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ORIGINAL ARTICLE

Seroprevalence of Hepatitis A Antibodies in Patients with Chronic Liver Diseases

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ABSTRACT

Keyword: HAV, CLD, HAV IgG.

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Background: Hepatitis A virus (HAV) is a positive-strand RNA virus spread by the fecal-oral route through person-to-person contact. **Aim:** To estimate the prevalence of Hepatitis A IgG antibodies in cases with chronic liver disease (CLD). **Patients and methods:** This cross-sectional investigation has been carried out on 148 cases with CLD. Data has been collected from the gastroenterology and hepatology outpatient clinic of Aswan University Hospital. **Results:** 108(73%) cases were negative for HAV IgG while 40(27%) cases were positive for HAV IgG. A statistically insignificant distinction between the two groups according to pelvi-abdominal ultrasound findings regarding liver cirrhosis ,liver size and focal lesions, splenomegaly, ascites, PV dilation Also, there was no statistically distinction between the two groups as regard ascites, edema, flapping tremors, pallor, jaundice and hepatomegaly, There was statistically significant distinction among both groups according to lab investigation of CLD cases regarding immunity against HAV regarding Hemoglobin, Albumin (g/dl), T. Bilirubin (mg/dl)**. Conclusion:** Seroprevalence of Hepatitis A(IgG) antibodies among cases with CLD varies significantly compared to the general population, Acute HAV infection in these cases could lead to in acute-on-chronic liver failure, which is correlated with poor results , so we recommend Vaccination of chronic liver disease cases who are not immunized against HAV, and these results underscore the importance of considering Hepatitis A vaccination strategies tailored to the needs of cases with CLD, aiming to mitigate the risk of acute hepatitis A infection**.**

INTRODUCTION

Outbreaks are often related to poor sanitation, overcrowding, and food and water pollution. The diagnosis is made by identifying immunoglobulin M antibodies that are directed against Hepatitis A Virus, and treatment is supportive. The primary aspect of prevention is vaccination, which must to be administered prior to exposure whenever it is possible. [1]

Liver failure is a prevalent illness that is correlated with an elevated death rate, and the frequency of this illness is growing as a result of the consumption of alcohol as well as the prevalence of diabetes and obesity. [2] Acute hepatitis or acute liver injury prognosis is influenced by the presence of CLD, including metabolic associated fatty liver disease and

alcoholic liver disease, co-infection with other viruses, and genetic factors that can correlate with severe hepatitis A. Additionally, cirrhosis and extrahepatic diseases like metabolic, malignant, and psychiatric illnesses, along with host factors like advanced age and obesity, play significant roles; however, the etiology of acute insults remains a critical risk factor for the progression to severe liver diseases. HAV infection is a predominant cause of acute hepatitis globally. Hepatitis A virus infection sometimes results in acute liver failure. A superinfection of HAV in cases with chronic HCV infection has been reported to be correlated with fulminant hepatitis, while several studies deny this association. HAV infection rarely results in acute liver failure in the absence of pre-existing chronic liver diseases. [3] Circulating Immunoglobulin M (IgM) antibodies indicate an active infection persisting for up to six months. One to two weeks following the release of IgM antibodies, IgG antibodies appear, providing lifetime immunity against HAV. An elevated concentration of IgG antibodies indicates a prior infection or vaccination. Hepatitis A Virus Immunoglobulin M, HAV genetic diversity, and genotypes may be identified in serum utilizing ELISA testing, PCR sequencing, and phylogenetic analysis, correspondingly. [4]

Hepatitis A is an essential public health issue globally. Hepatitis A vaccine (HepA) has been first licensed in 1992. Inactivated HepA (HepA-I) and live attenuated HepA (HepA-L) are highly immunogenic and well tolerated, with immune protection following vaccination might last for at least twenty years. HepA is efficient for preexposure and postexposure prophylaxis, particularly in kids and young adults. [5] Inactivated HepA is approved for IM delivery in a two-dose regimen, with a variable interval among the 1st and 2nd doses ranging from six months to four to five years, typically six to eighteen months. [6]

The HepA vaccine promotes immunological protection through humoral and cellular mechanisms. The geometric mean concentration (GMC) and seroconversion rate of anti-hepatitis A virus are the most often utilized indicators for assessing the immunogenicity of Hepatitis A. Reference [7]

Liver diseases in Egypt are prevalent, with several documented etiologies, involving parasitic, bacterial, viral, and metabolic causes. The Egyptian population health survey estimated that 2.9% of individuals aged one to fifty-nine exhibit liver diseases. [8]

Cases with CLD lacking HAV antibodies must be administered HAV vaccination. This strategy may decrease morbidity, mortality, and medical costs associated with HAV infection in cases with chronic liver disease. [9]

The objective of this investigation was to assess the occurrence of Hepatitis A IgG antibodies in cases with chronic liver diseases.

