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The Liver and Celiac Disease

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Abstract

Celiac disease is a multisystem disorder. Celiac hepatitis characterized by gluten-responsive mild elevation of transaminases is the more common liver manifestation of celiac disease. Celiac disease may also be associated or coexist with other chronic liver disorders. Shared genetic risk and increased intestinal permeability has been suggested to be the most relevant events in the pathogenesis of liver injury in celiac disease. The aim of this article is to review the full spectrum of liver disorders in patients with celiac disease.

Keywords

Hepatitis; Cirrhosis; Alanine Aminotransferase

Introduction

Celiac disease (CD) is a multisystem disorder characterized by permanent intolerance to gluten (wheat, barley, and rye).[1,2] Although the hallmark of CD is enteropathy; other organs including the liver may also be affected. Liver abnormalities in untreated CD are common.[3] CD can cause direct liver damage (celiac hepatitis) but also may be associated with other liver conditions.[4] Abnormal liver blood tests (especially hypertransaminasemia) may be the sole manifestations of hitherto unrecognized CD. The pathophysiology of liver injury in CD remains poorly understood. The aim of this study is to review the full spectrum of liver injury related to CD.

Initial Work-Up

A complete liver test panel is strongly recommended in patients with newly diagnosed CD.[3] Mild elevation of transaminases (3-5 times the upper limit of normal) in the absence of clinical manifestations of chronic liver disease is characteristic of celiac hepatitis. Resolution of the abnormal liver tests after strict adherence to a gluten-free diet (GFD) confirms the

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diagnosis.[3] Thus, if liver tests were abnormal at the time of diagnosis, it should be re-checked after 6-12 months on a strict GFD.[3,5] In patients with typical findings for celiac hepatitis, it is reasonable to treat with a GFD first and plan for further investigation in the subset of patients (10%-25%) with persistent liver test abnormalities after 1 year on strict adherence to GFD. However, an initial evaluation is strongly recommend for coexistent liver disorder in patients with symptoms or physical signs that suggest chronic liver disorder and/or transaminases levels greater than 5 times the upper limit of normal (see Fig. 1).[6-8]

Isolated elevation of alkaline phosphatase is not characteristic of celiac hepatitis. Metabolic bone disease may be the most common explanation for an isolated alkaline phosphatase in patients with CD.[2,9] Check calcium, phosphate, 25 (OH) vitamin D, and parathyroid hormone for evaluation for osteomalacia.[10] A very low 25-(0H) vitamin D, low calcium and phosphate, and elevated parathyroid hormone strongly support the diagnosis of malabsorption-related osteomalacia. Dual energy x-ray absorptiometry is suggested for all patients with newly-diagnosed CD.[10] Thyroid stimulant hormone measurement is also useful.[10] Chronic cholestatic liver disorders should be considered after exclusion of non-liver causes for isolated elevation of alkaline phosphatase.

Liver biopsy is not necessary in most patients with newly diagnosed CD who have isolated hypertransaminasemia.[6,11] Liver biopsy may be useful in selected patients with suspicion of chronic cholestatic liver disease with negative non-invasive tests, unexplained persistent hypertransaminasemia (after 1-year on strict adherence to GFD), and coexistent liver disease in which the liver biopsy has therapeutic or prognostic significance.[3]

Celiac Hepatitis

Celiac hepatitis is a gluten-dependent injury and liver abnormalities resolved on a GFD, typically after 12 months of strict adherence.[5-7,12,13] Histological changes also improve after a GFD.[14]

Hypertransaminasemia is frequent in untreated CD (13%-60%) (see Table 1).[6,7,12] Conversely, CD is present in as many of the 9% of persons with unexplained hypertransaminasemia.[15,16] Celiac patients have both an increased risk of subsequent liver disease and risk of death from liver cirrhosis than the general population. [3,15,17,18]

The mechanisms underlying celiac hepatitis are poorly understood.[19] Intestinal permeability was quantitatively higher in patients with CD and hypertransaminasemia than in those with CD and normal liver tests.[11] The phenomenon is gluten-dependent as demonstrated for normalization of both intestinal permeability and elevation of transaminases with a GFD.[11] It has been speculated that increased intestinal permeability may facilitate the entry to the portal circulation (and then to the liver) of toxins, microbial and other antigens, cytokines, and/or other mediators of liver injury (see Fig.2).[7,16,20,21] However, liver injury is not commonly seen in other intestinal disorders associated with increased intestinal permeability.

