Hepatobiliary and pancreatic disorders in celiac disease

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Abstract

A variety of hepatic and biliary tract disorders may complicate the clinical course of celiac disease. Some of these have been hypothesized to share common genetic factors or have a common immunopathogenesis, such as primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune forms of hepatitis or cholangitis. Other hepatic changes in celiac disease may be associated with malnutrition resulting from impaired nutrient absorption, including hepatic steatosis. In addition, celiac disease may be associated with rare hepatic complications, such as hepatic T-cell lymphoma. Finally, pancreatic exocrine function may be impaired in celiac disease and represent a cause of treatment failure.

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INTRODUCTION

A number of hepatobiliary and pancreatic disorders occur in celiac disease, a genetically-based small intestinal disorder that resolves with the complete restriction of dietary gluten[1]. Almost 3 decades ago, liver changes in celiac disease were first recognized by Hagander et al[2]. Later, Dickey et al[3] have confirmed these findings in a prospective evaluation of celiac disease patients and extended observations to results of gluten-free diet therapy. In some, these liver test changes are entirely reversible following administration of a gluten-free diet, while in others, clinically significant liver disease is not amenable to diet treatment alone[3]. Now, almost a decade after this report, recognition of celiac disease has been substantively improved, in part, a result of more modern serological assays for screening[4], the detection of tissue transglutaminase (tTG) as an autoantigen in celiac disease[5] and the increasingly widespread serological use of tTG ELISA to screen for celiac disease[6]. As a result of improved recognition of celiac disease, even more precise estimates of the overall disease burden related to hepatobiliary tract and pancreatic disorders will emerge.

In patients with unexplained elevations of liver enzymes, several studies using serological screening methods have estimated that almost 10% will prove to have celiac disease[7-9]. For example, Volta et al[7] examined endomysial and gliadin antibodies in 55 patients with elevations of liver chemistry tests in the absence of a known cause. Five patients had positive serological studies and small intestinal biopsies showed changes of celiac disease that responded to a gluten-free diet. Liver biopsies done in some patients showed a nonspecific inflammatory process and liver chemistry tests normalized with a gluten-free diet. Bardella et al[10] screened 140 patients with chronically elevated transaminase values for gliadin and endomysial antibodies; of these, 13 were seropositive. After 1 year on a gluten-free diet, 12 patients had normalization of liver enzyme tests.

In patients with known celiac disease, abnormal liver enzyme tests also occur[9-11]. Hagander et al[2] described elevated liver enzymes in 30 of 75 (40%) patients, while Bonamico et al[9] showed increased levels in 39 of 65 (60%) children, and Jacobsen et al[11] documented almost 50% with increased liver enzymes. In some, liver biopsy showed a nonspecific inflammatory process, although a more specific “chronic active hepatitis” was detected in 5 of 37 (13.5%) patients. Bardella et al[10] evaluated 158 consecutive adults with celiac disease and showed that 42% had abnormal liver enzyme values. A gluten-free diet for 1 to 10 years resulted in complete normalization of liver chemistry tests in 95% patients.

In celiac disease, persistently abnormal liver chemistry tests may reflect the presence of a clinically occult hepatobiliary tract disorder with a possibly common immunopathogenesis. Specific examples of immune-mediated disorders include primary biliary cirrhosis, primary (lymphocytic, autoimmune) sclerosing cholangitis or autoimmune hepatitis. Alternatively, in some, a common genetically-based disorder, including altered control of small intestinal iron absorption resulting in a concomitant iron overload disorder, may be present, such as hemochromatosis. In addition, chronic changes
in liver chemistry tests may reflect a direct effect of the celiac disease. For example, impaired absorption and resultant malnutrition may lead to deposition of fat in the liver, related, in part, to reduced fat mobilization from hepatocytes. Indeed, massive hepatic steatosis has occasionally been reported in celiac disease. Finally, but very rarely, patients may develop a specific complication of celiac disease that involves the liver, such as a T-cell form of lymphoma.

HEPATOBILIARY TRACT DISEASES

Primary biliary cirrhosis

In 1978, Logan et al[12] described the first cases of primary biliary cirrhosis with celiac disease. Later, numerous additional cases have been reported[13-16]. In both disorders, other conditions having an immunological basis have been described, including diabetes and thyroiditis[16-19]. In addition, co-existence of primary biliary cirrhosis and celiac disease has not only been reported in Europe and the Americas, but also in migrants from South Asia[20] and the Coast Salish, an aboriginal population inhabiting the west coast of Canada thought to be of Asian descent[21]. To date, however, a definitive genetic predisposition or specific immunological alteration has not been clearly identified. Loss of weight, malabsorption, osteopenic bone disease, steatorrhea and elevated alkaline phosphatase activities are common features of both diseases, so that early in their coexistence, celiac disease or primary biliary cirrhosis may not be easily appreciated. In patients reported with both disorders, regardless of geographical origin or race, restriction of dietary gluten may have improved the diarrhea, but abnormal liver chemistry tests were usually not significantly altered with a gluten-free diet.

