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ORIGINAL PAPER

Chronic Hepatitis C Virus and Celiac Disease, is there an Association?

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Abstract Celiac disease (CD) has been epidemiologically associated with chronic hepatitis C (HCV), and CD activation after the initiation of interferon (IFN-α) in patients with HCV is documented. However, clear association of CD and HCV is lacking. A prospectively maintained database of 878 CD patients showed a prevalence of 0.68% (six patients). Symptoms of diarrhea, weight loss, and depression prompted the diagnosis of CD during or after IFN-α therapy in four cases. Also, 294 subjects with liver disease (195 with HCV, 80 normal controls and 19 disease controls) were prospectively screened for CD. The mean age of the subjects was 50.1 years (SD 12.3), 58% males:42% females. A total of 30% received IFN-α therapy (16% at the time of testing for CD). Two HCV patients (1%) had positive tTG-IgA but these had negative endomysial antibody (EMA) and normal duodenal biopsies. CD prevalence is not increased in patients with HCV. Routine screening of CD in HCV patients is not warranted, however, the presence of CD should be considered in the setting of clinical deterioration during or after IFN-α therapy.

Keywords Transglutaminase · Hepatitis C · Celiac · Autoimmune · Interferon · Prevalence

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Introduction

Celiac disease is a common immune-mediated disorder. Its presence has been documented in North and South America, Europe, North Africa, south and west Asia, and Australasia [1, 2]. Celiac disease, once considered a rare disease in the United States, is now recognized to occur in up to 1% of the population, similar to Europe [3–7]. The clinical classification of celiac disease depends on the presence of gastrointestinal symptoms, mainly diarrhea. Classical celiac disease is the diarrhea-predominant presentation, whereas silent celiac disease may be atypical or asymptomatic. Celiac disease is seen in many individuals with liver disease, especially autoimmune-associated liver diseases, including primary biliary cirrhosis [8–10], autoimmune hepatitis [11, 12] and primary sclerosing or autoimmune cholangitis [13–16]. In addition, there is a suggested epidemiological association of chronic hepatitis C (HCV) and celiac disease [17]. In view of the paucity of studies addressing this relationship in the United States, we analyzed a prospectively maintained database of patients with celiac disease to identify subjects with concomitant chronic HCV and performed a prospective cross-sectional study to determine the prevalence of celiac disease in chronic hepatitis C patients in New York City.

Materials and methods

Database analysis

We analyzed a prospectively constructed anonymous database of celiac disease patients seen between July 1, 1981, and July 1, 2006, at a referral center for celiac

disease. We only assessed those patients diagnosed after 1990, when assays for HCV became available [18]. Only those patients who were older than 18 years and had diagnoses established by biopsy were included. We identified those with HCV, documenting age at the time of diagnosis of HCV, gender, ethnicity and therapy given for HCV.

Cross-sectional analysis

The second phase of the study was a prospective cross-sectional analysis of chronic liver disease patients screened for celiac disease. Patients were seen from July 2004 to November 2005; all of the subjects were patients with HCV or chronic liver disease seen at the center for liver disease at Columbia University College of Physicians and Surgeons and the hepatology clinics of Beth Israel Medical Center, New York. Patients seen at these sites were offered enrollment by participating gastroenterologists during initial or follow-up visits. Patients with chronic liver diseases other than HCV were included into the disease control group. Normal controls were patients that attended general medicine clinics and were healthy subjects with normal levels of liver transaminases, and negative tests for HCV. The study was approved by the internal review board of the respective institutions.