PATIENTS AND METHODS

This cross sectional investigation has been carried out on 148 cases with chronic liver diseases. Data has been collected from the gastroenterology and hepatology outpatient clinic of Aswan University Hospital.

Inclusion and exclusion criteria: Any patient with chronic liver disease and above 18 years old eligible for enrolment in this study. The only exclusion criterion is refusal to participate in this study.

Sample size:

Sample size has been calculated utilizing open epi software with confidence level 95%, and confidence limit 5%, the required sample size is 148 cases.

Administrative Design:
Consent has been obtained from cases included in the investigation and approval of ethical committee was obtained as well.
Following data was reported to all patients: Careful medical history, clinical examination and lab investigation: Complete blood count, complete liver function, kidney function test, HAV IgG and Virology (HCV antibody and HBV surface antigen) and ultrasonography
Statistical analysis:
The information gathered has been edited, classified, and tabulated utilizing SPSS (IBM Corporation, IBM SPSS, 2017). Data normality: The Kolmogorov-Smirnov test has been conducted to identify any departures from the normality of the data distribution. Descriptive statistics: Mean (± SD) Standard deviation for parametric numerical data. Median (minimum-maximum) for non-parametric data. percentage and Incidence of non-numerical data. Statistical analysis: The Student's t-test has been utilized to assess the statistical significance of the distinction among the means of two study groups. The Mann-Whitney U test has been utilized to assess the statistical significance of a non-parametric variable distinction among two study groups. The Chi-Square and Fisher's exact tests have been utilized to analyze the association among qualitative variables. The Chi-Square test ($\chi 2$) has been utilized to compare two or more groups. The Fisher Exact Test (FET) has been utilized as a correction for the Chi-Square test when over twenty percent of cells in (2*2) tables had counts below five. The p-value is regarded as significant if it is less than 0.05 at a 95% confidence interval.

RESULTS
The mean ± SD of CLD cases age was 60.46 ± 12.7 with median (range) 62 (17 - 96). There were 62.9% (93). Male and 37.1% (55) female.
Clinical presentation of CLD cases were Ascites, Edema, Splenomegaly, Flapping tremors, Pallor, Jaundice and Hepatomegaly (48.6%, 47.9%, 27.7%, 5.4%, 6.1%, 16.2% and 5.4%).
HAV IgG results among CLD cases were negative in 73% (108) and positive t in 27% (40).
A statistically significant distinction has been observed among studied groups based on lab investigation of CLD cases regarding immunization against HAV regarding Hemoglobin, Albumin (g/dl), T. Bilirubin (mg/dl). A statistically insignificant distinction has been observed among studied groups based on lab investigation of CLD cases regarding immunization against HAV regarding TLC(×109/L), Platelets(×109/L), ALT(U/L), AST(U/L), D. Bilirubin (mg/dl), INR, Creatinine (mg/dl), Urea (mg/dl), Age (years) and Gender **(Table 1)**.
A statistically insignificant distinction has been observed among studied groups based on clinical presentation of CLD cases regarding immunization against HAV regarding ascites, edema, flapping tremors, pallor, jaundice and hepatomegaly **(Table 2).**
A statistically insignificant distinction has been observed among studied groups based on Ultrasound examination of CLD cases regarding immunization against HAV regarding Liver (Enlarged, Cirrhotic and Focal lesions), splenomegaly, ascites and PV dilation **(Table 3).**

