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Seroprevalence of Hepatitis E Virus Infection among Patients with Hematological Malignancies in Zagazig University Hospitals, Egypt

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Abstract: ***Background and aim of the work: HEV problem in Egypt is often underestimated. This may be because acute viral hepatitis due to HEV is rare while seroincidence is a common event. This study aimed to assess the seroprevalence of HEV in patients with Hematological Malignancies and to evaluate the association of HEV infection to other patients' parameters. Patients and methods: This cross sectional, descriptive study has been carried out on 82 patients, and their hematological malignancies diagnosed clinically, histopathologically and radiologically. laboratory investigations and HEV IgG by ELISA was done to all patients. Results: The overall prevalence of HEV among the studied population was 52.4%. The highest prevalence is seen in patients with lymphoma 66.6%. Comparison between HEV IgG positive and negative patients showed that there were no significant differences as regards demographic, laboratory or sonographic data of these patients. Conclusion: Hematological malignancies and chemotherapy do not affect the seroprevalence of HEV among those patients when compared to general population.***

Keywords: Hepatitis, HEV IgG, hematological malignancy, immune suppression

1. Introduction

The hepatitis E virus (HEV) is an RNA virus transmitted by the fecal–oral route. It is endemic in developing countries. Recently, it has become clear that locally acquired sporadic hepatitis E also occur in Western countries.[1]Epidemic outbreaks in developing countries are typically caused by HEV genotype 1 strains. In contrast, sporadic HEV cases in industrialized countries are most likely of zoonotic origin and usually are caused by HEV genotype 3 strains. Signs and symptoms of hepatitis E virus (HEV) infection comprise jaundice, nausea, vomiting, myalgia, abdominal pain, fever and elevated transaminases. The overall disease mortality is low, but fulminant hepatitis is frequent among pregnant women in HEV-endemic regions.[2]

The immunoglobulin against hepatitis E appear 3-4 weeks from natural infection and persist for more than ten years and provide the basis for diagnosis. The HEV particles are shed in stool of the patients and can cause viremia during acute hepatitis. [3]

Many case reports and case series have been suggesting that among immunecompromised patients e.g. HIV, organ transplant recipients and hematological malignancy patients HEV infection can become chronic with patient's week immunity failing to clear the virus and this condition needs interference with antiviral treatment to avoid the sequelae of chronic hepatitis like liver cirrhosis and liver cell failure. [4]Other studies reported Chronic HEV infection in hematological malignancy patients receiving chemotherapy. The clinical and laboratory features of chronic HEV in these patients have been treated successfully with pegylated interferon or ribavirin as monotherapies.[5]

In immunosuppressed patients, HEV is transmitted via the same modes as in the general population, i.e., feco-oral route. In addition to the classical routes, HEV can be transmitted by blood transfusion, via the allograft, or by nosocomial transmission. Cases of HEV transmission via blood products have been reported.[6]

2. Aim of the Study

This study aimed to assess the seroprevalence of Hepatitis E virus infection in patients with Hematological Malignancies (Leukemia, Lymphoma, Multiple myeloma and Others), admitted to Zagazig university hospitals in the period between january 2016 and October 2016 and to detect the association of Hepatitis E seropositivity with other demographic and laboratory parameters of those patients.

3. Patients and Methods

This cross sectional, descriptive study has been carried out in Internal Medicine, Tropical Medicine, medical Oncology and Clinical Pathology Departments in Faculty of Medicine, Zagazig University. All oncology patients admitted to Zagazig University Hospitals during the period between January 2016 and October 2016 fulfilling the inclusion criteria were consequently enrolled in the study. The patients included in this study were 82, and their hematological malignancies diagnosed clinically, histopathologically and radiologically and were receiving the specific chemotherapy for their conditions with good response.

Exclusion Criteria

a) Patients<18 and >60
b) Patients refused to give informed consent to participate in the study
c) Patients with chronic infections e.g.; tuberculosis,
d) Patients with impaired renal functions
e) Patients with other immunecompromising conditions e.g. solid organ transplants, HIV infected
f) Patients recieving immunesuppressive therapy for autoimmune condtions e.g. systemic lupus erythermatosus (SLE), rheumatoid arthritis and others.
g) Patients with chronic liver disease for any reason e.g. HCV or HBV infection, Autoimmune Hepatitis, Metabolic liver diseases like Wilson disease, Hemochromatosis and Alcoholic liver disease, Drug induced Liver Injury.

All the studied patients were subjected to the following:

a) Full History taking, with special attention of age, sex, residence, smoking, drug, alcohol intake, duration of illness, discovery of HCV or HBV.
b) Clinical Examination.
c) Investigations Including:

A) Radiological imaging: pelvi-abdominal U/S, X- Ray, C.T., and MRI.
B) Laboratory investigations:

1) General Laboratory investigations: Complete blood picture and blood film, Liver function tests , serum creatinine , INR, Prothrombin time (PT) and Partial Thromboplastin Time (PTT), ESR , C-Reactive Protein, LDH ,S. uric acid.
2) Viral Hepatitis Markers (HBs Ag and HCV Abby ELISA).
3) Autoimmune Hepatitis Markers (ANA, ASMA and ALKMA).
4) Assesment of serum level of iron, ferritin, copper, ceruloplasmin
5) Anti-HEV immunoglobulin G (HEV IgG) measurement: for detection HEV infection by enzyme-linked immunosorbent assay (ELISA) kit, DIA-PRO, Italy according to the manufacturer's instruction.

