

Original Article

Prevalence of Celiac Disease in Patients with Primary Biliary Cholangitis

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ABSTRACT

Background: Primary biliary cholangitis (PBC) frequently coexists with other autoimmune diseases, including celiac disease (CeD). Although the prevalence of CeD is high among cohorts with PBC, few studies have directly compared this prevalence to those among individuals with other liver diseases (OLD).

Aim: To compare the prevalence of CeD between a cohort with PBC and a cohort with OLD.

Methods: Retrospective study from January 2013 to December 2016. All consecutive patients with an anti-transglutaminase (tTG) assay requested by a hepatologist and a diagnosis of chronic liver disease were included. CeD diagnosis was confirmed by duodenal biopsies.

Results: We included 399 consecutive patients (53.1 years SD 14.0, 54.1% women), notably 51 individuals with PBC and 348 individuals with OLD. PBC group included significantly more women (90.2% versus 48.9% $P < 0.0001$). The prevalence of CeD was higher in the group with PBC compared to the group with OLD (11.8 versus 2.9%, $P < 0.003$). In the OLD group, the prevalence of CeD was comparable regardless of the etiologic subgroup (nonalcoholic steatohepatitis 2.7% versus alcoholic liver disease 4.3%, versus viral 1.5% versus other autoimmune liver diseases 3.3%, NS). The presence of gastrointestinal symptoms at the time of the tTG assay was comparable between PBC and OLD groups (31.4 versus 29.6%, NS).

Conclusion: There is a higher prevalence of CeD in the PBC group compared to other liver diseases.

Keywords: *celiac disease; primary biliary cholangitis; liver diseases; hepatology; chronic liver disease; anti-transglutaminase; transglutaminase; auto-immune disease; duodenal biopsy*

INTRODUCTION

Primary biliary cholangitis is an autoimmune chronic liver disease, affecting mostly women (1). It is characterized by a progressive granulomatous destruction of the small to medium intra-lobular and septal bile ducts, resulting in cholestasis (1). This can lead to cirrhosis, may potentially require liver transplantation or cause death in some cases (1).

Celiac disease, on the other hand, is a T-cell-mediated enteropathy of the small bowel (2). It is induced in individuals with a genetic predisposition after gluten consumption (2). In

individuals with active disease, an intraepithelial lymphocytosis and villous atrophy of the small intestinal mucosa can be seen (2). The main gastrointestinal signs and symptoms are diarrhea, abdominal pain and weight loss (3). However, silent and latent forms are often more common presentations (3).

PBC frequently coexists with other autoimmune diseases such as Sjögren's syndrome, Hashimoto's thyroiditis, systemic sclerosis and CeD (4). Studies of the prevalence of CeD in patients with PBC compared to the general population also show a stronger association in patients with PBC (5, 6). However, it is unclear whether or not celiac disease is more prevalent in

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patients with PBC compared to other liver diseases (OLD) (7–9). PBC has a specific autoimmune mechanism (1, 6). Since PBC and CeD are both mediated by intestinal T cells and share common features such as associated autoimmune disorders, environment infectious factors and genetic polymorphisms, we hypothesize that there is a greater link between CeD and PBC than CeD with OLD. In this study, we report a higher prevalence of CeD in patients with PBC compared to patients with OLD.

PATIENTS AND METHODS

Study Population

Retrospective study including consecutive patients with anti-transglutaminase (tTGA) assays requested by a hepatologist and a concomitant diagnosis of chronic liver disease, between January 1, 2013 and December 31, 2016, at the Centre Hospitalier de l'Université de Montréal. Patients included in this study are part of a cohort previously described (10). The study population was not extended until 2019, because we did not anticipate that extending to 2019 would significantly change the results, since there were no new guidelines recommending a change in the screening of celiac disease among individuals with chronic liver diseases. For the present report, we excluded all patients with tTG assays who did not have chronic liver disease.

Electronic medical records were reviewed for clinical characteristics. Data collected included age, sex, reasons of tTGA, GI symptoms, duodenal biopsy result, liver workup and presence of cirrhosis. Etiology and diagnosis of liver diseases were established by our liver specialists according to recommended clinical, serological and/or histologic criteria. Multiple hepatologists were involved in the screening. The presence of cirrhosis was confirmed according to clinical presentation, liver ultrasound result, histologic evaluation and/or transient elastography with liver stiffness measurements, according to the etiology of liver disease.

