Original Article

Association of Hepatitis (B, C & D) Viral Infection to Gallstones in Cirrhosis of Liver

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ABSTRACT

Objective: To observe the association between hepatitis viral (B, C & D) infection to gallstones in liver cirrhosis.
Study Design: A cross-sectional and hospital based study.
Place and Duration of Study: This study was carried out at the Hepatology Clinic of CMC, Larkana during January 2011 to December 2011.
Materials and Methods: 913 patients of cirrhosis of liver presenting at Hepatology Clinic of CMC, Larkana during January 2011 to December 2011 were enrolled for study. After informed written consent, blood samples were drawn for HBsAg, anti – HCV antibodies, and anti-HDV Antibodies by ELISA. Ultrasound of all cases was performed to detect gallstones and study the related radiological features. The data was transferred and analyze using SPSS version 17. Means of numeric response variables and categorical response variables were compared by chi-square test and odd ratios calculated when and where applicable. P value less than 0.05 was taken as statistically significant.
Results: HBsAg, Anti-HCV Ab and Anti-HDV Ab were documented in 272 (42.2%), 253 (39.3%) and 178 (27.6%) patients respectively. HCV co infection with HBV and HDV was documented in 56 (8.7%) and 44 (6.8%). Gallstones were detected in 269 (29.5%) cirrhotic patients, of these 136 (14.9%) were multiple. Statistically significant association was observe between gallstones and HBsAg seropositivity with odd of 2.17 (95% CI: 1.62 – 2.90) and p value less than 0.001. There was no statistically significant association between Anti-HCV Ab and Anti-HDV Ab seropositivity with gallstones in cirrhosis of liver.
Conclusion: HBV infection is documented more frequently in cirrhosis with gallstone. Female were more likely to be infected. HBV infection may be one of the risk factor for development of gallstones in cirrhosis of liver.
Key Words: HBsAg, HDV, HCV, Association, Gallstones.

INTRODUCTION

Worldwide 7% male and 15% females between the ages of 18- 65 years develop gallstones (GS), with overall prevalence of 11%.[1] In Pakistan, 10 – 15% normal healthy population harbours GS, as compared to 23.3 to 31% patients of liver cirrhosis.[2,3,4] The well established risk factors for development of GS are age, sex, obesity, drugs and pregnancy. Recent studies have documented that, liver cirrhosis is also a substantial risk factor for development of gallstones, especially in male.[5,6,7] Gallstones (GS) in cirrhosis are usually asymptomatic and surgery is rarely required but, when surgery is required, these patients carry a higher risk of morbidity than the general population undergoing cholecystectomy.[8]

The pathogenesis of GS in liver cirrhosis may be multifactorial.[9,10] This may be due to high level of estrogen impairing the emptying seen in cirrhosis.[11] Chronic hemolysis secondary to hypersplenism and hyperestrogenism leading to changes in the proportion of biliary lipids, reduction in hepatic synthesis and transport of bile salts and unconjugated bilirubin leading to an impaired binding and polymerization of calcium ions, could in part explain the higher GS frequency in cirrhosis. Gall bladder dysmotility and abnormal contraction due gallbladder wall thickness may encourage GS formation in cirrhosis.[12,13,14]

Another possible explanation of increased GS frequency is persisting infection with viral hepatitis especially HCV. Stroffolini T et al., reported that gallstones were seen in 23.3% anti-HCV positive and 12.4% HBsAg positive patients.[15]HCV can successfully infect gall bladder epithelial cell, it may potentially impair or alter gall bladder mucosal function and contribute to the development of GS.[16] HCV binds to lipoproteins and induce fatty changes of liver. Bile duct damage and hepatic bile duct damage and hepatic steatosis have been cited as histological features of chronic HCV infection both HCV antigens and HCV have been detected in biliary and gallbladder epithelium in patients with chronic HCV infection that correlates with biliary damage and gall stone formation.[17,18,19,20]

Therefore we intend to observe the frequency and association of GS with chronic viral hepatitis in cirrhotic patients. This study will not only inform us regarding the magnitude of disease in cirrhotic patients, but also enable us to understand the association with viral hepatitis.

MATERIALS AND METHODS

Design: A cross-sectional and hospital based study was designed.
Duration: The study duration was one year. Started in January 2011 till December 2011.

Setting: The cases were enrolled from the weekly hepatology clinic and wards of Medicine Department, Chandka Medical College (C.M.C), Larkana at Shaheed Mohtarma Benazir Bhutto Medical University.

Sampling Technique: Purposive sampling.

Inclusion Criteria:

- All known diagnosed cases of cirrhosis of liver presenting to hepatology clinic and wards of medicine.
- Of either gender.

