Int.J.Curr.Microbiol.App.Sci (2020) *9*(1): 1086-1092

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 9 Number 1 (2020)**
Journal homepage: http://www.ijcmas.com

Original Research Article https://doi.org/10.20546/ijcmas.2020.901.123

Spread of Hepatitis E Viral Infection among Hemodialysis Patients in Pazardzhik District, Bulgaria

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Keywords

hepatitis E viral infection, seroprevalence, hemodialysis treatment

Article Info

Accepted:
15 December 2019
Available Online:
20 January 2020

A B S T R A C T

Hepatitis E virus is the major cause of non A enteral hepatitis. It is usually transmitted by fecal oral route, but infection is possible after bloodproducts transfusion and during birth. The medical literature data are controversial whether dialysis patients are at higher risk of infection. The aim of the study was to investigate the distribution of HEV infection (seroprevalence) in hemodialysis patients from Pazardzhik region, Bulgaria. 102 patients (58.8% men and 41.2% - women) on dialysis treatment were tested. The mean age of the men was 58.7 years, of the women – 59.7. We used epidemiological surveillance and serological testing. From the studied patients 14.7% were anti HEV IgA+IgM+IgG positive. The seroprevalence was significantly higher in male gender (p=0.039). The distribution of HEV infection in hemodialysis patients was lower in comparison to general population (14,7% vs.17%). The conclusion stresses on the need of periodic serological testing for Hepatitis E in patients on hemodialysis.

Introduction

Hepatitis E virus (HEV) is the most common cause of enteral non-A hepatitis. It causes subclinical, acute and chronic infection with the most common clinical manifestation being icteric hepatitis. Hepatitis E is a significant health problem in some parts of the world.

According to WHO (2017) data, 20 million HEV infections occur each year, of which 3.3 million are clinically manifested. WHO estimates that hepatitis E caused approximately 44 000 deaths in 2015 (accounting for 3.3% of the mortality due to viral hepatitis). Up to about 10 years ago, hepatitis E cases reported in Europe were thought to be associated with travels to endemic regions, but it is currently accepted that 5 -15% of unspecified hepatitis is caused by HEV and is considered local rather than imported infection (Mrzljak, 2019; WHO 2017).

Seroprevalence in Europe varies widely - 0.6 - 52.5% and depends on the population studied and the geographical region. Despite differences in the spread between different European countries, there are also differences in the spread of HEV infection in different regions of the same country(Mrzljak *et al.,* 2019; Hartl *et al.,* 2016).

According to the European Center for Disease Prevention and Control (ECDC, 2017), the number of reported cases of hepatitis E over a 10-year period (2005-2015) has increased tenfold - from 514 in 2005 to 5617 in 2015 and these data include only countries where a disease surveillance and registration system is in place. Since January 14, 2019, Hepatitis E is included in Ordinance 21 on the Procedure for Registration and Reporting of Infectious Diseases in Bulgaria.

At this stage not all issues covering epidemiology, pathogenesis, clinical manifestations and therapy of Hepatitis E have been clarified.

HEV is the only member of the Hepeviridae family (Smith, 2014). Its genome is represented by single stranded RNA with positive polarity. All viruses causing infections to humans are of the genus *Orthohepevirus*, species *Orthohepevirus A.* Up to now, 4 genotypes are known to cause disease in humans - HEV 1 - 4. Genotypes 1 and 2 are obligate human pathogens, genotypes 3 and 4 have their reservoirs in pigs (wild and domestic). There is just one reported case of hepatitis caused By HEV - 7 (isolated from camels) (Woo *et al.,* 2014). Single reports of hepatitis in humans caused by rat specific HEV are also available (Andonov *et al.,* 2019; Siddharth *et al.,* 2018).

HEV - viruses have a characteristic geographical distribution and in this respect HEV is unparalleled among other viruses. In endemic regions of Asia and Africa, HEV 1 and 2 are prevalent and in economically developed countries - HEV 3 and 4 genotypes (Dalton *et al.,* 2008; Donnelly *et al.,* 2017).

The main mechanism of transmission of the infection is fecal-oral - with the intake of contaminated water (in endemic regions) and with the consumption of primarily contaminated food (meat) in developed countries.Contagion can also occur during transfusion of bioproducts, as well as through a vertical pathway - from a pregnant woman to the fetus (Khuroo *et al.,* 1995; Khuroo, 2003).

