Section: Gastroenterology

Original Research

PREVALENCE OF CELIAC DISEASE IN PATIENTS OF LIVER CIRRHOSIS: A CROSS SECTIONAL SINGLE CENTRE STUDY

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Abstract

Background: Celiac disease(CD) is an autoimmune phenomenon and association of celiac disease with other autoimmune disease is well known. However, data were still insufficient and only a few studies had been done on the evaluation of celiac disease in patients already with liver cirrhosis. **Objective**: To determine the prevalence of celiac disease in patients with liver cirrhosis. **Materials and Methods:** This observational study was undertaken among patients who were attending OPD or admitted in the Department of Gastroenterology and Hepatology, Motilal Nehru Medical College, Prayagraj. A total of 134 patients who met the inclusion criteria were included in the study and cases were selected randomly. **Result:** This study of assessment of celiac disease in patients with liver cirrhosis was conducted on 134 patients with liver cirrhosis out of these studied, 50.8% patients were in between 31-50 years. Mean age was 42.8 +/- 17.19. Out of 134 patients only 18 (13.4 %) had raised serum levels of anti tTGIgA,out of which 4 had biopsy proven celiac disease and rest had asymptomatic rise in the level. In the patients with asymptomatic rise in anti tTG IgA none had levels more than 30. Biopsy was normal in 124 patients 6 had minimal changes in duodenal mucosa i.e non-specific duodenitis and only 4 patients had marsh grade 3 biopsy abnormalities. **Conclusion:** Our study shows that CD is at least twice more common in cirrhotic patients than in the general population. Screening for CD is warranted during the evaluation of patients with cirrhosis. Our study confirms prior findings that high titers of anti tTG levels can be diagnostic of CD in the absence of a SB biopsy in patients with cirrhosis.

INTRODUCTION

Liver cirrhosis is a pathologically defined entity that reflects irreversible chronic injury of the hepatic parenchyma in association with extensive fibrosis. Damage causes tissue repair and subsequent formation of scar tissue, which over time can replace normal functioning tissue leading to the impaired liver function of cirrhosis. Typically, the disease develops slowly over months or years.[1] Early in the course of disease, there are often no symptoms but various symptoms develops slowly over time. Early symptoms may include tiredness, weakness, loss of appetite, unexplained weight loss, nausea and sickness, and abdominal discomfort. With declining liver function, other signs and symptoms may develop such as cognitive impairments, confusion, memory loss, sleep disorders, and changes in personality. Further decline may result in buildup of fluid in the lower legs and feet, severe bloating of the abdomen from a fluid build-up known as ascites, jaundice, itchyskin.2 Some of these symptoms may be secondary to subsequent portal hypertension Cirrhosis is most commonly caused by alcohol, hepatitis B, hepatitis Cand non-alcoholic fatty liver disease.[1,2]

In medicine, Child-Pugh score (sometimes the Child-Turcotte-Pugh score) is used to assess the prognosis of chronic liver disease. The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5-15. Child-Pugh class is either A (a score of 5-6), B (7-9), or C (10 or above). Decompensation indicates cirrhosis with a Child-Pugh score of 7 or more (Class B). This level has been the accepted criterion for listing for liver transplantation.[3]

Celiac disease is a long-term immune disorder that primarily affects the small intestine. Classic symptoms include gastrointestinal problems like

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chronic diarrhea, abdominal distention, malabsorption, loss of appetite and among children failure to grow normally. Non-classic symptoms are more common, especially in people older than two years.[4,5] There may be mild or no gastrointestinal symptoms, a wide number of symptoms involving any part of the body or no obvious symptoms. Celiac disease occurs in people who are genetically predisposed. Upon exposure to gluten, an abnormal immune response may lead to the production of several different autoantibodies that can affect a number of different organs.[6,7]In the small bowel, this causes an inflammatory reaction and may produce shortening of the villi the small intestine (villous atrophy). Celiac disease affects the mucosa of the small intestine; the submucosa, muscularispropria and serosa usually are not involved. The mucosal lesion can vary considerably in severity and inextent.[8]

After excluding other causes of liver disease and because of the high prevalence of liver disorders in CD, the levels of liver enzymes should be evaluated in all patients at the time of diagnosing CD.[9] However data were still insufficient and only a few studies had been done on the evaluation of celiac disease in patients already with liver cirrhosis. So, we were performed an observational study to determine the prevalence of celiac disease in patients with liver cirrhosis.