Most patients with celiac hepatitis have no symptoms or signs of liver disease.[6,7,15] Thus, the presence of palmar erythema, jaundice, ascites, splenomegaly, encephalopathy,

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coagulopathy, or portal hypertension suggests advanced liver disease or the coexistence with other chronic liver disease.[3,6] Mild to moderate (less than 5 times the upper limit of normal) levels of aspartate aminotransferase and/or alanine aminotransferase are typical.[6,7,12,16] The ratio aspartate to alanine aminotransferase is usually less than 1.[3] Elevated alanine aminotransferase is associated with poor growth and severe villous atrophy in children.[22]

Conjugated hyperbilirubinemia is not expected in the absence of advance cirrhosis.[6,10,23] Abdominal ultrasound is not necessary during the initial work-up, and findings on the liver vary according to the degree of liver injury; from normal (most common) to coarse echo texture.[23] Other non-specific abdominal ultrasound findings suggestive of CD include dilated small bowel loops, enlarged mesenteric lymph nodes, non-occlusive intussusception, abnormal jejunum folds, and increased fasting gallbladder volume.[24,25]

Liver biopsy is rarely needed for celiac hepatitis. Mild and/or nonspecific histological changes are seen.[13,26] Extensive fibrosis and cirrhosis are rare (see Table 2).[23]

Finally, there is considerable evidence and expert opinion support for testing for CD in patients with unexplained abnormal liver tests.[27] Advanced liver disease is associated with false positive results of the tissue transglutaminase antibody (especially if titer is less than 3 times upper limit of normal).[3] Endomysial antibodies are more specific in this context and may be helpful in the diagnostic evaluation of patients with advanced liver disease. Biopsy confirmation of CD is strongly recommended.[3]

Celiac Disease and Selected Liver Disorders

Autoimmune Liver Disorders

Primary biliary cholangitis and autoimmune hepatitis may be associated with CD.[3,28,29] The frequency of CD in patients with primary biliary cholangitis (1% - 7%) and primary biliary cholangitis in patients with CD (0.1% - 3%) is variable between studies (see Table 3 and Table 4).[8,30-37] CD is present in 4% -6% of patients with both type 1 and type 2 autoimmune hepatitis.[3,28-30] There are also case reports of primary sclerosing cholangitis and CD.[38]

The reasons for the association between CD and autoimmune liver disorders are unknown. Shared genetic susceptibility to autoimmunity and perhaps vulnerability of both biliary and small intestine epithelium to immune-mediated damage may play a role.[32] CD and primary sclerosing cholangitis share the at risk gene risk HLA-DQ2. The presence of HLA-DQ2 is associated with an increased rapid progression of the liver disease in primary sclerosing cholangitis.[39] Likewise, homozygosity for DQ2 increase CD risk and perhaps severity.[40,41] A GFD appears to have little effect on coexistent liver disease outcome as it may not improve liver tests or symptoms.[29,31]

Viral Hepatitis and Vaccines

There is no association between CD and chronic hepatitis C.[42] Most patients with concurrent CD and hepatitis C have a well-defined route of transmission for hepatitis C.[43] Hepatitis C treatment with interferon-α and/or ribavirin may activate silent or latent CD.[3,44,45] The clinical relevance of this observation has decreased with the newly available direct active