Two subgroups of patients were formed, one with PBC and the other including all OLD. Patients were considered with PBC if they had either a positive biopsy concordant with the diagnosis, positive antimicrobial antibodies or positive anti-sp100. OLD group included any diagnosis for liver disease, such as nonalcoholic steatohepatitis (NASH), alcoholic liver disease, chronic viral hepatitis (hepatitis B and C), other autoimmune liver diseases (ALLD) such as primary sclerosing cholangitis or autoimmune hepatitis and other diseases (Other) such as Fontan hepatitis, post-transplant hepatitis, drug-induced hepatitis, etc.

tTG assay used during the study period at our institution was Bioplex 2200 Celiac IgA Kit (Bio-Rad, USA), with a threshold of 15. All new or previous diagnosis of CeD had to be confirmed by a small intestinal biopsy. This study was approved by the institutional review board at Centre Hospitalier de l'Université de Montréal.

Statistics

Continuous variables were presented as median and interquartile range or mean \pm standard deviation (SD). Dichotomous

variables were expressed as frequencies and proportions. Mann–Whitney *U* tests were performed to compare continuous data, while Fisher's exact tests were conducted for dichotomous data. Statistical significance was defined as a *P*-value < 0.05 . Statistical analyses were performed using GraphPad Prism, version 7.03 (La Jolla, California).

Results

A total of 399 patients (53.1 years, SD 14.0, 54.1% women) met our inclusion criteria. This cohort included 51 individuals with PBC and 348 individuals with OLD. The PBC group included significantly more women (90.2% versus 48.9% women, $P < 0.0001$). The prevalence of CeD was higher in the group with PBC compared to the group with OLD (11.8 versus 2.9%, $P < 0.003$; Table 1). In the OLD group, the prevalence of CeD was

Table 1. Characteristics of PBC group compared to OLD group

	PBC	OLD	<i>P</i>
	<i>n</i> = 51	<i>n</i> = 348	
Demographics			
Female gender (%)	90.2	48.9	<0.0001
Prevalence of CeD (%)	11.76 (6)	2.87 (10)	<0.003
Other characteristics			
Most common reasons for CeD screening (%)	Presence of PBC (33.3)	Etiologic assessment of liver disease (39.1)	
	Etiologic assessment of liver disease (31.4)	Hepatic cytolysis (25.6)	
Other reasons for CeD screening ^a (%)	35.3	35.3	
Presence of gastrointestinal symptoms ^b (%)	31.4	29.6	NS
Cirrhosis (%)	39.2 (20)	37 (129)	
Cytolysis (%)	60.8 (31)	69 (240)	
Known CeD (%)	11.76 (6)	1.72 (6)	
Positive biopsies (%)	5.88 (3)	2.01 (7)	

CeD, celiac disease; OLD, other liver diseases; PBC, primary biliary cholangitis.

^aOther reasons included presence of abdominal symptoms, anemia, osteoporosis, other autoimmune diseases, veno-occlusive disease and unknown reasons.

^bGastrointestinal symptoms included diarrhea, abdominal pain, dyspepsia, weight loss, bloating.

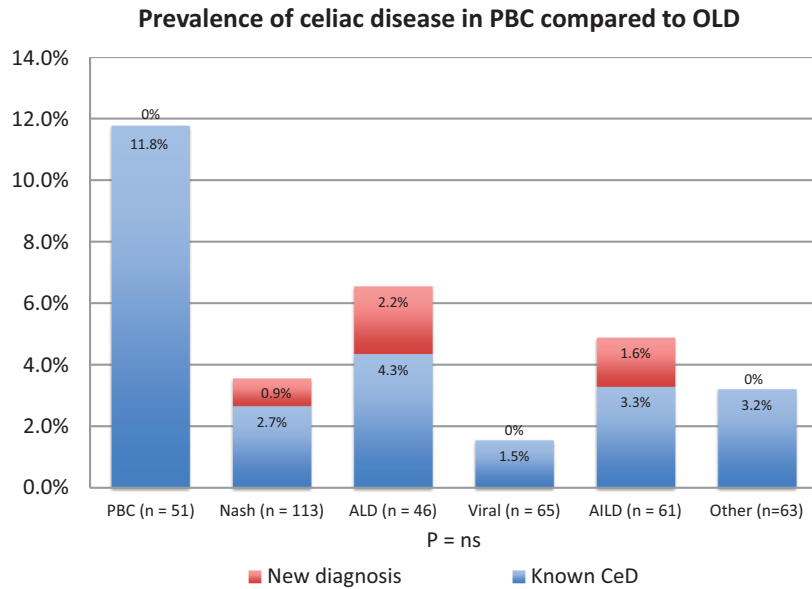


Figure 1. Prevalence of confirmed celiac disease in different groups of liver diseases.