Some more recent studies have explored serological testing in primary biliary cirrhosis or celiac disease. Kingham and Parker[22] used a patient registry in the United Kingdom and defined the prevalence of primary biliary cirrhosis in 143 celiac patients as 3%, while the prevalence of celiac disease in 67 primary biliary cirrhosis patients was 6%. As a result, screening with antimitochondrial antibodies in celiac disease was recommended, while in primary biliary cirrhosis, serological screening with gladin antibodies or small intestinal biopsy was suggested. Dickey et al[23] found similar findings of 7% (4/57) primary biliary cirrhosis patients based on initial evaluation using endomysial antibodies (11% positive), followed by later duodenal biopsy confirmation. Despite 12 to 24 mo on gluten-free diets, however, improvement in liver chemistry tests was not detected even though endomysial antibodies disappeared. Using Danish and Swedish registry data based on over 8 000 patients with celiac disease, Sorensen et al[24] also suggested an increased risk of primary biliary cirrhosis. Using stored sera from 378 Canadian patients with primary biliary cirrhosis, Gillett et al[25] found that screening for IgA antibodies to endomysium and primary biliary cirrhosis were both positive in 10 (2.6%) patients and 5 patients had small intestinal biopsies confirming celiac disease. Interestingly, however, another 44 primary biliary cirrhosis patients had raised IgA tissue transglutaminase antibodies but were negative for IgA endomysium antibody. In 255 patients with autoimmune cholestatic liver disorders, including 173 with primary biliary cirrhosis, Volta et al[26] found 9 with celiac disease (including 7 in those with primary biliary cirrhosis, 4%). In some recent studies, however, the importance of biopsy confirmation in patients with primary biliary cirrhosis has been demonstrated in sero-positive patients as false-positive IgA or IgG tTG antibodies may occur in primary biliary cirrhosis[27,28].

In a recent study using a general practice longitudinal database from the United Kingdom[29], an overall 3-fold risk of primary biliary cirrhosis was demonstrated in 4 732 patients diagnosed with celiac disease as compared with 23 620 age- and sex-matched controls.

Primary sclerosing cholangitis

Primary sclerosing cholangitis was first found to be associated with celiac disease in 1988 in 3 patients with diarrhea and steatorrhea[30]. Two also had concomitant “ulcerative colitis” (one with “inactive” quiescent disease and one with “mild” or “minimal change” colonic disease), a disorder known to be associated with primary sclerosing cholangitis. Although hepatobiliary tract changes were defined by cholangiography and liver biopsy, these did not respond to a gluten-free diet. Later, other cases were reported[31-33]. In one, the predominant lymphocytic nature of the portal inflammatory process was emphasized with increased intra-epithelial lymphocytes in biliary ductal epithelium[30], an observation also noted in gastric and colonic epithelium of celiac patients[31,32]. To date, despite some case report data[34], it has been difficult to show good evidence for a response of the hepatobiliary tract disease to a gluten-free diet. This may, in part, reflect sampling difficulties associated with liver biopsy as well as the response or lack of response of relatively non-specific liver chemistry test markers of cholestasis (e.g., serum alkaline phosphatase). Indeed, the origin of alkaline phosphatase activities measured in serum include the hepatobiliary tract and other tissues that may be substantially altered in celiac disease (i.e., bone and the intestine); conceivably all might be improved with a gluten-free diet.

Autoimmune hepatitis and cholangitis

This has been evaluated in only a limited numbers of case reports and survey studies. Unfortunately, many appeared before hepatitis C testing[35,36]. Jacobsen et al[37] performed liver biopsies in 37 of 171 celiac patients and found changes of “chronic active hepatitis” in 5 (2.3%) patients. Using antibodies to endomysium and gladin, Volta et al[38] surveyed 157 patients with type 1 autoimmune hepatitis and 24 with type 2 autoimmune hepatitis for celiac disease. They found that 8 of these 181 (4%) patients were positive for endomysial antibodies, including 6 (4%) with type 1 disease and 2 (8%) with type 2 disease. Five of the 8 patients had a duodenal biopsy, most being asymptomatic, and all showed changes of subtotal villous atrophy, consistent with untreated celiac disease. The effects of steroid with or without azothioprine treatment on the underlying small intestinal histological changes were considered and also may have masked intestinal symptoms. Unfortunately, in this study, the effects of gluten-free
diet administration on the hepatic and intestinal changes were not reported. Recently, Villalta et al[37] evaluated 47 consecutive patients with autoimmune hepatitis, including 39 with type 1 disease and 8 with type 2 disease. Anti-IgA tissue transglutaminase and endomysial antibodies were positive in 3 (6.4%) patients and small intestinal biopsies confirmed the presence of the celiac disease histological changes[37].