Table (1): Lab investigation of CLD cases regarding immunization against HAV

Parameter		CLD (n=148)		p-value
		Positive HAV IgG n=40	Negative HAV IgG n=108	
TLC ($\times 10^9$/L)		5.5 (2.5 - 20)	6 (2- 23)	p=0.93 z=0.08
Platelets ($\times 10^9$/L)		122.5 (56 -450)	185 (32- 444)	p=0.1 z=1.6
Hemoglobin (g/dl)		9.6 (5.7 -14.8)	11 (4.4- 15)	**p=0.03*** z=2.14
ALT (U/L)		36 (12 -665)	44 (12- 975)	p=0.48 z=0.7
AST (U/L)		44 (17 -598)	43.5 (11- 285)	p=0.49 z=0.68
Albumin (g/dl)		2.85 (2 - 4)	3 (1.5- 4)	**p<0.001*** z=0.3.3
T. Bilirubin (mg/dl)		1.7 (0.7-11.6)	1.22 (0.3- 28)	**p=0.004*** z=2.87
D. Bilirubin (mg/dl)		0.7(0.03- 9)	0.7 (0.03- 27)	p=0.24 z=1.18
INR		1.28 ± 0.29	1.19 ± 0.29	p=0.09 t=1.67
Creatinine (mg/dl)		1.0 (0.5 -4)	1 (0.4 -8.3)	p=0.85 z=0.18
Urea (mg/dl)		44 (13- 222)	40 (12- 238)	p=0.66 z=0.43
Age (years)		65 (25- 96)	60 (17- 85)	p=0.055 z=1.92
Gender	**Male** n (%)	20.0 (50%)	73.0 (67.6%)	p=0.05 $\chi 2$=3.8
	Female n (%)	20.0 (50%)	35.0 (32.4%)	

Parameters have been expressed as mean ± SD for normality distributed data, median (range), or frequency (percentage) for qualitative variables. t: Student-t test for normally distributed data, z: Mann-Whitney-U test for non-normally distributed data, *χ2:* Chi-square test, *: Statistically significant (if *p*-value less than 0.05), TLC: Total leukocytes count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalized ratio.

Table (2): Clinical presentation of CLD cases regarding immunization against HAV

Clinical presentation		CLD (n=148)				*p-value*
		Positive HAV IgG n=40		Negative HAV IgG n=108		
		N	%	N	%	
Ascites	Yes	23	57.5%	49	47.5%	*p=0.19* *χ2=1.7*
	No	17	42.5%	59	52.5%	
Edema	yes	24	60%	47	67.5%	*p=0.07* *χ2=3.1*
	No	16	40%	61	32.5%	
Splenomegaly	yes	16	40%	25	30%	***p=0.04**** *χ2=4.1*
	No	24	60%	83	70%	
Flapping tremors	yes	1	2.5%	7	6.5%	*p=0.34* *FET=0.9*
	No	39	97.5%	101	93.5%	
Pallor	yes	3	7.5%	6	5.5%	*p=0.66* *FET=0.19*
	No	37	92.5%	102	94.5%	
Jaundice	yes	9	22.5%	15	13.9%	*p=0.2* *χ2=1.59*
	No	31	77.5%	93	86.1	
Hepatomegaly	yes	4	10%	4	3.7%	*p=0.13* *FET=2.2*
	No	36	90%	104	96.3%	

Data have been expressed as frequency (percentage). Chi-square and Fischer-exact tests have been applied. *: Significant if $p<0.05$, CLD: Chronic liver disease.

Table (3): Ultrasound examination of CLD cases regarding immunization against HAV

US examination			CLD (n=148)				*p-value*
			Positive HAV IgG n=40		Negative HAV IgG n=108		
			n	%	N	%	
Liver	Enlarged	yes	5	12.5%	8	7.4%	*p=0.33* *χ2=0.94*
		No	35	87.5%	100	92.6%	
	Cirrhotic	yes	25	62.5%	50	46.3%	

		No	15	37.5%	58	53.7%	*p=0.07* *χ^2=3.06*
	Focal lesions	**yes**	6	15%	6	5.5%	*p=0.06* *χ^2=2.3*
		No	34	85%	102	94.5%	
Splenomegaly		**yes**	16	40%	36	33.3%	*p=0.45* *χ^2=0.56*
		No	24	60%	72	66.7%	
Ascites		**yes**	23	57.5%	49	45.4%	*p=0.19* *χ^2=1.7*
		No	17	42.5%	59	54.6%	
PV dilation		**yes**	5	12.5%	6	5.5%	*p=0.15* *χ^2=2.4*
		No	35	87.5%	102	94.5%	

Data have been expressed as frequency (percentage), Chi-square test has been applied. CLD: Chronic liver disease.

DISCUSSION

The mean ± SD of CLD cases age was 60.46 ± 12.7 with median (range) 62 (17 - 96). There were 62.9% (93). Male and 37.1% (55) female

Consistent with our investigation, Wong et al. [10] stated that the mean age of the participants was 33.18 ± 10.97 years. The seroprevalence of HAV among cases with chronic Hepatitis C virus was 94.9%. The incidence of anti-HAV elevated with advancing age. However, a statistically insignificant distinction in the HAV positive rate has been observed among age groups (P = 0.242) or other case features.