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antiviral drugs. Non-response to hepatitis B vaccine given prior to diagnosis of CD is frequent (54%- 68%).[46,47] Rate of seroconversion correlated with the amount of gluten ingestion and greater than 95% of CD patients vaccinated after treatment with a GFD may respond.[48] HLA-DQ2 may play a role in vaccine non-response.[46,49]

Nonalcoholic Fatty Liver

The frequency of CD in patients with nonalcoholic fatty liver disease is 3% - 7%.[50,51] Screening all patients with nonalcoholic fatty liver disease for CD is controversial. However, a high index of suspicion may result in early diagnosis. Active screening is reasonable in patients with nonalcoholic fatty liver disease with unexplained anemia, nutritional deficiencies, and recurrent abdominal symptoms.[51] The GFD may improve liver tests in patients with nonalcoholic fatty liver disease and CD, but it is unclear if this effect is independent of nutritional factors.[50] Moreover, there is an increased risk of nonalcoholic fatty liver disease (hazard ratio = 2.8) following a GFD and close monitoring of weight is recommended after GFD.[52] Increased risk was higher in children and non-overweight CD patients.[52,53] Nonalcoholic fatty liver disease risk remains elevated even beyond 15 years after the diagnosis of CD.[52]

Liver Transplantation

The prevalence of CD in liver transplant patients with end-stage liver disease of multiple causes varied from 3% - 4.3%.[23,54] Strict adherence for 6 months to a GFD in a small group of enlisted patients with CD and end-staged liver disease improved liver function to the point that made liver transplant unnecessary. [23,54,55] A large Swedish study showed no increased risk of liver transplantation in diagnosed CD despite increased risk of acute hepatitis, chronic hepatitis, primary sclerosing cholangitis, fatty liver disease, liver failure, liver cirrhosis/fibrosis, and primary biliary cholangitis.[17]

Mortality of Liver Cause in Celiac Disease

Mortality of liver cause is increased in patients with CD (standardized mortality ratio 3.10) although the absolute risk of liver-related mortality is modest.[56]

Conclusion

Liver blood tests abnormalities are common in patients with CD. Conversely, abnormal liver blood tests (especially hypertransaminasemia) may be the sole manifestations of unrecognized CD. Celiac hepatitis is the most common liver manifestation of CD and responsive to GFD. Finally, CD may be associated with selected liver conditions especially immune-mediated and the effect of GFD on the progression of coexistent liver disease is unclear.

Abbreviations:

CD	celiac disease
GFD	gluten-free diet

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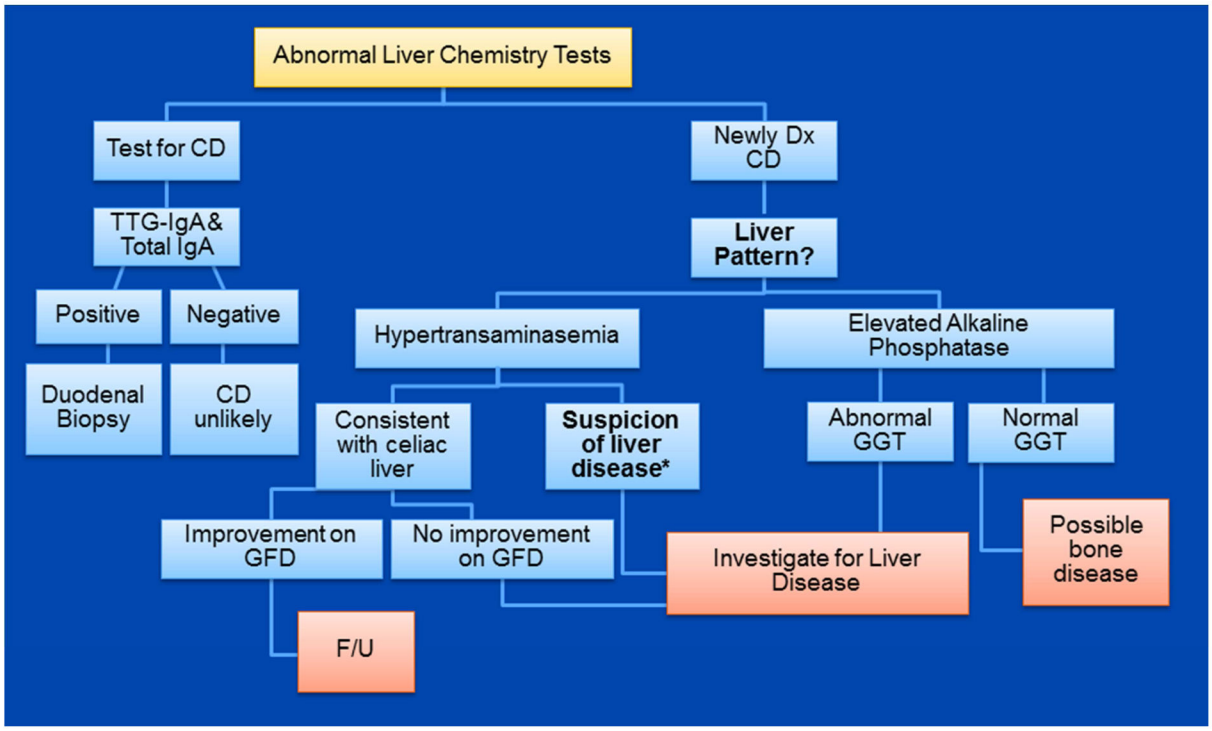