Exclusion Criteria:

- Patients younger than 15 years and older than 75 years.
- Patients receiving antiviral injectable or oral therapy for hepatitis B, C or D.
- Patients suffering from congenital or familial biliary or hepatic disorders.
- Uses of oral contraceptives,
- Drugs like ceftriaxone, octeriotide, somatostatin and clofibrate.
- History of multiple pregnancies.
- Obesity.
- Suffering from chronic hemolytic disorders.
- Diabetes mellitus.

Data Collection: Informed written consent was taken from patients meeting our selection criteria. Detailed clinical examination was conducted to document ascites, hepatic encephalopathy and spleenic status. Spleen was labeled was labeled to be enlarged if it was clinically palpable or pecussable. Blood samples were drawn and sent to central laboratory C.M.C Larkana for detection of viral serology and biochemical indices as HBsAg, Hepatitis C Virus antibodies (Anti-HCV Ab) and Hepatitis D Virus antibodies (anti-HDV Ab) on 3rd generation ELISA, serum bilirubin, serum albumin and international normalized ratio (INR). LFTs were performed by Slectra – E Merck (Germany) auto-analyzing machine.

Abdominal ultrasound (US) of all selected patients were done for gallstones, spleen size, liver parechymal change, portal vein (PV) size, common bile duct (CBD) diameter and gall bladder wall thickness. Ultrasonological examination was done by a senior radiologist with more than 10 years experience, at the Radiology Department C.M.C Teaching Hospital. Toshiba SSA-70 U/S machine was used to carry out U/S examination. A separate Performa was filled for each case entered into the study to record the data of these investigations and demography. All investigations were performed at the laboratory of CMC teaching hospital.

Data Analysis: The collected data was transferred to and analyzed using SPSS version 17. Numeric response variables as age, portal vein diameter, common bile duct diameter and gall bladder wall thickness and categorical response variables such as age (15 – 24 years, 25 – 34 years, 35 – 44 years, 45 – 54 years, 55 – 64 years, 65 – 74 years), gender (male, female), portal vein diameter (normal < 12 mm, dilated > 12mm), common bile duct diameter (CBDD < 4 mms, CBDD > 4 mms), gall bladder wall thickness (GBWT < 6cms, GBWT > 6 cms), gall stones (none, solitary, multiple), splenomegaly (none, mild, moderate, massive) ascites (present, absent) and CTP classes (A, B, C) were compared in gall stones positive and negative cases by Chi-square test. Odd ratios (OR) and 95% Confidence Interval (CI) were calculated to assess the association of variables and viral hepatitis with presence of gallstones in cirrhotic patients. Probability value (p-value) of less than 0.05 (<0.05) was considered to be statistically significant.

RESULTS

A total of 913 cases of liver cirrhosis were enrolled in our study during the specified period with mean age of 43.92 ± 16.24 years. Majority (n = 646, 70.8%) were male. HBsAg, Anti-HCV Ab and Anti-HDV Ab were documented in 272 (42.2%), 253 (39.3%) and 178 (27.6%) patients respectively. Co-infection of HCV with HDV and HBV with HCV was documented in 44 (6.8%) and 56 (8.7%) as shown in table 1. Gallstones were detected in 269 (29.5%) cirrhotic patients, of these 136 (14.9%) were multiple. Gall bladder wall was thickened in 286 (31.3%) patients of liver cirrhosis. (Table 2)

Table No. 1: Baseline Characteristics of 913 CLD Patients

Characteristics	Number	Percentage
AGE		
Mean ± SD	43.92 ± 16.24 years	
Range (Max – Min)	59 (74 – 15)	
GENDER		
Male	646	70.8%
Female	267	29.2%
AGE CATEGORIES		
15 – 24 years	121	13.3%
25 – 34 years	116	12.7%
35 – 44 years	250	27.4%
45 – 54 years	139	15.2%
55 – 64 years	153	16.8%
65 – 74 years	134	14.7%
CHILD TURCOT PUGH (CTP) CLASS		
CTP CLASS A	242	26.5%
CTP CLASS B	287	31.4%
CTP CLASS C	384	42.1 %
VIRAL HEPATITIS SEROLOGY		
HBV	272	42.2%
HCV	253	39.3%
HDV	178	27.6%
HBV & HCV	56	8.7%
HCV & HDV	44	6.8%