Finally, celiac disease and other types of autoimmune liver and biliary tract disease may coexist. A case report of autoimmune cholangitis[38], a cholestatic liver disorder with biochemical evidence of cholestasis, histological evidence of inflammatory bile duct damage and an absence of mitochondrial antibodies, was has been described in a patient with celiac disease. Interestingly, this patient's small intestinal biopsies were reported to be normal without a gluten-free diet while being treated with steroids and azathioprine. In another case, Sedlack et al[39] reported an improvement in hepatic biochemistries without use of immunosuppressive agents.

HEMOCROMATOSIS OR IRON OVERLOAD LIVER DISEASE

Celiac disease has been associated with hemochromatosis, which is not surprising, since both are relatively common disorders based on a common Celtic ancestry, so any association could be coincidental[40-42]. Iron absorption largely occurs in the proximal duodenum, the site most often histologically altered in celiac disease. Indeed, “isolated” iron deficiency with anemia may be the initial clinical manifestation of clinically occult celiac disease. In contrast, in iron overload liver disease, inappropriate iron absorption from the proximal small intestine occurs as body iron stores are markedly increased. In one of these early case reports, treatment of celiac disease and improvement in the pathological small intestinal changes led to worsening liver chemistry test values and recognition of occult iron overload liver disease (C282Y-negative), presumably related to improved intestinal uptake of dietary iron[41]. Another similar case of C282Y-positive hemochromatosis presented with diarrhea, positive antigliadin and endomysial antibodies. Subsequent small bowel biopsies showed villous atrophy[42]. Interestingly, in this latter case, phlebotomy therapy had to be terminated early because of an unexpectedly rapid fall in the serum ferritin measurement. A genetically-based linkage was also suggested since both diseases are associated with the HLA-region on chromosome 6. Later investigations have sought to resolve this possible relationship. Butterworth et al[43] observed that HFE (hemochromatosis susceptibility gene) locus mutations are common in celiac disease patients from the United Kingdom and may be important in protecting the celiac from iron deficiency, while others suggested that the significance of these observations may be controversial[44]. More recent studies in an Italian population with untreated celiac disease found that HFE mutations failed to protect against the development of iron deficiency[45]. Interestingly, in a recent case study of a patient with homozygous C282Y and celiac disease[46], reduced expression of the divalent metal transporter 1 (DMT1) was observed, but not ferroportin 1 (FP1) or transferrin receptor 1 (TfR1).

OTHER LIVER DISORDERS IN CELIAC DISEASE

Hepatic steatosis

Common causes of hepatic steatosis include alcohol-induced steatosis, diabetes mellitus, NASH syndromes and some forms of drug therapy, including corticosteroids. In some countries, dietary protein deficiency and kwashiorkor are important causes. Intestinal malabsorption is often associated with hepatic steatosis in patients with a prior jejunoileal bypass procedure for morbid obesity[47,48] and, sometimes, in those with inflammatory bowel disease, particularly after extensive intestinal resections[49]. Because celiac disease is now frequently recognized in a clinically occult form before manifestations of marked nutrient depletion are detected, hepatic steatosis is probably less common than in other intestinal diseases.

Several cases of fatty infiltration of the liver, often massive, have been described in adults with celiac disease[50-53]. Presumably, lesser degrees of hepatic fat deposition may occur. Most often if massive steatosis is evident, elevated transaminase and alkaline phosphatase activities have been documented along with alterations in coagulation. However, in most, clinical and biochemical changes attributed to the hepatic steatosis were improved with a gluten-free diet. In a patient with massive hepatic steatosis[54], a gluten-free diet for about 1 year also resulted in histological improvement in the fatty changes detected in the liver.

The mechanisms involved in fat deposition in the liver are not defined. Interestingly, after jejunoileal bypass, reduced serum levels of some essential and nonessential amino acids may be observed[47,48]. In addition, changes in serum amino acids have been recorded in patients with starvation-associated kwashiorkor[55,56]. Based on these nutritional disorders, it has been suggested that malabsorption in celiac disease might lead to chronic deficiency of a lipotropic factor (e.g., choline), with an associated pyridoxine deficiency, hepatic steatosis might occur[57]. Further studies are needed to define the precise pathogenetic mechanism or mechanisms for fatty liver in celiac disease.