In endemic regions, the disease occurs most often in the form of water epidemics and their occurrence coincides with natural disasters.Young people (15 - 40 years) are affected by the illness - and the disease is characterized by severe course and high lethality in pregnant women, especially in the third trimester of pregnancy (Khuroo, 2003).

In economically developed countries, the disease occurs sporadically or in the form of small outbreaks. Males are more commonly affected (male to female ratio: 3: 1) and regardless of gender, age over 50 is the most affected(Dalton *et al.,* 2008, Donnelly *et al.,*

2017). Persons in contact with animals (e.g. pigs) are also at risk of infection (Dalton *et al.,* 2008; Donnelly *et al.,* 2017; World Health Organisation, 2017)

Acute clinically manifested hepatitis E does not differ in symptoms from other forms of hepatitis. Most often it ends with definitive recovery in 4-6 weeks. Lethality is 0.5 – 4.0% (Dalton *et al.,* 2008, Donnelly *et al.,* 2017, Ramachandran *et al.,* 2004).

HEV infection can be chronic in immunocompromised persons - mainly those with transplanted organs, but also with haematological diseases, HIV infection and persons undergoing immunosuppressive therapy (Pasal., 2012; Pischke *et al.,* 2012; Rostamzadeh *et al.,* 2011).

Recently, increasing attention has been paid to extra-hepatic manifestations associated with HEV - infection - mainly neurological, hematological, renal, and others (Dalton *et al.,* 2008; Donnelly *et al.,* 2017).

The first case of Hepatitis E in Bulgaria was registered in 1995 (Teoharov *et al.,* 1995) and by 2008 there were only single reports; after that the number of reported cases in Bulgaria increased(Golkocheva-Markova *et al.,* 2017, Pishmisheva *et al.,* 2018).

Parenterally transmitted forms of hepatitis B and C are known to be a significant cause of liver disease in patients with chronic renal failure (CRF) on hemodialysis treatment (HDT) (Alter *et al.,* 1986 Edey *et al.,* 2010; Fabrizi *et al.,* 2002). In recent years, preventive measures have been implemented to control these infections and the results have been good(Edey *et al.,* 2010, Fabrizi *et al.,* 2002). Part of the liver damage in these patients due to other causes remains unclear.

A number of studies have found an unexpectedly high prevalence of specific anti HEV IgG in hemodialysis patients (Scotto *et al.*, 2015; Haffar *et al.,* 2017; Lee *et al.,* 2005; Hosseini-Moghaddam *et al.,* 2010; Sylvan *et al.*, 1998). Higher seroprevalence in these may be associated with impaired immunity, increased susceptibility to infections, and decreased immune response to antigenic stimuli (Cohen *et al.,* 1997; Litjens *et al.,* 2008). These patients are at increased risk of contact with nosocomially transmitted agents and the role of enteric transmitted hepatitis viruses must be well defined.

In Bulgaria, HDT patients are monitored for hepatitis B and C infection, but not for other kinds of hepatitis. So far there is no research in the country about the spread of the HEV-infection among this specific group of patients, which is the purpose of our study.

AIM: To study the prevalence of HEV-infection among patients undergoing hemodialysis treatment at the multi-profile hospital in Pazardzhik.

Materials and Methods

A total of 102 HDT patients from the Pazardzhik region were examined. The sera were collected in February 2019 and tested at the Clinical Laboratory – Acibadem City Clinic, Tokuda Hospital, Sofia, and at the National Reference Laboratory on Hepatitis Viruses (National Center of Infectious and Parasitic Diseases, Sofia). Methods of epidemiological study, serological tests - detection of specific anti HEV IgA+IgM+IgG by ELISA method (Euroimmun, Germany) and analytical statistical methods - Chi square analysis, t-test were used.

Results and Discussion

Of the 102 patients with HDT, 60 were men and the rest (42) were women. The average age of both sexes is over 50 years. (Table. 1)

Bulgarian ethnicity was declared by 66 (64.7%) of the participants in the study and 36 (35.3%) were of Roma origin.

The average duration of HDT is 8.4 years. (1.6 – 21 years).

All the studied patients have concomitant diseases – shown on Table 2.

Arterial hypertension, secondary anemia and osteodystrophy are commonly found as complications of chronic renal failure and dialysis treatment.

Transfusion of bioproducts was reported by 68 (66%) of patients.

Serological data (anti HEV) for hepatitis E viral infection was detected in 15 (14.7%) of the tested subjects. All (100%) seropositive patients had cardiovascular disease, 8 (53.3%) - had diabetes mellitus, in 1 patient data revealed hepatitis B viral infection - HBsAg (+) positive.

