Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Prevalence of celiac disease in cirrhosis and outcome of cirrhosis on a gluten free diet: A prospective study

Jamile' Wakim-Fleming[1,*], Mangesh R. Pagadala[1], Arthur J. McCullough[1], Rocio Lopez[2], Ana E. Bennett[3], David S. Barnes[1], William D. Carey[1]

[1] *Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH, United States;* [2]*Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, United States;* [3]*Anatomic Pathology, Cleveland Clinic, Cleveland, OH, United States*

Background & Aims: Current consensus suggests CD to be a multi-systemic disease that could affect any organ system including the liver. It remains under-diagnosed in the US and its prevalence and management in cirrhotic patients has not been studied. Our aim was (1) to estimate the prevalence of CD in cirrhosis, (2) to characterize cirrhotic patients with abnormal celiac serology and normal small bowel biopsy and (3) to evaluate the effect of a GFD on the liver.

Methods: A total of 204 consecutive patients with biopsy proven cirrhosis scheduled for an upper endoscopy (EGD) to assess and treat gastro-esophageal varices (GEV) at the Cleveland Clinic between 5/1/2008 and 5/30/2010 were enrolled in the study and followed for 2 years.

Results: CD affects 2.5% of cirrhotic patients and more than twice the prevalence in the general population. Abnormal EMA >1/10 and high hTTG levels >20 IU can be used to diagnose CD in cirrhosis. Sensitivities and specificities are 100% for EMA and 80% and 94% for hTTG, respectively. After a GFD, patients with CD showed a return to normal levels of their celiac serology, small bowel biopsy and liver enzyme abnormalities.

Conclusions: CD is at least twice more common in cirrhotic patients than in the general population and GFD improves liver tests. CD can occur coincidentally with other liver disorders and screening may be warranted during the evaluation of patients with cirrhosis. Abnormal EMA and high hTTG levels can be used to diagnose CD in cirrhosis.

Keywords: Celiac disease; Cirrhosis; Human tissue transglutaminase; Endomysial antibody; Celiac serology; Marsh.

Received 16 December 2013; received in revised form 17 April 2014; accepted 7 May 2014; available online 16 May 2014

* Corresponding author. Address: Department of Gastroenterology and Hepatology, 9500 Euclid Avenue, A51, Cleveland, OH 44195, United States. Tel.: +1 216 445 4871; fax: +1 216 445 5477.

E-mail address: Fleminj1@ccf.org (J. Wakim-Fleming).

Abbreviations: CD, Celiac disease; GFD, gluten free diet; hTTG, human Tissue Transglutaminase; EMA, Endomysial Antibody; HCV, Hepatitis C; SB, Small Bowel; HLA, Human Leucocyte antigen; EGD, Upper endoscopy; GEV, Gastroesophageal varices; MELD, Model for End stage Liver disease.

Introduction

Celiac Disease (CD) is a chronic immune-mediated disease that begins with damage to the small bowel (SB) mucosa when genetically predisposed individuals, with HLA haplotypes DQ2 or DQ8, ingest gluten containing food [1,2]. Damage to the SB mucosa can be patchy and progressive eventually leading to villous atrophy and malabsorption. Biopsy findings on SB tissue specimens are reported according to Marsh or Oberhuber grades [3,4]. They can be reversible upon withdrawal of gluten-containing foods from the diet [5].

Thought initially to involve primarily the gut, CD is now recognized to be associated with extra-intestinal manifestations in up to 30% of patients suggesting a far greater systemic effect beyond the gut [6]. Current consensus suggests CD to be a multi-systemic disease that can affect any organ including the liver. The most common liver disorders associated with CD are primary biliary cirrhosis (PBC) [7], autoimmune hepatitis (AIH) [8], sclerosing cholangitis (PSC) [9], and non-alcoholic fatty liver disease (NAFLD) [10]. Isolated hyper-transaminasemia can be the presenting feature in the absence of a specific liver disorder [11], and the prevalence of elevated liver enzymes in the adult population with CD is in the order of 40% [12]. In addition to the high prevalence high prevalence, reasonable data suggest that liver enzyme abnormalities are usually mild and respond to a GFD [2,13]. Data also shows that most patients who have both celiac disease and liver disease have non-specific changes on liver biopsy specimens described as Kupffer cell hyperplasia, minimal macrovesicular steatosis, piece meal necrosis and focal ductular proliferation [12,14]. Cirrhosis is rarely described in patients with CD but case reports are emerging in the younger population [15–17]. Cirrhosis affects up to 10% of the general population worldwide and its prevalence is rising [18]. Once established, cirrhosis is often progressive and associated with increased morbidity and mortality, loss of work productivity, decrease in health related quality of life and substantial health care costs [18]. Without a liver transplantation survival is very poor and prevention of cirrhosis and its progression are considered standard of care, therefore recognizing CD in the setting of cirrhosis is essential in order to institute a GFD and potentially prevent further morbidity and mortality associated with both diseases. CD remains under-diagnosed in the US [2] and its prevalence is close to 1%

in the general population [19]. However, data on the prevalence of CD in cirrhosis and its outcome with a GFD are lacking. We conducted the study to (1) estimate the prevalence of CD in cirrhosis, (2) characterize cirrhotic patients with abnormal celiac serology and normal small bowel biopsy, and (3) evaluate the effect of a GFD on the liver.

Materials and methods

Study design

This is a prospective case-series study of subjects with cirrhosis of the liver.

Selection of patients and data collection

A total of 204 consecutive patients with biopsy proven cirrhosis scheduled for an upper endoscopy (EGD) to assess and treat gastro-esophageal varices (GEV) at the Cleveland Clinic between 5/1/2008 and 5/30/2010 were enrolled in the study and followed for 2 years.