Serologic screening

Celiac disease serologies included: (1) semiquantitative immunofluorescence for the presence of antiendomysial IgA antibody (EMA-IgA) using a commercially available kit, employing monkey esophagus as the substrate (Scimedx in NJ, USA). (2) Human IgA anti-transglutaminase 2 antibody (tTG-IgA) by commercially available enzyme-linked immunosorbent assay (Eurospital in Trieste, Italy). Following the consensus criteria for the serologic screening of celiac disease, we ruled out selective IgA deficiency among our patient population by including additional serology to the above tests; we measured antigliadin (AGA) IgA and IgG antibodies using a non-commercially available assay (CFCR in Baltimore, MD). If a patient was positive for antigliadin IgG antibodies but negative in antigliadin IgA, antiendomysial IgA, and anti-tissue transglutaminase IgA tests, their serum total IgA was then quantified. Serum samples were coded, kept at –80°C. A total of 250 µl were transported for analysis, following all conservation and safety guidelines, to the center for celiac research at the University of Maryland School of Medicine, Baltimore, MD. Patients with positive tTG-IgA or EMA-IgA were offered upper-GI endoscopy for the purpose of obtaining biopsies from the distal duodenum.

Subjects

Demographics recorded from all the recruited patients included: age, gender, ethnicity (non-Hispanic whites, non-Hispanic blacks, Hispanics and others). Additional data were collected from those diagnosed with chronic hepatitis C: total viral load (EQ/ML), hepatitis C virus genotype; classifying our subjects into two groups (type 1 and 2/3), length of HCV infection (years), treatment regimen (INF/ribavirin, PEG-IFN-α l-2a or PEG-IFN α-2b) and duration of treatment (months). Further data were collected from HCV patients with positive celiac serology; allele typing by means of polymerase chain reaction with allele-specific primers identifying HLA-DQ2 and HLA-DQ8, carried out by an outside commercial lab (Quest diagnostics, USA); finally, they were screened for history of poor response to HCV treatment.

Statistical analysis

Data are expressed as percentages or absolute number for categorical variables, and means and SD's for continuous variables. The prevalence of tTG-IgA and EMA antibodies in the patient and control groups were compared by chi-square, and a Student *t* test was performed. In our literature review, we ran Fischer exact tests in order to determine a difference of prevalence of celiac disease in patients with HCV versus normal controls, as well as disease controls, and reproduced them in our summary tables when these were not reported by the articles reviewed. In addition, we performed a chi-square analysis and a *z* test of prevalence of celiac disease in HCV patients using the pooled HCV patient population from all the prospective studies reviewed.

Results

Database analysis

We only analyzed those patients seen after 1990, when HCV could be assessed. This involved 878 patients. Among these patients with celiac disease, six (0.68%) with concomitant HCV were identified. Their characteristics are shown in Table 1. Males predominated, and five were non-Hispanic white, one Hispanic. HCV was the initial diagnosis in the majority (five of six patients), one patient had both diseases diagnosed in the same month. The symptoms that prompted the diagnosis of celiac disease were diarrhea, weight loss, iron deficiency anemia and depression. In three of the patients, these symptoms occurred during or after IFN-α therapy and in one after liver transplantation. A

Table 1 Characteristics of CD patients with concomitant HCV

Sex	Ethnicity	Age at HCV diagnosis (years)	Sequence of diagnosis	EMA or tTG IgA	Symptoms that prompted the diagnosis of CD	HCV therapy	Poor response to IFN	Liver transplant
M	W	46	HCV 4 years prior to CD	+	Nausea, diarrhea and weight loss after IFN therapy	IFN/ribavarin	Yes	–
M	H	58	HCV >10 years prior to CD	+	Vomiting/dyspepsia and flatulence after IFN therapy	IFN/ribavarin	No	–
M	W	40	HCV 2 years prior to CD	–	Dermatitis herpetiformis	None	–	–
M	W	46	HCV >10 years prior to CD	–/on immunosuppressant	Diarrhea, weight loss	None	–	Yes
F	W	47	Simultaneous	+	Iron-deficiency anemia	IFN/ribavarin	Yes	–
M	W	43	HCV >10 years prior to CD	+	Depression	IFN/ribavarin	Yes	–

W = non-Hispanic white, H = Hispanic, M = male, F = female, CD = celiac disease.

total of four patients received IFN-α therapy, in one patient diagnosed with dermatitis herpetiformis, IFN-α therapy was withheld because of a risk of aggravation of the dermatitis.