comparable regardless of the etiologic subgroup (NASH 2.7% versus alcoholic liver disease 4.3%, versus viral 1.5% versus other autoimmune liver diseases 3.3% versus other 3.17%, NS; [Figure 1](#)). Among all patients in this study with CeD, 12 were already known for the disease, while 4 new cases were diagnosed. The most common reasons for CeD screening among PBC patients were the presence of PBC itself (33.3%) and etiologic assessment of liver disease (31.4%), whereas for patients with OLD, the most common reasons were etiologic assessment of liver disease (39.1%) and elevated transaminases (25.6%). The presence of gastrointestinal symptoms, ranging from diarrhea, abdominal pain, dyspepsia, weight loss and bloating was comparable between PBC and OLD groups (31.4 versus 29.6%, NS; [Table 1](#)).

Discussion

To our knowledge, this is the first study to compare the prevalence of CeD in PBC compared to OLD within the same cohort, which showed a higher prevalence of CeD in PBC compared to OLD. The putative association between CeD and PBC was already suggested by several studies, showing prevalence of CeD among PBC population as high as 7% ([5](#), [6](#), [11–13](#)). Many similarities in the pathogenesis of these two diseases may explain this association.

Compared to other AILD, a specific autoantigen was identified in PBC, the E2 component of the pyruvate dehydrogenase multienzyme complex (PDC-E2) ([14](#)). Environment probably plays a significant role in the pathogenesis of PBC, notably through molecular mimicry between some bacteria and PDC-E2, but also through xenobiotics and toxins that may increase the immunogenicity of PDC-E2, stimulating an immune-mediated biliary epithelial injury ([1](#), [15](#)). Although

no particular xenobiotic candidate common to both PBC and CeD have been proposed, previous virus exposures may also have a significant impact on the development of CeD, priming Th1 immunity ([16](#), [17](#)). Intestinal permeability may also have a major effect by allowing microbial antigens and activated T cells translocation in the portal circulation and subsequent development of PBC, and inversely, the intestinal permeability associated with PBC may promote interactions between gliadin peptides and intestinal mucosal immunity ([6](#)). As CeD is also characterized by the loss of oral tolerance to gluten ([18](#)), low antigenic diversity may contribute to the loss of tolerance of biliary epithelial cells in PBC ([19](#)). Finally, although PBC is not associated with HLA DQ2 or 8 like CeD, these two diseases share a few common polymorphisms, notably STAT4, HLA-DQB1 and IL18R1 which have roles in T cell differentiation and IFN γ production ([6](#), [19](#)).

No patient characteristic was predictive of the higher prevalence of CeD in patients with PBC. Although one third of the cohort was screened for CeD exclusively because of the association between these two autoimmune disorders, no differences in terms of GI symptoms were observed. The higher prevalence of PBC among women is well known and is also present in a lesser extent in CeD ([20](#), [21](#)). However, the reason why PBC is female predominant compared to OLD still remains unexplained ([22](#)). Moreover, it is surprising to observe no increased prevalence of CeD in patients with other AILD, considering the increased seroprevalence reported in other studies ([23–26](#)). This finding may be explained by an obvious selection bias, since the individuals with NASH, alcoholic liver disease and viral hepatitis included in this study possibly had a higher pretest probability of CeD, explaining the higher prevalence of CeD in each subgroup compared to the general population. Nevertheless,

the striking increased prevalence of CeD among PBC patients highlights a stronger association with this specific AILD.

More studies are required to explain why CeD could be more linked to PBC compared to AILD. However, we recognize that additional possible bias may have influenced our results, as CeD may be systematically screened in asymptomatic patients with PBC compared to OLD and the rate of screening among patients with liver diseases is unknown, since we do not have a data bank containing all of the patients followed in hepatology at our center independently of tTG testing. Moreover, the absence of incident cases among the PBC cohort is surprising, but may be explained by the fact that our cohort was based on individuals who had tTG assays performed in our institution, excluding subjects who had their blood tests elsewhere. Finally, this study may be under-powered to study the prevalence of CeD in each specific liver condition, given that some groups had fewer patients compared to other groups.

Conclusion

In summary, our findings suggest a higher prevalence of CeD in the PBC group compared to the OLD group. Therefore, prospective studies are needed to assess the strength of this association and perhaps, lead to an official recommendation of screening for CeD in patients with PBC.

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