is rarely detected, it is the most common form of acute hepatitis in adults in the endemic areas in Asia. The transmission mode of HEV is mainly fecal–oral, and epidemics are typically caused by contamination of water [1]. There is disagreement about other means of viral transmission, and some researchers have maintained that fecal–oral transmission is the only route [1,2]. However, recently other means of transmission such as skin contact, blood transfusion [3–5] and mother-to-infant transmission have been proposed [6].

In a number of studies, the seroprevalence of HEV in various community groups have been compared. However, the published results have been inconsistent. While one study rejected a higher HEV seroprevalence in injecting drug users [6], another study supported it [7,8]. There have also been contradictory reports concerning haemodialysis patients. While some studies claimed that there were no significant differences between haemodialysis patients and the normal population [9], others reported significant differences [10]. The major causes of these contradictions appear to be due to a lack of matched criteria between selected groups, issues including socioeconomic status, age and so on [11].

Based on several recent studies, while the prevalence of hepatitis E in the Islamic Republic of Iran is lower than in Turkey, it is higher than Saudi Arabia, Pakistan and Iraq [12,13]. Because the city of Zanjan is near the endemic hepatitis E areas of the 2 neighbouring countries of Iraq and Turkey, and also due to the limited number of studies related to this disease in dialysis patients in Islamic Republic of Iran [12–20], we decided to analyse the prevalence of anti-HEV antibody (Ab) in a cohort of Iranian haemodialysis patients.

## Methods

### Study design and sample

In this descriptive, cross-sectional study, all the haemodialysis patients referred to Zanjan haemodialysis centres (Vali-e-Asr and Shahid Beheshti hospitals) in 2011, who were willing to participate, were included on a census basis.

### Data collection

Demographic and clinical variables were recorded using a questionnaire survey designed for that purpose, including age, sex, educational level, residency, source of drinking water and duration and frequency of haemodialysis. Histories of hepatitis B (HBV) and C virus (HCV) or human immunodeficiency virus (HIV) infection were extracted from the patient records.

A sample of blood (3 mL) was taken from each patient, quickly centrifuged and kept at  $-70^{\circ}\text{C}$ . Following sample collection, the anti-HEV-Ab level was measured by an enzyme-linked immunosorbent assay method by using Bindlaver kit (ELISA, DiaPro, Diagnostic Bioprobes) and the results were recorded on a checklist. All positive samples were tested a second time for conformation.

The study was approved by the ethics committee of Zanjan University of Medical Sciences, and informed consent was obtained from each

participant. No intervention outside of routine procedures was done, and there were no additional costs imposed on the participants. Specifications and information about all patients were kept confidential.

## Data analysis

The chi-squared test was performed for statistical analysis using SPSS, version 16. A  $P$ -value  $< 0.05$  was considered significant.

## Results

A total of 93 patients [49 males (52.7%) and 44 females (47.3%)] with chronic renal failure with a mean age of 57.0 (SD 18.5) years (range 16–88 years) who had been admitted to the Zanjan haemodialysis centres (Vali-e-Asr and Shahid Beheshti hospitals) were studied. A summary of the patients' important demographic data including sex, residence, education level and source of drinking water is shown on Table 1.

Antibodies against HEV were positive in 25 (26.9%) patients and negative in 68 (73.1%). Patients who were anti-HEV-Ab positive were slightly more likely to be male, older age, illiterate, living in a village and using unfiltered water. However none of these differences were statistically significant ( $P = 0.698$ ,  $P = 0.298$ ,  $P = 0.769$ ,  $P = 0.335$  and  $P = 0.081$  respectively) (Table 1).

The mean duration of dialysis in patients who were positive for anti-HEV-Ab was 39 months (range 1–24 months) compared with 38 (SD 43) months (range 1–220 months) for anti-HEV-Ab negative patients. A higher rate of HEV infection was seen in patients who had undergone  $> 1$  year of haemodialysis (31.3%) than those who had  $\leq 1$  year of dialysis (15.4%) but the difference was not statistically significant ( $P = 0.365$ ) (Table 1).

Only 2 people were suffering from chronic HBV, 1 of them was positive for anti-HEV-Ab. None of the patients showed evidence of chronic HCV or HIV infection.

## Discussion

Among the 93 participants enrolled in the study, 25 (26.9%) were found to be positive for anti-HEV-Ab. Only 1 of the patients had chronic HBV in addition to HEV, and none were positive for HCV or HIV. Statistical analysis of the relationship between the variables including sex, age, education, water, residency and history of HBV infection, showed no significant relationship between these variables and HEV infection. This observation is in line with a

2008 study in the province of Isfahan, reporting no significant difference between the sexes [3].