MATERIALS AND METHODS

This observational study was undertaken in the Department of Gastroenterology and Hepatology, Motilal Nehru Medical College,Prayagraj between august 2020 and august 2021. Ethical clearance was taken from institutional Ethical committee.

Sample size: A total of 134 patients who met the inclusion criteria were included in the study. Cases were selected randomly.

Inclusion Criteria

a) Patients who were known cases of liver cirrhosis.
b) Patients given informed consent for the study.

Exclusion Criteria

a) Patients with inflammatory bowel disease, inflammatory arthritis, severe coagulopathy or active upper GI bleed.
b) Pregnant women.
c) Patients already on gluten free diet.
d) Patients with known bleeding disorder.
e) Patients not given consent for the study.

All patients who fulfilled the inclusion criteria were considered for the study. Patients particular were noted and detailed history was taken. A complete general physical examination and detailed systemic examination carried out in all the patients.

Blood has been drawn from median cubital vein of right upper limb following sterile precautions and sent for relevant investigations like complete blood count, liver function test, HBsAg, HCV antibody, serum calcium, phosphorus, prothrombin time and INR. Ultrasound abdomen and Fibroscanhad also been performed in selected patients

Cirrhosis was diagnosed by clinical, biochemical, histological or imaging studies.

All the patients with liver cirrhosis were further evaluated for celiac disease. IgA anti tTG and total IgA was sent in laboratory and upper GI endoscopy was done. While doing so duodenal characteristics was noted carefully and biopsies from D1 and D2 part of duodenum were taken.

Biopsy samples were placed on filter paper with proper alignment and thenwere placed in vials containing 10% of buffered formalin solution for fixation and sent for further processing and histopathological evaluation.

3-4 □m section taken and stained with hematoxylin and eosin. After which sectioned were examined in 10x and 40x and characteristics were noted down.

Other Laboratory Investigations

- Prothrombin Time, INR
- Kidney Function Test
- USG Abdomen was done for detection of ascites and for assessment of the portal hypertension
- UGIE was done to assess esophageal varices and for taking duodenal biopsies
- Fibroscan- In Selected patients

Statistical Analysis

Results on continuous measurements were presented on mean □ SD and results on categorical measurements were presented in number (%). The statistical software named SPSS version 25.0 was used for the analysis of the data and Microsoft word and Excel had been used to generate graphs, tables etc.

RESULT

Out of 134 patients studied, 50.8% patients were in between 31-50 years. Mean age was 42.8 +/- 17.19. Table 2 depicts male predominance (66.4%) as compared to females (33.6%). Overall alcohol (36.5%) was the most common etiology followed by HBV related cirrhosis (24.6%). All of the patients with alcoholic cirrhosis were male except one. Females predominated males in autoimmune and HBV etiology. Among patients with cryptogenic cirrhosis 63.6% were males as compared to females 36.3%. Wilson disease was etiology in 3 patients out of which 2 were male and 1 was female [Table 1].

Table 1: Etiology

	Alcohol	HBV	HCV	Autoimmune	Cryptogenic	EHPVO	Wilson	Total
Males	48	16	8	3	7	7	2	89
Female	1	17	7	10	4	3	1	45

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Total	49 (36.5%)	33 (24)	15 (11.2%)	13 (9.7%)	11 (8.2%)	10 (7.4%)	3 (2.2%)	134

Albumin was normal in 6.7% of patients. 54.5 % of the patients had albumin level < 2.8 % showing severe malnutrition.
15 (11.2%) patients were of CTP class A, 83 (61.9%) patients were of class B and 36 (26.8%) patients were of class C [Table 2].