Table No. 2: Radiological Features of 913 CLD Patients

Characteristics	Number	Percentage
SPLEENOMEGALY		
Mild	533	58.4%
Moderate	189	20.7%
Massive	78	8.5%
None	113	12.4%
ASCITIES		
Present	700	76.7%
Absent	213	23.3%
GALLSTONES		
Absent	644	70.5%
Present	269	29.5%
Solitary	133	14.6%
PORTAL VEIN DIAMETER		
Mean ± SD	13.91+2.52mm	
Normal	236	25.8%
Dilated	677	74.2%
GALL BLADDER WALL THICKNESS (GBWT)		
Mean ± SD	5.45+2.11mm	
GBWT > 6 mm	286	31.3%
GBWT ≤ 6 mm	627	68.7%
COMMON BILE DUCT DIAMETER (CBDD)		
Mean ± SD	4.18+0.72	
CBDD > 4 mm	291	31.9%
CBDD ≤ 4 mm	622	68.1%

Patients having gallstones were older than those having no gallstones, with mean age of 49.92 ± 17.35 years as compared to 41.42 ± 15.08 years. Female were more likely to have gallstones with p value < 0.002. Gallstones were more frequently detected in patients aging 65 – 74 years (p < 0.001) with odds of 3.43 (95% CI: 2.35 – 4.99). Patients with gallstones were more likely to have advanced liver disease and were more likely to be in CTP class C (p < 0.001) with odds of 5.17 (95% CI: 3.79 – 7.04) as mentioned in table 3. Patients with gallstones had statistically significant thickened gall bladder wall (p < 0.001) with odds of 4.48 (95% CI: 3.30 – 6.08). (Table 4)

Statistically significant association was observe between gallstones and HBsAg seropositivity with odd of 2.17 (95% CI: 1.62 – 2.90) and p value less than 0.001. The association was also statistically significant for HBV co-infection with HDV and HCV. There was no statistically significant association between Anti-HCV Ab and Anti-HDV Ab co-infection with Anti-HCV Ab seropositivity with gallstones in cirrhosis of liver as tabulated in table 5.

DISCUSSION

Gallstones (GS) is a common problem and is commonly attributed to "4F" (Female, Forty, Fertile, and Fatty). Our study bring light to an other "F", that is Fibrosis (liver fibrosis / cirrhosis). Our study documented that high percent of patients of liver cirrhosism had gallstones. GS were more frequently seen with aging and detoriating hepatic function. Besides, females were more likely to have stones than males. When we evaluated the serology of patients, it was noted that no statistically significant association was documented between GS and HCV. But the association was significant for HBV, whether it was present in isolation or with HCV and HDV.

Table No. 3: Comparison of Baseline Characteristics of CLD Patients with and without Gall Stones

CHARACTER	GALLSTONES (N = 269)	NO GALLSTONES (N = 644)	P value*	ODD RATIOS OR (95%CI)
AGE				
Mean ± SD	49.92 ± 17.35	41.42 ± 15.08	< 0.001**	NA
GENDER				
MALE	171 (63.6%)	475 (73.8%)	< 0.002**	0.62 (0.45 – 0.84)
FEMALE	98 (36.4%)	169 (26.2%)		
AGE CATEGORIES				
15 – 24 years	31 (11.5%)	90 (14.0%)	< 0.319	0.80 (0.51 – 1.23)
25 – 34 years	18 (6.70%)	98 (15.2%)	< 0.001**	0.40 (0.23 – 0.67)
35 – 44 years	62 (23.0%)	188 (29.2%)	< 0.058	0.72 (0.52 – 1.01)
45 – 54 years	35 (13.0%)	104 (16.1%)	< 0.229	0.77 (0.51 – 1.17)
55 – 64 years	51 (19.0%)	102 (15.8%)	< 0.250	1.24 (0.85 – 1.80)
65 – 74 years	72 (26.8%)	62 (9.60%)	< 0.001**	3.43 (2.35 – 4.99)+
CHILD TURCOT PUGH (CTP) CLASS				
CTP CLASS A	28 (10.4%)	214 (33.2%)	< 0.001**	1.38 (1.28 – 1.48)+
CTP CLASS B	54 (20.1%)	233 (36.2%)	< 0.001**	1.23 (1.14 – 1.33)+
CTP CLASS C	187 (69.5%)	197 (30.6%)	< 0.001**	5.17 (3.79 – 7.04)+

*Chi – square test (2 - sided significance). ** Statistically Significant p values (p < 0.05).
+ Statistically significant high odd ratios. NA (Not Applicable)