Figure 1.

Suggested approach to abnormal liver test and celiac disease. *Clues for suspicion of concurrent liver disease includes: hyperbilirubinemia, hypertransaminasemia >5 times upper limit of normal, AST: ALT ratio >1.0, and abnormal physical exam.

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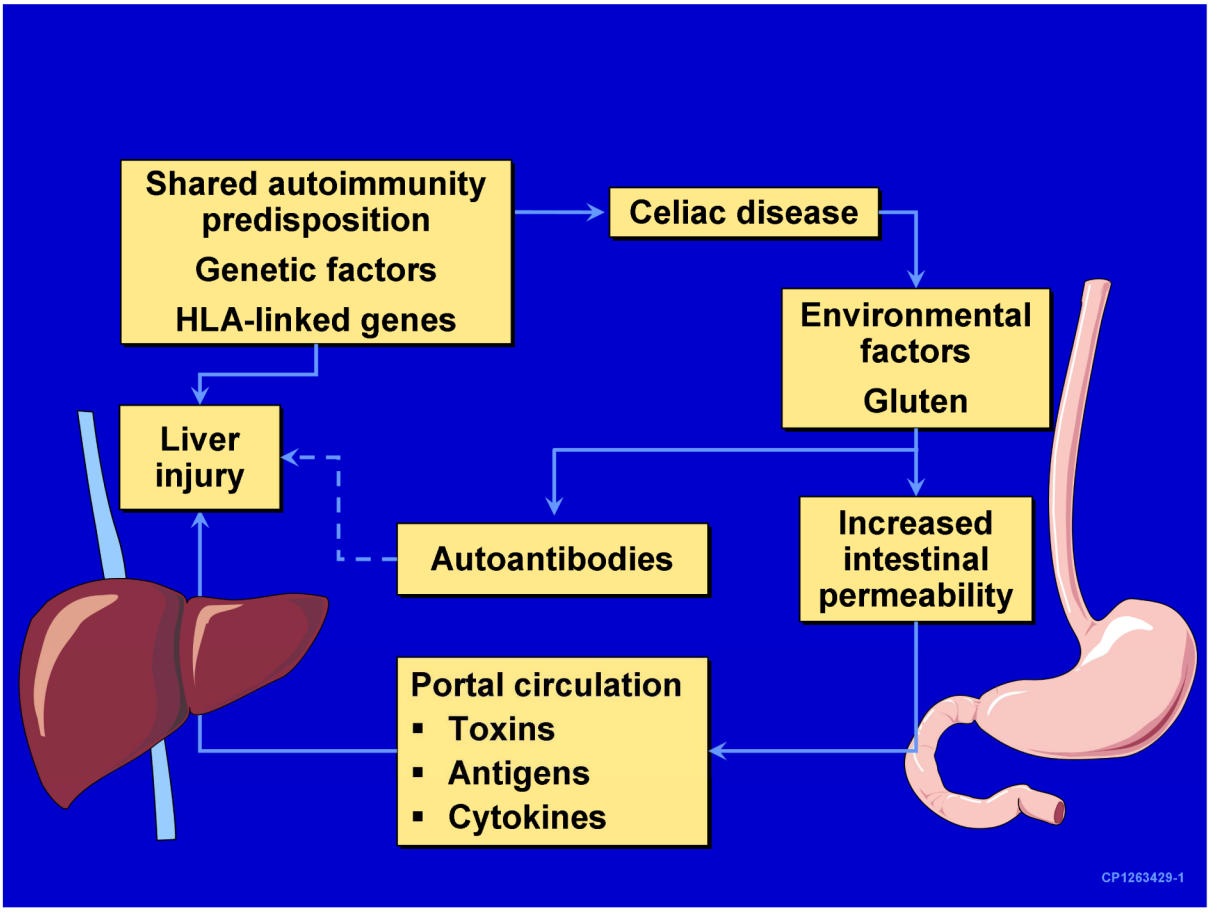

