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ORIGINAL ARTICLE

Prevalence of celiac disease among pediatric patients with cryptogenic cirrhosis and effect of gluten-free-diet

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Abstract

Background Liver involvement in celiac disease (CD) is classified into autoimmune and cryptogenic. The association between CD and autoimmune liver diseases like autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis is well-established; however, the data on patients with cryptogenic cirrhosis, particularly from India, are scanty. So we did this study to find the prevalence of CD in patients with cryptogenic cirrhosis.

Methods This was a prospective observational study, involving children of less than 18 years old attending Pediatric and Gastroenterology clinic with a diagnosis of cryptogenic cirrhosis. The patients were evaluated for CD and divided into two groups: chronic liver disease (CLD) with CD, and CLD without CD. Both the groups were followed up for 6 months. CLD with CD group was treated with gluten-free-diet (GFD) and CLD without CD group was followed up without any specific intervention except standard care of CLD.

Results Out of 84 patients, 11 (13.1%) were diagnosed as CLD with CD. There was an improvement in hemoglobin levels, liver function tests, and Child-Pugh score after initiation of GFD in CLD with CD group.

Conclusion The prevalence of CD in cryptogenic cirrhosis was 13.1%. Screening for CD is recommended for cryptogenic cirrhosis. Hepatic functions improve with a GFD in CD patients with cirrhosis.

Keywords Celiac disease · Child-Pugh score · Cryptogenic cirrhosis · Gluten-free-diet

Introduction

Celiac disease (CD), also known as gluten-sensitive enteropathy or celiac sprue, is defined as a permanent intolerance to ingested gluten (the storage protein components of wheat, barley, rye, and oat). The intolerance to gluten results in immune-mediated damage to the mucosa of the small intestine characteristically inducing villous atrophy and crypt hyperplasia that usually resolve with the removal of gluten from the diet [1]. The prevalence of CD in northern India is 0.3% to 1.04% [2, 3]. Although CD is defined by the small intestine injury and resulting malabsorption, more recently, it has been recognized to be a multisystem disorder that may affect other organs such as the nervous system, bones, skin, heart, and the liver [4–6]. The clinical presentation of CD can vary from a classical malabsorption syndrome to more subtle atypical gastrointestinal (GI) manifestations or extraintestinal presentations like growth retardation, infertility, osteoporosis, iron deficiency anemia, and liver dysfunction [1, 7].

Liver involvement in CD has a wide spectrum of manifestations varying from an asymptomatic isolated elevation of hepatic transaminases to severe liver insults like the acute liver failure, chronic liver disease (CLD), and even end-stage liver disease [8]. Such different types of liver injuries may represent a spectrum of the same disorder, where host factors such as genetic predisposition and environmental factors like duration of exposure to gluten may collectively influence the severity of liver damage and the final outcome. Although the spectrum of liver abnormalities associated with CD is very wide, two main forms of liver damage, namely, cryptogenic and

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autoimmune, appear to be particularly related to gluten-sensitive enteropathy [9]. The cryptogenic liver damage is more frequent; it is typically asymptomatic and is characterized by mild elevation in serum transaminase levels. It is not associated with auto-antibodies other than CD auto-antibodies [10].

The association between CD and autoimmune liver diseases like autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis is a well-established fact; however, the data on patients with cryptogenic cirrhosis, particularly from India, are scanty. So we did this study to find the prevalence of CD in patients with cryptogenic cirrhosis.