Statistical analysis

All data were coded, checked, entered and analyzed using SPSS software version 17. Data were expressed as mean ± SD for quantitative data and number and percentage for qualititative data and comparison was done by t test for the quantitative data and Mann Whitney for data lacking criteria of normal distribution and Chi-square teat X^2 for categorical and qualitative data.

4. Results

Table 1 and 2 represent description of the demographic and laboratory parameters of the studied patients. Table 3 shows the seroprevalence among different gender, residence and disease groups in the studied group of patients.

Table 1: Descriptive analysis of demographic characteristics and medical history of the study population:

	Total number=82	
	No	%
Age (Years) Mean± SD	41.3±13.2	
Sex		
Male	43	52.4
Female	39	47.6
Residence		
Rural	58	70.7
Urban	24	29.3
Smoking status		
Yes	48	58.5
No	34	41.5
Chronic illness (diabetes, hypertension)		
Yes	73	89.02
No	9	10.98
Duration of hematological malignanacy in months Mean± SD	13.6±10.8	

Table 2: Some laboratory parameters of the hematological malignancy patients in the study:

Mean ±SD	*Total number=82*
Complete blood count	
WBC's count (x10 ^{3} cells/ml)	7.4±3
Hemoglobin (g/dl)	9.5±1.3
Platelet count (x10 ^{3} plt/ml)	210.22±58.5
Liver function tests	
Total bilirubin (mg/dl)	1.3±0.71
Total protien (g/dl)	7±0.6
S.lbumin (g/dl)	3±0.3
ALT (IU/ml)	48.6±30.5
AST (IU/ml)	43.8±25.6
Kidney function tests	
S.Creatinine (mg/dl)	0.91±0.35

Table 3: Seroprevalence among different gender, residence and malignancy groups of the study

	Total number =82	
Total Seroprevalence	43/82	52.4%
Gender:		
Males	19/43	44.2%
Females	24/39	61.5%
Residence:		
Rural	33/58	56.8%
Urban	10/24	41.6%
Different diseases groups:		
Lymphoma	8/12	66.6%
Leukemia	33/64	51.5%
Multiple myeloma	1/2	50%
Myelodysplatic syndrome	1/4	25%

Table 4 shows comparison between patient comparison between seropositive and seronegative patients as regards their demographic data show that there were no significant differences as regards any of them. Table 5 shows that there were no significant differences between seropositive and seronegative patients as regards any of their laboratory parameters. Table 6 shows that there were no significant differences between HEV IgG positive and negative patients as regards hepatomegally, splenomegally and lymphadenopathy detected by abdominal ultrasonography examination.

Table 4: Comparison between HEV IgG positive and HEV IgG negative patients as regards demographic data

		HEV IgG positive N=43		HEV IgG negative N=39		Test value	P
Age (years) **Mean ±SD**		40.8±11.9		42±14.9		T= 0.65	0.51 (NS)
Duration of hematological malignancy (months) **Mean ±SD**		13.2±11		13.97±10.8		T= 0.32	0.74 (NS)
		No	%	No	%	X^2	P
Gender	Male	19	44.2	24	61.5	2.97	0.11 (NS)
	female	24	55.8	15	38.5		
Residence	Rural	33	76.7	25	64.1	1.58	0.2 (NS)
	Urban	10	23.3	14	35.9		
Chronic illness (diabetes and/or hypertension)	positive	37	86	36	92.3	0.09	0.7 (NS)
	negative	6	14	3	7.7		
smoking	Positive	26	60.5	22	56.4	0.14	0.7 (NS)
	negative	18	39.5	17	43.6		

Table 5: Comparison between HEV IgG positive and HEV IgG negative patients as regards laboratory parameters

	HEV IgG positive N=43	HEV IgG negative N=39	T	P
Complete blood count				
WBC's count (x10 ^{3} cells/ml) **Mean ±SD**	7.37 ± 3.05	7.68 ± 3.13	**MW** 1020	0.615 (NS)
Hemoglobin concentration (g/dl) **Mean ±SD**	9.3±1.4	9.7±1.3	1.07	0.28 (NS)
Platelet count (x10 ^{3} plt/ml) **Mean ±SD**	216.18±65.85	202.36±50.13	0.55	0.58 (NS)
Liver function tests				
Total bilirubin (mg/dl) **Mean ±SD**	1.54 ± 0.77	1.18 ± 0.63	2.82	0.06 (NS)
Total protien (g/dl) **Mean ±SD**	7.1±0.6	6.98±0.6	1.2	0.23 (NS)
Albumin (g/dl) **Mean ±SD**	3±0.3	3.1±0.2	1.29	0.19 (NS)
ALT (IU/ml) **Mean ±SD**	49.66 ± 30.51	46.10 ± 29.82	**MW** 881	0.508 (NS)
AST (IU/ml) **Mean ±SD**	42.12 ± 25.41	46.80 ± 29.01	**MW** 1085	0.293 (NS)
Kidney function tests				
Creatinine (mg/dl) **Mean ±SD**	0.9±0.3	0.95±0.4	0.9	0.36 (NS)