Table 2: Evaluation of Child- Pugh Class

Gender	Number of patients	Percentage (%)
A	15	11.2%
B	83	61.9%
C	36	26.8%
Total	134	100%

All the admitted patients underwent upper GI endoscopy. 23.1% had no esophageal varices. 32.8% had grade 1, 26.9% had grade 2 and 17.1% had grade 3 varices[able 3].

Table 3: Upper GI endoscopy

UGIE	Number of patients	Percentage(%)
Normal	31	23.1%
Grade-1 EVx	44	32.8%
Grade-2 EVx	36	26.9%
Grade-3 EVx	23	17.1%
Total	134	100%

Out of 134 patients only 18 (13.4 %) had raised serum levels of anti tTG IgA. Out of which 4 had biopsy proven celiac disease and rest had asymptomatic rise in the level. In the patients with asymptomatic rise in anti tTG IgA none had levels more than 30 [Table 4].

Table 4: Evaluation of Anti tTG IgA

Anti tTG IgA (Value)	Number of patients	Percentage (%)
<20	116	86.5%
>20	18	13.43%
Total	134	100%

Cause of cirrhosis could not be found in most of the patients with positive celiac serology. However, all of the patients with asymptomatic rise in serology had normal duodenal biopsy [Table 5].

Table 5: Profile of the patients with positive celiac serology

Etiology	Number of Patients	Percentage (%)
Alcohol	4	22.2%
Autoimmune	2	11.1%
Cryptogenic	7	38.9%
EHPVO	3	16.7%
HBV	1	5.5%
HCV	1	5.5%

Biopsy was normal in 124 patients. 6 had minimal changes in duodenal mucosa i.e non-specific duodenitis and only 4 patients had marsh grade 3 biopsy abnormalities[Table 6].

Table 6: Characteristics of the patients with Celiac disease

Patient	1	2	3	4
Gender	F	M	F	F
Age	10	50	14	16
Etiology	Cryptogenic	Cryptogenic	Autoimmune	EHPVO
ALT	128	32	68	43
Bilirubin	4.8	1	6.8	0.4
Albumin	2.8	3.4	3.3	3.7
UGIE	Gr1EVx	Grade 1 EVx	Grade 2 EVx	Grade 2 EVx
CTP Score	11	8	9	6
Total IgA	326	146	406	240
Anti t TG IgA	114	39	116	58
Marsh. Stage	3	3	3	3

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DISCUSSION

In this study the maximum prevalence of cirrhosis was observed in the age group of 31-40 and 41-50 years (each constituted 25.4 %) with mean age being 42.8 years. Mukherjee et al10 in their multicentric study in India also found that the mean age of diagnosing cirrhosis was 42.8 +/- 14.4 years.

On assessing the gender distribution amongst patients with liver cirrhosis we found that male predominance was present overall when compared with females (66.4% Vs 33.6%). This goes in accordance with the multicentric study conducted by Mukherjee et al10 in which male predominance was observed with 78.6% being male. Sharma et al11also found male predominance with a male to female ratio of 2.3:1.

In our study the most common etiology of liver cirrhosis was found to be alcohol. Alcohol was the etiology of cirrhosis in 36.6% patients followed by HBV (24.6%) and HCV (11.1%). Above result is in accordance with the study conducted by Mukherjee et al.[10] where alcohol was the most common cause of liver cirrhosis (34.3%).HBV was the most common cause of non-cirrhotic CLD in the same study. Similarly Sharma et al.[11] found alcohol as the most common etiology of cirrhosis in 62.9% followed by HBV. Solanki et al.[12] found alcohol as an important cause of cirrhosis in 34.5%.