Table No. 4: Radiological Comparison of CLD Patients with and without Gallstones

CHARACTER	GALLSTONES (N = 269)	NO GALLSTONES (N = 644)	P value*	ODD RATIOS OR (95%CI)
SPLEENOMEGALY				
YES	218 (81.0%)	582 (90.4%)	< 0.001**	1.32 (1.11 – 1.57)
NO	51 (19.0%)	62 (9.60%)		
ASCITES				
PRESENT	221 (82.2%)	479 (74.4%)	< 0.011**	1.58 (1.10 – 2.27)+
ABSENT	48 (17.8%)	165 (25.6%)		
GALLSTONES				
SOLITARY	133 (49.4%)	0 (0.00%)	< 0.001**	5.73 (4.92 – 6.68)+
MULTIPLE	136 (50.6%)	0 (0.00%)	< 0.001**	5.84 (5.00 – 6.82)+
PORTAL VEIN				
Mean ± SD	14.33 ± 2.79 mm	13.73 ± 2.38 mm	< 0.519	NA
NORMAL	67 (24.9%)	169 (26.2%)	< 0.674	0.93 (0.67 – 1.29)
DILATED	202 (75.1%)	475 (73.8%)		
GALL BLADDER WALL THICKNESS (GBWT)				
Mean ± SD	6.87 ± 2.00 mm	4.86 ± 1.85 mm	< 0.001**	NA
GBWT > 6 mm	148 (55.0%)	138 (21.4%)	< 0.001**	4.48 (3.30 – 6.08)+
GBWT ≤ 6 mm	121 (45.0%)	506 (78.6%)		
COMMON BILE DUCT DIAMETER (CBDD)				
Mean ± SD	4.16 ± 0.63 mm	4.19 ± 0.75 mm	< 0.856	NA
CBDD > 4 mm	81 (30.1%)	210 (32.6%)	< 0.460	0.89 (0.65 – 1.21)
CBDD ≤ 4 mm	188 (69.9%)	434 (67.4%)		

*Chi – square test (2 - sided significance). ** Statistically Significant p values (p < 0.05).
+ Statistically significant high odd ratios. NA (Not Applicable)

Table No. 5: Association of Viral Hepatitis (B, C & D) Infection with Gallstone in 913 Patients of CLD

VIRUS	GALLSTONE	NO GALLSTONE	P VALUE*	ODD RATIOS
HBV	165 (61.3%)	272 (42.2%)	<0.001**	2.17 (1.62 – 2.90)
HCV	77 (28.6%)	178 (27.6%)	< 0.762	1.05 (0.76 – 1.44)
HDV	143 (53.2%)	253 (39.3%)	<0.001**	1.75 (1.31 – 2.33)+
HBV& HCV	42 (15.6%)	56 (8.70%)	<0.002**	1.94 (1.26 – 2.98)+
HCV & HDV	27 (10.0%)	44 (6.80%)	<0.099	1.52 (0.92 – 2.51)

*Chi – square test (2 - sided significance). ** Statistically Significant p values (p < 0.05).
+ Statistically significant high odd ratios

GS in liver cirrhosis occur due to multiple adverse factors. In non cirrhotic fertile females, increase secretion of cholesterol in bile under the influence of estrogen, percipitate GS formation. In liver cirrhosis, there is decreased clearance of estrogen due to hepatic insufficiency, which may produce a state of hyperestrogenemia and pecipitate GS formation.[21] Another, possible explanation can be increased gall bladder wall thickness induced decreased contractility of gall bladder. This may be due to hypoalbuminemia secondary to hepatic insufficiency, resulting in decreased oncotic pressure and increased venous hydrostatic pressure. These factors lead to edematous, thickened and non contractile gallbladder, that promote nucleation of GS.[22]

Another possible explanation can be, subclinical autonomic neuropathy resulting in gallblaber dysmotility, as described by Chawla and his colleages.[23] When gallbladder contraction in response to fatty meals is assessed by ultrasonograpy, there is poor contraction in cirrhotic patients. This response (contractility) further detoriates with worsening liver function. [24,25]

Conte D etal., (Italy, 1999), studied the relation between cirrhosis and gallstones. GS were documented in 29.5%. Declining hepatic function and increasing age were strongly associated with GS development. But, there was no role documented for gender and underlying cause of cirrhosis in GS formation. Coelho JCU et al., (Brazil, 2010), documented GS in 24% of patients undergoing transplantation. GS were present independent of age and sex. [26, 13]

CONCLUSIONS

Based on our study and international literature, it can be concluded that,

⇒ Liver cirrhosis is a strong risk factor for development of gall bladder stones. Though the pathogenesis is multifactorial, but GS increases with detoriating liver function.

⇒ We documented strong relation of GS with aging and female gender, but this matter is internationally controversial.

⇒ HBV seropositivity in isolation or co infection with HCV or HDV is strongly related to GS development in cirrhosis.

Recommendations

- Since there is no curative therapy available for HBV eradication, so role of nucleoside / nucleotide inhibitors should be evaluated in context to suppressing HBV proliferation and decreasing the risk of GS formation.
- Large scale multicentre and randamized controlled trials are need of time to reinforce or refuse the findings of our study.

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