Methods

This study was a prospective observational study, involving children of less than 18 years old attending Pediatric and Gastroenterology clinic with a diagnosis of CLD recruited from January 2015 to December 2017. Informed written consent was taken from the parents/guardian of all the patients. Detailed history, thorough clinical examination, slit lamp examination of the eye and relevant laboratory investigations were recorded in a preset proforma. Diagnosis of CLD was based on the demonstration of splenomegaly, ascites, and other signs of portal hypertension clinically and/or abdominal ultrasonography, presence of varices in upper gastrointestinal endoscopy (UGIE) together with the presence of at least one of the following four features: hypoalbuminemia (serum albumin < 3.0 g/dL) with reversal of albumin: globulin ratio, persistent elevation of prothrombin time (PT) (> 5 s above control), which was not corrected by parenteral vitamin K administration, one or more episodes of hepatic encephalopathy, and presence of clinical stigmata of CLD. The esophageal varices were classified according to Paquet's classification and the gastric varices were classified according to Sarin's classification [11]. All the patients underwent the following etiological evaluation: ultrasound of the abdomen with portal and hepatic vein doppler study, serum hepatitis B surface antigen (HBsAg), anti-hepatitis C (HCV) antibody, auto-antibodies (antinucelar antibody [ANA], anti-smooth muscle antibody [ASMA], anti-liver kidney microsomal [LKM] antibody), serum ceruloplasmin, iron studies, and α_1-antitrypsin levels. After excluding all the known causes of liver disease, a diagnosis of cryptogenic CLD was made and further evaluation for CD undertaken.

All the patients were inquired and examined for the intestinal and extraintestinal manifestation of the CD. They were further evaluated by IgA anti-tTG antibody test and UGIE along with the duodenal biopsy. Antibody testing was done in private laboratories due to unavailability of the test in our institution. Multiple biopsies were taken from the second part of the duodenum. Biopsies were analyzed by the two histopathologists for CD changes. The modified Marsh grading system was used to grade the histopathology changes [12]. As per Oslo definitions, patients with positive tTG antibody test and duodenal biopsy showing raised intraepithelial lymphocytes with or without architectural changes were diagnosed as CD [13].

Patients diagnosed to have CLD with CD were considered as cases and those with CLD but no CD were considered as controls. Both the groups were then followed up for next 6 months. Patients in CLD with CD group were treated with strict gluten-free-diet (GFD) for 6 months and effect of GFD was studied on clinical as well as laboratory parameters, whereas patients in CLD without CD group were followed up without any specific intervention except for standard care of CLD. The parameters evaluated during follow up included the Child-Pugh score (CPS), which is a prognostic indicator of the severity of CLD [14]. The study protocol was approved by the institutional ethical committee.

Statistical analysis

Data were analyzed by SSPS version 17 statistical software. Before comparing the groups studied, each variable was tested for normality distribution. The discrete variables were presented as percentages along with their 95% confidence intervals. These variables were analyzed using the chi-square test and Fisher's extract test, whichever was appropriate. The continuous variables were analyzed using unpaired t test. The p-values of < 0.05 were considered as significant.

Results

Total of 84 cases was enrolled in this study. Out of 84 cases 11 (13.1%) were diagnosed to have CD. Mean age at the time of presentation was 9.8 years (SD: 3.6 years) in CLD with CD group and 8.1 years (SD: 3.3 years) in CLD without CD group. The prevalence of cryptogenic CLD was higher in males as compared to females with the male to female ratio of being 2.5:1. In CLD with CD group, 27.2% of cases were found to have a history of CD in one or more family members, which was statistically higher in comparison to the group of patients with CLD without CD, none of whom had family history of CD. On comparing the liver function tests between two groups, the mean values of aspartate aminotransferase (AST), and alanine aminotransferase (ALT), alkaline phosphatase and direct bilirubin were higher in CLD with CD group (Table 1). The mean value of serum albumin improved and mean PT decreased after 6 months of GFD among patients with CLD with CD (Table 2).

Anti-tTg antibody

Anti-tTg antibody testing was positive in 16 patients and among them, 11 patients had positive histopathological changes. The remaining 5 patients with positive serology and negative biopsy were excluded from the study. Three patients had anti-tTg antibody titer > 10-folds, five patients had 5–10-folds, six patients had 2–5-folds and the remaining two had < 2-folds. Follow up was possible in 9 patients, among them 8 patients were negative for anti-tTg antibody and the other patient had antibody titer of >5-folds as he was non-compliant to GFD.

Histopathology

Modified marsh grading in the diagnosed patients with CLD with CD was as follows: grade 1 in 2 patients, grade 3a in 5, grade 3b in 3, grade 3c in 1 patient.