Gallstone disease

Several studies have focused on gallbladder function in celiac patients. In some studies, slow emptying of the gallbladder has been documented[58,59], along with impaired contraction response to fat[59]. Studies of enteric endocrine cells showed significant quantitative changes in celiac patients, including complete absence of mucosal secretin cells[59]. In addition, studies with test meals have suggested impaired secretion of cholecystokinin in patients with celiac disease[59] or, possibly, impaired gallbladder responsiveness to cholecystokinin[59].

In spite of these physiological alterations, there does not appear to be a significant predisposition to gallstones in celiac disease. Only 9 of 350 patients had a cholecystectomy for gallstone disease[59]. However, in a
survey of elderly celiacs initially diagnosed after the age of 60 years, 6 of 30 (20%) had gallstone disease.

Hepatic vein obstruction
Although mesenteric vascular ischemia and vasculitis have been described in celiac disease, there are also reports of a unusual Budd-Chiari-like syndrome among celiac children from North Africa, particularly Tunisian and Algerian patients. Hepatic vein obstruction has also been documented in 3 adults. Deficiencies in protein C and antithrombin III are detected, and malabsorption of vitamin K in celiac disease has been proposed to cause transient protein C or protein S deficiencies. Further studies are needed to identify possible factors, either dietary or environmental agents, that may be important.

More recently, a celiac patient with a Budd-Chiari syndrome associated with membranous obstruction of the inferior vena cava treated successfully with percutaneous balloon angioplasty has been reported.

Hepatic malignancies
While hepatocellular cancer has been reported in 1 patient, cirrhosis was also present. Occasionally, the liver may be involved with lymphoma, the most frequently detected malignant disorder in celiac disease patients.

In some patients with celiac disease, lymphomatous deposits have been detected in the liver, presumably as metastatic lesions. For example, lymphoma in the liver is apparently secondary to jejunal lymphoma, complicating celiac disease. In general, involvement of the liver in celiac disease patients with lymphoma is limited and overshadowed by the clinical course of the intestinal disease. However, a fulminant cholestatic syndrome has been described in a celiac disease patient, resulting in hepatic failure. Later investigations have shown widespread hepatic involvement with an unusual lymphoid neoplasm classified as a hepatosplenic lymphoma, a rare type of peripheral T-cell lymphoma with rearrangement of the gamma-delta T-cell receptor.

Liver failure
In patients with severe liver failure from a variety of causes in celiac disease, dietary treatment reverses hepatic dysfunction, even in patients with consideration for possible liver transplantation.

PANCREATIC DISEASE
While celiac disease is associated with insulin-dependent diabetes, pancreatic exocrine insufficiency and celiac disease have only occasionally been recorded. Pancreatic calcification is most often associated with chronic or persisting pancreatic inflammation which is usually due to excessive consumption of alcoholic beverages. Atrophy, fibrosis and altered pancreatic function have been observed in experimental animals treated with diets deficient in protein, in adults with protein-energy malnutrition, in children with kwashiorkor and in some early autopsy studies of patients with celiac disease. In addition, pancreatic calcification has been reported with chronic protein malnutrition in the Indian subcontinent and in some African countries. Finally, a patient with celiac disease and pancreatitis with calcification has been described.

Although the frequency of pancreatic disease in celiac patients is not known, impaired pancreatic function occurs and may be a cause of persistently impaired nutrient assimilation and malnutrition. It has been estimated that over 20% of children with celiac disease have defective exocrine pancreatic function. This may be related to several factors. Impaired secretion and/or release of pancreatic stimulating hormones from the diseased proximal small intestine may be important. Immunohistochemical studies have demonstrated alterations in enteric endocrine cells, and in biopsies from patients with untreated celiac disease, an absence of secretin cells has been reported. Studies with test meals in celiac patients have suggested impaired secretion of cholecystokinin-pancreozymin resulting in reduced pancreatic exocrine cell stimulation. In addition, a deficiency of amino acids may result from impaired small intestinal amino acid uptake, leading to a reduction in precursors for pancreatic enzyme synthesis. Also, protein malnutrition may lead to structural changes in the pancreas, including atrophy of acinar cells and pancreatic fibrosis, resulting in impaired pancreatic exocrine function. In a more recent study, pancreatic enzyme measurements were reduced with mucosal atrophy and could be inversely correlated with the degree of intestinal damage.

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