Giugliano et al. [11] stated that liver disease (hepatitis, cirrhosis): Parenchymal liver disease induces elevated vascular pressure, resulting in increasing spleen size. Hematologic malignancies (leukemias, lymphomas, myeloproliferative diseases) result in neoplastic cell infiltration of the spleen, resulting in splenomegaly.

A statistically insignificant distinction has been observed among studied groups based on ultrasound examination of CLD cases regarding immunization against HAV regarding liver (enlarged, cirrhotic and focal lesions), splenomegaly, ascites and PV dilation.

Jain et al. [12] stated that cases with cirrhosis exhibit significant immunological impairment. They face an elevated possibility of viral and bacterial infections, like HAV.

Acute HAV infection in these cases might lead to acute-on-chronic liver failure, which correlates with poor results.

Sharma et al. [13] demonstrated that ultrasound evaluation is among the most prevalent and cost-effective imaging techniques for chronic liver disease. Ultrasound assesses the size, echogenicity, and nodularity of the liver, facilitating the diagnosis of liver cirrhosis. Additional advantages of ultrasound in CLD involve the measurement of portal vein diameter, which enlarges in portal hypertension, and the evaluation of thrombosis in the hepatic vein (Budd-Chiari) and portal vein in cases of portal vein thrombosis.

HAV IgG results among CLD cases were negative in 73% (108) and positive in 27% (40), these The results may be due to enhanced socioeconomic conditions, increased sanitation, and better hygiene practices, all contributing to the consistent reduction in the frequency of HAV infection.

A statistically insignificant distinction has been observed among studied groups according to lab investigation of CLD cases regarding immunization against HAV.

Helmy et al. [14] demonstrated that just thirty percent of cases with CLD undergo testing for HAV serology in our locality. This signifies that doctors must enhance their awareness of the necessity to screen high-risk populations. Furthermore, HAV serology should be assessed in cases of chronic liver disease exhibiting recent decompensation.

A statistically significant distinction has been observed among studied groups based on lab investigation of CLD cases regarding immunization against HAV regarding Hemoglobin, Albumin (g/dl), T. Bilirubin (mg/dl). A statistically insignificant distinction has been observed studied groups based on lab investigation of CLD cases regarding immunization against HAV regarding TLC(×109/L), Platelets(×109/L), ALT(U/L), AST(U/L), D. Bilirubin (mg/dl), INR, Creatinine (mg/dl), Urea (mg/dl), Age (years) and Gender.

El-Azab et al. [15] stated that CLD is characterized by inflammation and destruction of hepatocytes, resulting in the release of AST and ALT, which accounts for elevated levels of these indicators in the bloodstream. Other indicators, such as ALP and GGT, in liver function tests also seem raised in cholestatic diseases like primary biliary cholangitis (PBC). AST and ALT are often increased two to three times beyond the normal limit; nevertheless, normal values of these markers don't exclude the possibility of cirrhosis.

Sharma et al. [13] demonstrated that bilirubin generation escalates in cases of hemolysis, inefficient erythropoiesis, resorption of large hematomas, and hereditary conjugation abnormalities. The unconjugated bilirubin form in these cases doesn't independently indicate injury to the liver. Disproportionately isolated, unconjugated hyperbilirubinemia accompanied by low serum alkaline phosphatase (ALP) can happen as well in Wilson's illness. Conjugated hyperbilirubinemia usually appears in parenchymal liver disease and biliary obstruction.

In our study the results were 27% anti- hepatitis A virus seropositivity These results were less than the results by **Shoaei et al.** [16] who reported that the anti-hepatitis A virus seropositivity was 93.1% and 93.3% in the subjects in their twenties and thirties and less than the results by **Vasmehjani et al.** [17] showed that Anti-HAV IgG positivity reached 98.5% in a group of 136 chronic liver diseases cases, with a mean age of 39.1 ± 17.6 years. The investigation indicated that the hepatitis A vaccine is unnecessary for adult chronic liver diseases cases.

CONCLUSION

Seroprevalence of Hepatitis A(IgG) antibodies among cases with CLD varies significantly compared to the general population, Acute HAV infection in these cases might lead to acute-on-chronic liver failure, which is correlated with poor results , so we recommend Vaccination of chronic liver disease cases who are not immunized against HAV, and these results underscore the importance of considering Hepatitis A vaccination strategies tailored to the needs of cases with chronic liver diseases, aiming to mitigate the risk of acute hepatitis A infection. Additional research is warranted to explore the long-term immunity and vaccine efficacy in this vulnerable population.

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