Table 6: Comparison between HEV IgG positive and HEV IgG negative patients as regards sonographic parameters

Ultrasonography	+Ve HEV IgG N=43		-Ve HEV IgG N=39		X^2	P
	No	%	No	%		
Hepatomegaly	3	7	6	15.4	0.74	0.38(NS)
Splenomegaly	9	20.9	9	23.1	0.06	0.81(NS)
Lymphadenopathy	10	23.3	11	28.2	0.26	0.6(NS)

5. Discussion

Several previous case reports and case series implied that the HEV can become an emerging disease among immune compromised population. This immune compromised population is increasing in number with progress in the field of organ transplantation and the increasing number of transplant recipients worldwide. These reports imply that the self-limiting HEV induced acute hepatitis can be more severe and/ or chronic in nature and this can affect the overall condition of these patients. Among those immune compromised population the people with hematological malignancies seem to be of special importance due to the severity of their underlying illness and the complications of the therapy they are receiving. This condition raises concerns about a superimposed illness like HEV infection that can complicate their condition.[4,7]

Several reports, despite the well-known route of transmission of HEV which is the feco-oral route, have implied that the state of viremia during the acute phase of hepatitis makes it possible for the virus to be transmitted by blood transfusion because the screening tests for hepatitis E are not a routine test for donated blood. Being more exposed to repeated blood transfusions, patients with hematological malignancy seem to be a high risk population of this type of transmission. [8,9]

In Egypt, while most of the HEV infections are asymptomatic or subclinical, the concerns about an episode of viremia during blood donation that can lead to HEV laden blood and blood products are even more than in Asian countries where this episode of viremia must be accompanied by illness that contraindicates blood donation. In a previous study by **Ibrahim et al,**[10] they verified this

possibility and screened a number of blood donors for markers of HEV. Among 760 tested subjects, three were positive for anti-HEV IgM and two of them had HEV RNA as determined by RT-PCR. He concluded that tested healthy blood donors have low prevalence of ongoing subclinical infection with HEV and that the potential risk of transmission is low.

This study was done to assess Prevalence of Hepatitis E virus infection in patients with Hematological malignancies who were admitted to Zagazig University Hospitals and to detect relation of Hepatitis E infection to demographic and laboratory parameters. The overall seroprevalence in the sample was 52.4% this seroprevalence is more or less comparable to that found in previous studies that studied the seroprevalence of HEV among Egyptian healthy population. The seroprevalence in the study by **Abdel hady et al,** [11] was 45.5% and up to 67.7% in a study in rural areas **by Stoszek et al,** [12] these two studies included normal immune competent population. **Fix et al,[13]** Also said that the seroprevalence in Nile Delta healthy population exceeds 60% and peaks in the second decade of life. **Blackard et al,** [14] stated that Egypt has one of the highest HEV seroprevalences in the world, although the acute viral hepatitis due to HEV is rather uncommon.

The seroprevalence was higher among the rural inhabitants than urban inhabitants emphasizing that the poor water sanitation that facilitates the feco-oral transmission of HEV in the country side plays a role in this rather high seroprevalence. Rural residence is the most important risk factor for HEV infection as seen in the study by **Shata et al,**[14]who reported a seroprevalence of 80% among rural population in Assuit. However, when we compare the seropositive and seronegative patients according to residence we found that there was no significant difference. This may be because the the quality of water sanitation in the rural and urban areas in our governorate (Sharqueya) is nearly the same. The females in our study had higher prevalence than males; however when we compared seropositive and seronegative patients according to gender distribution that difference was not clear. The exposure in females is a subject of interest by many studies because of the poor outcomes of the disease among pregnant females. In a study by **Gad et al,[**15] the seroprevalence among females was more than 60%. This disagrees with **Tavitian et al,[16]** who found that the middle aged males are in higher risk of contacting the HEV illness. The study by **Amer et al,** [17] said that the higher education is related to a lower seroprevalence in Nile Delta semiurban societies. This finding may explain the rural vs urban as well as the females' vs males' seroprevalence differences in our study.
The mean ALT, AST and bilirubin of all patients was higher than normal, with exclusion of chronic liver disease. When we compared the seropositive and seronegative patients we found no significant differences as regards any of these parameters. This means that this elevation is liver enzymes and bilirubin may be related to the nature of the diease or the side effects of chemotherapy and the seropositivity of HEV doesn't have an impact on those patients liver function this agrees with **Sherman et al, [18]** who said that among immunecompromised European patients in his study the seroprevalence was 20% but active disease is not seen.

6. Conclusion

Hematological malignancies and chemotherapy do not affect the seroprevalence of HEV among those patients when compared to general population of Nile Delta .

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