Figure 2.
Potential mechanisms of liver injury in celiac disease (From Rubio-Tapia A, Murray JA. The liver in celiac disease. *Hepatology*. 2007;46(5):1650-1658, with permission.)

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Table 1

Frequency of abnormal liver chemistry test and the effect of a GFD in patients with celiac disease

Reference	Cases	Female (n, %)	Age (range) yrs	Abnormal liver test (n, %)	Response to GFD (n, %)	Time on GFD
Bardella[6]	158	127, 80%	18-68	67, 42%	60/67, 90%	6 months
Hagander[7]	74	43, 58%	14-73	29/53, 55%	N/A*	N/A
Bonamico[12]	65	43, 66%	0.5-18	37, 60%	N/A	N/A
Jacobsen[13]	132	64, 48%	25-86	62, 47%	24/32, 75%	2 years
Dickey[5]	129	88, 68%	17-88	17, 13%	15/17, 88%	6-12 months
Castillo, N[57]	463	328,71%	44 (+/−14)	190, 41%	79%	18 months
Lee, GJ[58]	388	235,61%	10	185, 48%	71% (only 21 repeat)	N/A
Aarela, L[22]	150	103, 69%	7.3 (4.3-11.8)	22, 15%	80%	12 months

*Transaminase levels fell significantly 2.5 - 8 weeks after starting a GFD

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Table 2

Liver pathology of patients with celiac disease

- Periportal inflammation *
- Mononuclear infiltration on the parenchyma *
- Steatosis
- Bile duct obstruction
- Hyperplasia of Kupffer cells
- Fibrosis (all stages)
- Granuloma
- Cirrhosis

* most common findings

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Table 3

Selected studies on screening of celiac disease with biopsy confirmation in primary biliary cirrhosis

Reference	Cases with PBC	Cases identified with CD, n (%)
Volta[30]	173	7 (4%)
Dickey[31]	57	4 (7%)
Kingham[32]	67	4 (6%)
Niveloni[33]	10	2
Floreani[34]	87	3 (3.4%)
Gillet[35]	378	5 (1.3%)

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Table 4

Selected studies on the prevalence of primary biliary cirrhosis in patients with celiac disease

Reference	Cases with CD	Cases identified with PBC, n (%)
Lawson[8]	4732	9 (0.1%)
Kingham[32]	143	4 (3%)
Bardella[36]	336	1 (0.3%)
Sorensen[37]	896	2 (0.2%)