Prospective study

A total of 195 subjects diagnosed with HCV were included. The control groups were divided into two populations: the normal control group, which had a total of 80 patients, and secondly, the disease control group, which included 19 patients with chronic liver disease (chronic hepatitis B $n = 7$, autoimmune hepatitis $n = 1$, alcoholic hepatitis $n = 3$, non-alcoholic fatty liver disease $n = 2$, cryptogenic chronic hepatitis $n = 3$, primary sclerosing cholangitis $n = 1$ and primary biliary cirrhosis $n = 2$). All subjects were screened for celiac disease using the serologies described above. Their characteristics are shown in Table 2. Only two HCV patients (1%) had a positive tTG-IgA, with negative EMA. None of these two patients had evidence of celiac disease on duodenal biopsy. All chronic liver disease controls had negative serologies. There was no one identified with selective IgA deficiency. Our results did not show a difference in prevalence when compared to the normal controls.

Discussion

Our study did not reveal an association between celiac disease and HCV. Retrospectively we identified only 0.7% of the patients seen in a referral center for celiac disease to have concomitant HCV, a similar figure to that reported by others [19], see Table 3. In addition, we identified no patients with celiac disease in our prospective study. The population size in our study was comparable to similar screening studies (see Table 3).

The patients seen in our celiac center are typical of those patients with celiac disease in that they are predominately female, white and middle-aged and have an increased rate of autoimmune diseases compared to the general United States population [20]. Celiac disease prevalence in the United States population is ~0.8%, similar to European populations [4]. However, celiac disease is generally underdiagnosed in the United States. Our study population was diverse and included a large Hispanic component (38% of the prospectively screened group). While celiac disease is diagnosed in ethnic minorities [21], we are not aware how common the disease is among the Hispanic population of New York.

In the prospectively screened HCV population, we found two subjects with positive tTG-IgA and negative EMA and duodenal biopsies. The tTG-IgA test is

Table 2 Characteristics of HCV patients

Age	50.1 (SD 12.3)	
Gender	Males	170 (58%)
	Females	124 (42%)
Ethnicity	Non-Hispanic white	123 (41.8%)
	Hispanic	109 (37.7%)
	Non-Hispanic black	39 (14.6%)
	Other	22 (7.4%)
% Receiving IFN therapy	Overall	58 (30%)
	Concurrent	31 (16%)
Mean duration of therapy	[a]24 months (SD 17.75)	
Mean viral load	1910885.33 (SD 3300693.63)	
Genotype	Type 1	148 (76%)
	Type 2/3	46 (20%)

[a] HCV treatment included patients who had past treatment as well as those with ongoing therapy

frequently used for screening for celiac disease. However, chronic liver disease, especially more advanced disease, may be associated with false positive tTG-IgA values [22, 23]. This occurs even with the newer-generation human recombinant tTG-IgA based tests.

In previous studies (Table 3), including the one study from the United States [17], cases of celiac disease have been identified in prospectively screened patients with HCV; none has, however, reached statistical significance. In our literature review, we found four prospectively designed screening studies (Table 3); of these, three had a normal control group [17, 24, 25]. The pooled population of HCV was 1,072 patients; of these, a total of 14 patients were positive for celiac disease. The pooled normal control population was 1,789 patients; of these, seven had celiac disease. A chi-square analysis showed a statistically significant difference in prevalence between the pooled patient population ($p = 0.012$).