Medical records were reviewed for age, ethnicity, gender, indications for EGD, imaging studies, and laboratory tests. Liver transaminases, bilirubin level, alkaline phosphatase, protime/INR, celiac serology panel, complete blood count with differential and viral hepatitis panel were recorded at the time of enrollment and after 2 years. Patients with CD were followed for 2 years after the institution of a GFD at which time all laboratory tests were also repeated and MELD scores calculated in order to assess the effect of GFD on the liver.

Patients were included if they were over 18 years old and able to give informed consent regardless of the etiology of cirrhosis.

Patients were excluded if they were pregnant, on dialysis, had a bleeding disorder or were actively bleeding at the time of endoscopy, taking anticoagulants or had INR greater than >1.5 or/and platelet count less than $30 \times 10^3/mm^3$. Also excluded were patients diagnosed with malabsorption, Crohn's disease, had a prior organ transplant, graft *vs.* host disease, food allergies, patients on a gluten free diet, and patients with malignancy taking chemotherapeutic agents.

Informed consent was obtained on all patients for celiac serology panel, genetic testing for celiac gene, and SB biopsy.

Celiac serology panel

Celiac serology panel included antibodies to human tissue transglutaminase (IgA for hTTG, QUANTA lite™ ELISA, Inova diagnostics, San Diego CA), endomysial antibodies (IgA EMA, Immunofluorescence Inova diagnostics San Diego CA), IgG and IgA antigliadin antibodies (Elisa, Inova diagnostics, San Diego CA), and total IgA levels by nephelometry (Beckman Coulter Immage/image 800 Immunochemistry system and Calibrator 1, Fullerton CA). Tests were consecutively analysed in the immunology laboratory at the Cleveland Clinic.

Abnormal serology panel is any value for IgA EMA titer above 1:10 dilution, or any value for IgA hTTG or Gliadin antibodies above 20 IU.

Although current testing for Gliadin antibodies is no longer recommended in the diagnosis of CD due to poor accuracy of the results, the celiac panel was used at the time of the study.

Histological diagnosis

Upper endoscopies were performed by gastroenterologists at the Cleveland Clinic. The gastroenterologists were not blinded to the study, and they were asked to obtain at least 3 biopsies from different segments of the duodenum including the duodenal bulb on all subjects. Biopsy specimens were placed in vials containing 10% of buffered formalin solution for fixation. Paraffin sections were prepared and stained by hematoxylin and eosin (HE) stains. Pathology slides were interpreted by a Cleveland Clinic pathologist (A.B.) experienced with the spectrum of mucosal changes in CD. The pathologist was blinded to names and underlying diagnosis and she graded findings according to the Marsh grading system [3,4].

In Marsh 0 mucosa and villous architecture are normal. In Marsh I villous architecture is normal, but intraepithelial lymphocytes are increased. In Marsh II there is intraepithelial lymphocytosis, enlarged crypts and increased crypt cell division. Marsh III is defined by villous atrophy, shortened blunt villi and enlarged hyperplastic crypts, and Marsh IV demonstrates hypoplastic mucosa. The diagnosis of CD was defined when positive celiac serology is associated with villous atrophy or Marsh III lesions. Cirrhosis was defined histologically according to Batts and Ludwig staging system. Severity of cirrhosis was assessed by calculating Child Turcotte Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores for all patients.

HLA typing for Celiagene (Prometheus, San Diego)

This test was performed on 5 ml of EDTA whole blood collected on ice in a lavender top tube and sent by overnight mail to Prometheus Laboratories, 9410 Carroll Park dr. San Diego, Ca. It uses Polymerase Chain Reaction amplification with sequence specific primes to evaluate for HLA DQ2/DQ8 alleles. Results were reported as strongly positive for the HLA DQ2 or DQ8 haplotypes or >10 fold increased risk over the general population.

Statistical analysis

Data are presented as mean ± standard deviation, median (25th, 75th percentiles) or N (%). Prevalence of celiac disease (CD) was estimated by calculating the percentage of patients with Marsh III; the corresponding 95% confidence interval is also reported. In addition, univariable analysis was performed to assess differences between patients without CD and abnormal serology and those without CD and normal serology. Analysis of Variance (ANOVA) for continuous variables and Pearson's χ^2 test for categorical factors were used to compare the groups. A p <0.05 was considered statistically significant. SAS version 9.2 (The SAS Institute, Cary, NC) was used to perform all analyses.

Results

Patient characteristics

Forty-six percent of patients were female, 83% were white and average age was 55.4 ± 11.4 years. The most common cause for cirrhosis was HCV (31%), followed by alcoholic liver disease (26%) (Table 1). Forty-five (22%) subjects were lost to follow-up

Table 1. Demographic and clinical characteristics of patients with cirrhosis.

Factor	Total (n = 204)
Female	94 (46.1)
Age	55.4 ± 11.4
Race	
Asian	1 (0.49)
Black	27 (13.2)
Hispanic	6 (2.9)
White	169 (82.8)
American Indian	1 (0.49)
HCC	5 (2.5)
PBC	12 (5.9)
NASH	28 (13.7)
HCV	64 (31.4)
Cryptogenic	17 (8.3)
PSC	12 (5.9)
HBV	5 (2.5)
AIH	10 (4.9)
Alcoholic liver disease	52 (25.5)
Renal disease	19 (9.3)
Liver transplant after small bowel biospy*	32 (20.1)
Deceased*	38 (23.9)

*Follow-up data not available.
Values presented as Mean ± SD or N (%).