In several studies conducted on the general population in Islamic Republic of Iran, the prevalence of HEV infection was reported to be between 1.1% and 30.8% (Table 2) [12–20]. Only one of these studies, however, was performed on haemodialysis patients: Taremi et al., reporting a 7.4% HEV infection prevalence in Tabriz [13]. By contrast, our estimate indicated almost a 4-fold (26.8%) higher prevalence of HEV infection in haemodialysis patients in Zanjan, a figure that is also much higher than the average estimate for the general population. In line with our results, Rostamzadeh Khameneh et al. reported a high prevalence of HEV infection (30.8%) among kidney

transplant recipients in Urmia, located in the north-west of Islamic Republic of Iran [20]. A possible explanation could be that Zanjan and Urmia are geographically close to the endemic areas of the 2 neighbouring countries to the west of Islamic Republic of Iran, Turkey and Iraq. It is also possible that this high seroprevalence of HEV might be due to infection with an unknown virus, which creates antibodies cross-reacting with HEV [21]. Finally, some studies have proposed blood transfusion as a potential route of HEV transmission, particularly in highly endemic areas [5,22].

Because of a 4-fold higher HEV infection prevalence in Zanjan compared with the normal population of Islamic Republic of Iran, we should pay special attention to the high risk of

**Table 1** Demographic and clinical characteristics of haemodialysis patients in relation to their anti-hepatitis E virus (HEV) status

Variable	Total	Anti-HEV -ve		Anti-HEV +ve		P-value <sup>a</sup>
	No.	No.	%	No.	%	
<b>Total</b>	93	68	73.1	25	26.9	
<b>Sex</b>						
Male	49	35	71.4	14	28.6	0.698
Female	44	33	75.0	11	25.0	
<b>Education</b>						
Illiterate	54	37	68.5	17	31.5	0.769
Secondary school or lower	28	22	78.6	6	21.4	
Highschool diploma	4	3	75.0	1	25.0	
Bachelor degree or higher	7	6	85.7	1	14.3	
<b>Age (years)</b>						
< 50	31	27	87.1	4	12.9	0.298
50–59	15	9	60.0	6	40.0	
60–69	20	13	65.0	7	35.0	
> 70	27	19	70.4	8	29.6	
<b>Location</b>						
City	73	54	74.0	19	26.0	0.335
Village	20	14	70.0	6	30.0	
<b>Drinking water</b>						
Filtration	83	63	75.9	20	24.1	0.081
No filtration	10	5	50.0	5	50.0	
<b>Duration of haemodialysis (years)</b>						
≤ 1	26	22	84.6	4	15.4	0.365
> 1	67	46	68.7	21	31.3	

<sup>a</sup>Pearson chi-squared test.

**Table 2 Seroepidemiology of hepatitis E virus (HEV) in various studies in the Islamic Republic of Iran**

Study [reference]	Province	Year	Population	Prevalence of anti-HEV+ %
Aminiafshar S et al. [12]	Tehran	2004	Blood donors	7.8
Safar MJ et al. [14]	Mazandaran	2005	General population	7.2
Taremi M et al. [13]	Tabriz	2005	Haemodialysis patients	7.4
Taremi M et al. [15]	Tabriz	2007	Blood donors	7.8
Ghorbani GA et al. [16]	Tehran	2007	General population	1.1
Ataei B et al. [17]	Isfahan	2008	General population	3.8
Taremi M et al. [18]	Nahavand	2008	General population	9.3
Assarehzadegan MA et al. [19]	Khuzestan	2008	Blood donors	11.5
Rostamzadeh Khameneh Z et al. [20]	Urmia	2011	Renal transplant recipients	30.8

transmission in this region, as well as the possible means of prevention. Two particular vulnerable groups at risk include pregnant women and those already affected with HBV. Unfortunately, at the moment, HEV vaccines have not been mass produced and are not available for public use [23]. However, if a vaccine became available, HEV vaccination should be a health priority in areas such as Zanjan.

Our data indicated a tendency towards a higher rate of HEV infection among patients with > 1 year of haemodialysis versus ≤ 1 year. It is possible that this is an indication of a rising trend

for HEV infection, or that patients who started dialysis in the previous year were somehow more exposed to the risk of infection, or that the risk of infection was simply higher for patients with a longer period of dialysis.

To summarize, the results of our study showed that particular attention should be paid to the problem of HEV epidemiology in the west of Islamic Republic of Iran and possibly in neighbouring countries. We recommend that health officials provide HEV awareness programmes in such areas. Furthermore, because chronic patients may have normal liver enzymes or remain

seronegative [24], long-term follow-up of haemodialysis patients seems advisable.

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### *Hepatitis E*

The hepatitis E virus is transmitted mainly through the faecal-oral route due to faecal contamination of drinking water. Other transmission routes have been identified, which include:

- foodborne transmission from ingestion of products derived from infected animals;
- zoonotic transmission from animals to humans;
- transfusion of infected blood products;
- vertical transmission from a pregnant woman to her fetus.

The highest seroprevalence rates of hepatitis E are observed in regions where low standards of sanitation increase the risk for transmission of the virus. Over 60% of all hepatitis E infections and 65% of all hepatitis E deaths occur in East and South Asia, where seroprevalence rates of 25% are common in some age groups. In Egypt, half the population aged above 5 years is serologically positive for the hepatitis E virus.

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