In this study all except one patient with alcoholic cirrhosis were male (97.9%). In HBV (51.5%) and autoimmune cirrhosis (76.9%), females were affected more than males. Our findings were consistent with those of Mukherjee et al.[10] and Sharma et al.[11] which showed that males accounted 98.4% and 94.6% respectively as a cause of alcohol related cirrhosis. Wilson was the cause of cirrhosis in 3 (2.2%) patients out of which 2 were male and 1 was female.

Esophageal varices were present in 76.9 % patients in our study. Rest of the patients had normal UGIE. Grade 1 varices was present in 32.8%, Gr 2 in 26.9% and Gr 3 in 17.1%.In a study done by Achinge et al.[13] in 2011,75 % of the cirrhotics had esophageal varices which was similar to our findings. Zainab et al.[14] also shown that 70.5 % of cirrhotics had esophageal varices however the prevalence of gr 2 varices was highest (35.5%)in contrary to our study in which prevalence of gr1 varices was highest.

This study also showed that in hospitalized patients with cirrhosis prevalence of patients with CTP-B(61.9%) was highest followed by CTP-C(26.8%) and CTP-A (11.2%). Zainab et al14found in their study that frequency of patients with CTP-A scores was 44.5%, CTP-B scores 35.5% and CTP-C scores 20%. Differences in this frequency may be due to the fact that in the covid era patients with early cirrhosis or with less severe disease did not visited hospital or could not be admitted in the ward and managed on OPD basis only.

AjitSoodet al.[15] in study found positivity rate of celiac serology ranging from 3% to 27% in different disease conditions(27% in iron deficiency anaemia and 3% in generalised epilepsy, 12% in infertile females). However, in their study celiac disease was present in 4% patients only. Vecchiet al.[16]concluded in their study that, the rate of positive anti-tTG was 17.1% in all liver disease patients and 31.6% in cirrhotics. And also the high prevalence of positive results among cirrhotic patients was associated with more advanced liver disease.

Danilo Villalta.[17]conducted study over 54 cirrhotic patients and found positivity rate of anti tTG IgA level ranging from 0% to 33% And that of IgG from 0% to11% depending upon methods used.Although more recently introduced methods which use nh-tTG or rh-tTG as antigen have demonstrated greater specificity than methods using gp-tTG.The largest number of false positives was found with methods that used tTG in association with gliadin peptides as antigen substrate. A significant association was found between IgA anti-tTG antibodies and serum immunoglobulin concentration.

Various studies including study done by Cunningham et al has shown the prevalence of selective IgA deficiency with a frequency of 1:400 in healthy population.[18] and 2.6% of patients with CD.[21]However, in our study none of the patients has found to be IgA deficient. This may be due to small sample size in our study.

Diagnosis of celiac disease is based on characteristic Marsh 3 duodenal biopsy and raised IgA anti tTG level. Its frequency in the general population is in the range of 0.7 to 1%20. Albeit it remains under diagnosed in many geographical areas. In our study, we found that CD affects 2.9 % of cirrhotic patients. In our study 92.5% patients had normal duodenal biopsy and 4.5% patients had presence of a few lymphocytes in the biopsied tissue ie- nonspecific duodenitis.None of the patients with Marsh 3 biopsy had normal celiac serology.

Wakimet al.[21]studied 204 cirrhotic patients. In the study total 8 patients (3.9%) had marsh 1 findings in their biopsy and 5 patients with marsh 3 biopsy. This finding is in concordance with our study in which 4.5 % had non-specific duodenitis.

According to Marjorie et al.[22] non-specific duodenitis is present in 5.4% of the general population diagnosed by > 25 IELs/ 100 ECs. This study also concluded that prevalence of non-specific duodenitis in seronegative subjects is 3.8%.

CONCLUSION

Our study shows that CD is at least twice more common in cirrhotic patients than in the general population. Screening for CD is warranted during the evaluation of patients with cirrhosis. Our study confirms prior findings that high titers of anti tTG

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levels can be diagnostic of CD in the absence of a SB biopsy in patients with cirrhosis.

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