Transfusion of bioproducts had 6 (40%) of anti HEV positive patients.

The distribution of seropositive persons by gender is presented in Table 3.

Seropositive patients were significantly greater in number among male subjects (p = 0.039). No statistically significant differences in age were found.

None of the seropositive patients on HDT had clinically manifested hepatitis E and none received immunosuppressive drugs 3 months prior to study.

No significant differences regarding transfusion of bioproducts were found between seropositive and seronegative patients.

Anti HEV seroprevalence among HDT patients was higher than in hepatitis B and C (7,8% for hepatitis B and 0,9% for hepatitis C) but the differences are not statistically significant.

HEV sero-prevalence found in this study (14.7%) is lower than that of the general population in Pazardzik region (17%), but the difference is not significant (own survey of sero-prevalence among the general population in Pazardzhik District for the period 2014-2017).

Hepatitis E virus infection is more common than previously thought and is often underestimated. According to different authors, among patients on HDT seroprevalence ranges from 0 - 44% (Haffar *et al.,* 2017). Studies have been conducted on the prevalence of HEV infection in a number of countries in patients with chronic dialysis and the results differ to a great extent (Dalekos *et al.,* 1998; Scotto, 2015; Haffar *et al.*, 2017; Lee *et al.,* 2005; Hosseini-Moghaddam *et al.,* 2010; Parana *et al.,* 1997; Psichogiou *et al.,* 1996; Seyed Mohammadmehdi Hosseini-Moghaddam *et al.*, 2010; Stefanidis *et al.,* 2004; Sylvan *et al.*, 1998). Some of them emphasize on higher rate of prevalence among these persons - in Japan, Saudi Arabia, etc. In Greece and Turkey, studies have been conducted in different regions of the countries with different results - in some sero-prevalence among patients with HDT is higher and in others - it is not significantly different from that of the general population.(Psichogiou *et al.*, 1996, Hosseini-Mohammadmehdi *et al.,* 2010, Stefanidis *et al.,* 2004). In contrast, no evidence of HEV infection was found in HDT patients in Brazil (Parana *et al.,* 1997).

Not all risk factors associated with the spread of HEV infection in dialysis units have been clarified.

The survey conducted in the Pazardzhik District found sero-prevalence in 14.7%, with seropositive patients being significantly higher in male population.

The risk factors for infection and whether they are related to the treatment being performed have not been clarified. It was not clear whether the infection occurred as a nosocomial infection or was acquired in society.

At this stage, it is difficult to assess the importance of transfusion of bioproducts for the spread of HEV - infection among the study group, as there is no study on its spread among blood donors.

Table.1 Distribution of patients by sex and age

Patients studied	Number - N	Percent - %	Average age- years
Male	60	58.8	58.7
Female	42	41.2	59.7
Total	102	100	

Table.2 Concomitant diseases in patients with HDT

Concomitant diseases	Number - N	%
Ischemic heart disease and myocardial infarction	38	37.2
A cerebrovascular accident	14	13.7
Diabetes mellitus	27	26.5
Other hepatitis viruses	9	8.8

Table.3 Distribution of seropositive persons by gender

Anti HEV (+)	**Number**	**% of total number**	**% of HEV(+)**
Male	13	21.6	86.6
Female	2	4.8	13.4
Total	15		100

Conclusions and recommendations are as follows:

Patients on hemodialysis are polymorbidic and any new infection aggravates their condition.

These patients should also be tested for hepatitis E viral infection, as they are potential recipients of organs, and chronic HEV – infection is often reported in these patients.

Testing for HEV together with that for hepatitis B and C is appropriate to be performed before starting of dialysis. This will differentiate patients with society acquired HEV infection.

It is also appropriate to carry out periodic HEV IgG tests in this group of patients as well as in the staff of hemodialysis wards and to assess the risk of nosocomial infections..

Screening of donor blood for hepatitis E virus infection should also be discussed and introduced if necessary.

Acknowledgement

The kind assistance and financial support of SGP – Sofia, Bulgaria are highly appreciated.

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How to cite this article:

Pishmisheva Mariya, Shikov Peter, Golkocheva-Markova Eliza, Kotsev Stanislav, Naseva Emilia, Vatev Nikolai and Argirova Radka. 2020. Spread of Hepatitis E Viral Infection among Hemodialysis Patients in Pazardzhik District, Bulgaria. *Int.J.Curr.Microbiol.App.Sci.* 9(01): 1086-1092. doi: https://doi.org/10.20546/ijcmas.2020.901.123