UGI endoscopy

Ten patients had esophageal varices at the time of presentation (grade 1: 3 patients, grade 2: 5, grade 3: 2 patients) and one patient had gastric varices. The esophageal variceal band ligation was done in 5 patients with the history of GI bleeding and all the patients were prescribed beta-blockers. There was no change in the grade of the varices after 6 months of GFD in 5 patients who agreed to undergo a repeat endoscopy after 6 months of GFD.

Child-Pugh score

Mean CPS was comparable in both the groups at the time of presentation (Table 2). Follow up was possible only in 9 out of 11 cases in CLD with CD group as two cases expired at first presentation. One patient presented with hepatic encephalopathy and the other patient had a history of pyrexia and oliguria. They died because of sepsis and renal failure, developed as a

Table 1 Comparison of baseline data between two groups

	CLD with CD ($n = 11$)	CLD without CD ($n = 73$)	p-value
Age group (years)			
n (%)			
0–5	1 (9.1)	22 (30.14)	
5–10	5 (45.45)	32 (43.84)	
> 10	5 (45.45)	19 (26.02)	
Gender			
Male, *n* (%)	7 (63.6)	53 (72.6)	
Family history of CD, *n* (%)	3 (27.3)	0	0.001*
Growth retardation[1], *n* (%)	11 (100)	37 (50.7)	0.0001*
Ascites, *n* (%)	6 (54.5)	55 (75.3)	0.15
Encephalopathy, *n* (%)	1 (9.1)	8 (10.9)	0.04*
Hematological profile, mean (SD)			
Mean Hb (g%)	5.19 (1.19)	6.16 (1.95)	0.113
Microcytic hypochromic anemia, *n* (%)	10 (90.9)	67 (91.78)	
Dimorphic anemia, *n* (%)	1 (9.1)	6 (8.22)	
Liver function tests, mean (SD)			
Mean AST (U/L)	142 (38.1)	59.1 (34)	0.0001*
Mean ALT (U/L)	145 (43.6)	54.8 (30.4)	0.0001*
Mean serum albumin (g/dL)	2.2 (0.9)	2.09 (0.6)	0.604
Mean total serum bilirubin (mg/dL)	2.28 (1.05)	1.9 (0.8)	0.165
Mean total direct bilirubin (mg/dL)	1.5 (0.7)	0.7 (0.6)	0.0001*
Prothrombin time (s)	31.45 (13.16)	36.21 (14.1)	0.036*
Mean serum ALP (U/L)	455 (120)	328 (77.3)	0.0001*

CD celiac disease, *SD* standard deviation, *Hb* hemoglobin, *AST* aspartate transminase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

*p-value < 0.05

[1] According to IAP body mass index (BMI) charts, growth retardation was defined as BMI < -3SD

Table 2 Comparison of various components of Child-Pugh score (CPS) initially and after 6 months of gluten-free-diet (GFD) in cases of chronic liver disease with celiac disease

Parameter	At presentation ($n = 11$)	After 6 months of GFD ($n = 9$)	p-value
Encephalopathy	1	0	
Ascites	6	2	
Serum albumin (g/dL) mean (SD)	2.22 (0.88)	3.5 (0.46)	0.001*
Serum bilirubin (mg/dL) mean (SD)	2.28 (1.05)	1.59 (1.42)	0.24
Prothrombin time (s) mean (SD)	31.45 (13.16)	16.44 (3.68)	0.001*

*p-value < 0.05

complication of community-acquired pneumonia. It was not possible to start GFD in these patients because of their critical condition. The mean CPS significantly improved after initiation of GFD in the remaining patients of this group except for one case who was non-complaint to diet.

Follow up was possible in 43 of 73 cases in CLD without CD; of the remaining 30 patients, 20 expired (12 at first presentation and 8 during follow up) and no information was available in 10 cases. The mean CPS did not improve during follow up period. Though no further clinical deterioration was found in the remaining cases, the mean CPS was higher in comparison to the mean CPS at the time of presentation.