In addition to the screening studies, there have been individual cases and case series of HCV associated with celiac disease or dermatitis herpetiformis [26–29]. These cases included a total of 22 patients, including the cases from our retrospective analysis. Of note, more than half of these cases were diagnosed after IFN-α therapy had commenced [26, 30–33] (see Table 4). We noted this in three of our patients. This suggests that IFN-α may precipitate the development of celiac disease in susceptible individuals. This is consistent with the known fact that IFN-α may precipitate or worsen autoimmunity in some individuals [34]. Screening for celiac disease before starting IFN-α therapy has been recommended [24, 26, 32, 35] though the studies do not support this. However, it would seem prudent to be aware that celiac disease is an autoimmune disease that may become evident after the commencement

Table 3 Celiac disease and hepatitis C

	HCV patients	DC	NC	Prevalence of CD			Year	Country	Reference
				In HCV	In DC	In NC or UH			
Prospective studies	161	571	1,350	1.2%	5.8%[b]	0.3% NC ($p = 0.12$)	2005	Greece	[23]
	259	552	221	1.2%	3.4%[c]	0.4% NC ($p = 0.63$)[a]	2001	USA	[17]
	195	99	0	0%[e]	0%	0% of NC	2006	USA	Current study
	102	182	165	0%	3.8%[d]	0.6% NC ($p = 1.0$)[a]	2003	Spain	[31]
	97[f]	206	0	1%	N/A	9% of UH	1999	Italy	[36]
	HCV patients	CD	NC	*n* on IFN	Prevalence of CD in HCV	Prevalence of HCV in CD	Year	Country	Reference
Retrospective studies	534	7	225	7/7	1.3% vs. 0.4 in NC ($p = 0.5$)	–	2004	Italy	[22]
	6	1,009	N/A	3/6	–	0.6%	2006	USA	Current study
	3	488	N/A	0	–	0.6%	2001	Austria	[18]

n: number of cases, NC: normal controls, HCV: chronic hepatitis C, DC: disease control, UH: unexplained hypertransaminasemia, IFN: interferon, N/A: not applicable, NS: not significant.

[a] Fischer exact test, using the numbers of patients reported in original article. Statistical significance when $p < 0.05$.

[b] Statistically significant higher prevalence when compared to normal controls. Reported to have $p < 0.05$ in original paper.

[c] Only autoimmune hepatitis had positive cases of CD.

[d] DC included patients with functional dyspepsia and UH with CD prevalence of 3.2% and 4.4% respectively.

[e] 2/195 HCV patients were positive of tTG but had normal biopsies.

[f] 303 patients with hypertransaminasemia in which 32% (97) had HCV. One of 97 HCV patients had CD. Study aim was to determine prevalence of CD in UH versus disease controls (not particularly in the HCV group).

Table 4 Case reports of patients with HCV diagnosed with CD

		References
Number	22	[Current study, 18, 24–27, 29, 30, 37–40]
HCV in patients with CD	11[a]	[Current study, 24–26]
DH in HCV	2	[Current study, 27]
CD/DH in HCV patients after IFN therapy	12[b]	[Current study, 24, 30, 37–39]
Presentation CD with classical symptoms	10	[Current study, 24, 26, 30, 38, 40]
Presentation with atypical symptoms		
(a) Iron deficiency/anemia/weight loss	5	[Current study, 18, 24, 29, 38, 39]
(b) Osteopenia	2	
(c) Depression/behavioral changes	1	
Improvement after discontinuing IFN therapy	8[c]	

[a] Bourliere et al. reported one case of HCV and CD. That remained symptom-free while on IFN and GFD combined.

[b] Adinolfi et al. reported a case that developed CD after adding ribavirin to IFN treatment.

[c] 4/8 in our study improved, the rest from other studies were also reported to improve. The remaining six reported cases did not specify improvement after treatment.

of IFN-α therapy. This is especially important because diarrhea, the hallmark symptom of celiac disease, is a frequent complication of IFN-α therapy [36–38].

It is not clear whether the development of celiac disease during IFN-α therapy is due to the general increased risk of the development of autoimmunity or is specifically related to the role of IFN-α in promoting T helper cell type 1 responses in the small intestine in celiac disease [39].

There is little evidence to support the role of screening HCV patients for celiac disease. Further studies are warranted to document whether celiac disease may account for the symptoms that may develop in individuals with HCV receiving IFN-α therapy. In addition, there should be a low threshold for obtaining celiac antibodies from patients who develop diarrhea or weight loss while on IFN-α therapy.

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