Comparison of the CPS data at presentation and 6 months after GFD among patients with CLD with CD revealed improvement following GFD (Tables 2 and 3).

Discussion

The prevalence of CD among the children of cryptogenic cirrhosis in our study was 13.1% in comparison to a figure of 6.5% in another Indian study [15]. The high prevalence in our study might be explained by two reasons; first, our study involved the pediatric patients and second, there is a high prevalence of CD in the northern parts of India [2]. The prevalence of CD in patients with a CLD is reported to be 10–15 times higher compared to the general population [16, 17]. A Finnish study on 185 patients undergoing liver transplantation for end-stage disease, reported a frequency of 4.3% of CD, which was four to ten times higher than the expected prevalence [18].

The mechanism of liver injury in CD is uncertain but may include increased intestinal permeability, systemic autoimmunity, mucosal damage, inflammation, malnutrition, and small intestinal bacterial overgrowth [19, 20]. Some of these mechanisms may be responsible for liver damage in patients with cryptogenic cirrhosis [19, 20]. The histologic findings in patients with CD are minimal macrovesicular steatosis, Kupffer cell hyperplasia, and focal ductular proliferation [10]. Chronic diarrhea, growth retardation, and anemia were present in both the groups but more in patients with CLD with CD. The result of our study, therefore, may suggest that CD should be suspected patients with cryptogenic cirrhosis in the presence of chronic diarrhea, growth retardation, and severe anemia.

CD is an important cause of serum transaminase elevation. It has been reported in about 40% of adults and in 54% of children with a classical presentation of CD at the time of diagnosis [21, 22]. Conversely, the CD is present in about 9% to 10% of patients with chronic unexplained hypertransaminasemia [21, 23]. Similarly, mean values of AST and ALT were significantly high in patients with CLD with CD in our study. So, screening for CD is recommended in patients with hypertransaminasemia and cryptogenic cirrhosis. [10, 24].

In the present study, all the patients had clinical and biochemical improvement after GFD except one, who was found to be non-compliant. Serum albumin, bilirubin levels improved, and PT reduced, and no patient developed encephalopathy or bleeding manifestations. Except for one non-compliant patient, IgA tTG test became negative after 6 months of GFD. These results and earlier studies may suggest that dietary treatment in patients with CLD with CD may prevent progression to hepatic failure, and delay liver

Table 3 Comparison of both groups in term of Child-Pugh score (CPS), initially and after 6 months of follow up *CD* celiac disease, *CLD* chronic liver disease

Parameter	At presentation	After 6 months	p-value
Mean CPS of CLD with CD, mean (SD)	9.18 (2.18) ($n = 11$)	6.33 (1.73) ($n = 9$)	0.037*
Mean CPS of CLD without CD, mean (SD)	10.66 (0.96) ($n = 73$)	11.09 (0.92) ($n = 43$)	0.068

*p-value < 0.05

transplantation [18]. These findings are also in agreement with most series dealing with CD patients, emphasizing that GFD is the mainstay of treatment in patients with CLD with CD [15, 25]. The GFD may not only delay the progression of liver damage in these patients but can also improve already damaged liver, even at the stage of end-stage liver disease who are listed for liver transplantation. GFD may also improve the nutritional status of these patients in addition to reduction in gluten-induced damage to the liver [25, 26]. Adequate nutrition therapy in patients with cirrhosis has been associated with better outcomes [27]. Lack of liver histology and small number of patients, particularly in CLD with CD group are the major limitations of our study.

In conclusion, CD is an underestimated and potentially treatable cause of cryptogenic cirrhosis with a frequency of around 13% of patients in pediatric age group and should always be ruled out before the diagnosis of cryptogenic CLD is made. This has important clinical implication as early diagnosis and treatment with GFD may delay or stop the progression of liver damage and improve outcome.

Compliance with ethical standards

Conflicts of interest AJ, SF, NK, PK, PG, and PCK declare that they have no conflict of interest.

Ethics statement The study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

The study protocol was approved by the institutional review board and ethics committee.

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