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Review article

Hepatitis B and Celiac Disease: A Cause for Concern?

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Abstract

Some theories suggest that the development of the immune response to clear hepatitis B triggers the intestinal tissue damage seen in celiac disease in genetically predisposed individuals. Although the role of hepatitis B virus infection in the development of autoimmune diseases has been widely discussed in the literature, it remains a controversial topic. Our objective is to review whether there is an association between hepatitis B and celiac disease and the particularities of vaccination against hepatitis B in celiac patients.

Keywords

Hepatitis B, celiac disease, interferon alfa, vaccine.

INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated disorder induced by gluten ingestion in genetically predisposed individuals[1]. Patients may present with classic clinical manifestations (diarrhea, anemia, weight loss) and involvement of other organic systems, such as the neurological, endocrinological, nephrological, and hepatic systems[2,3]. The diagnostic approach for CD in adults incorporates serological and histological data. Serologic testing for CD should consist of measurement of tissue transglutaminase (tTG) IgA antibodies while following a gluten-containing diet and simultaneous measurement of total IgA since the prevalence of IgA deficiency in patients with CD is 10 to 15 times higher than in healthy subjects[4,5]. A positive serological test supports the diagnosis, but no test is 100% specific for CD, and diagnostic accuracy varies considerably between laboratories[6]. The diagnosis of CD is definitively confirmed by lymphocytic infiltrate and villous atrophy in the small intestine biopsy according to the Marsh classification (**Figure 1**)[7].

Active screening for CD is recommended in patients with signs or symptoms suggestive of CD, including diarrhea, weight loss, abdominal pain, bloating, or laboratory abnormalities, such as unexplained elevated serum aminotransferase levels[4]. It is also recommended in some liver diseases, especially in those with autoimmune disorders, steatosis in the absence of metabolic syndrome, idiopathic

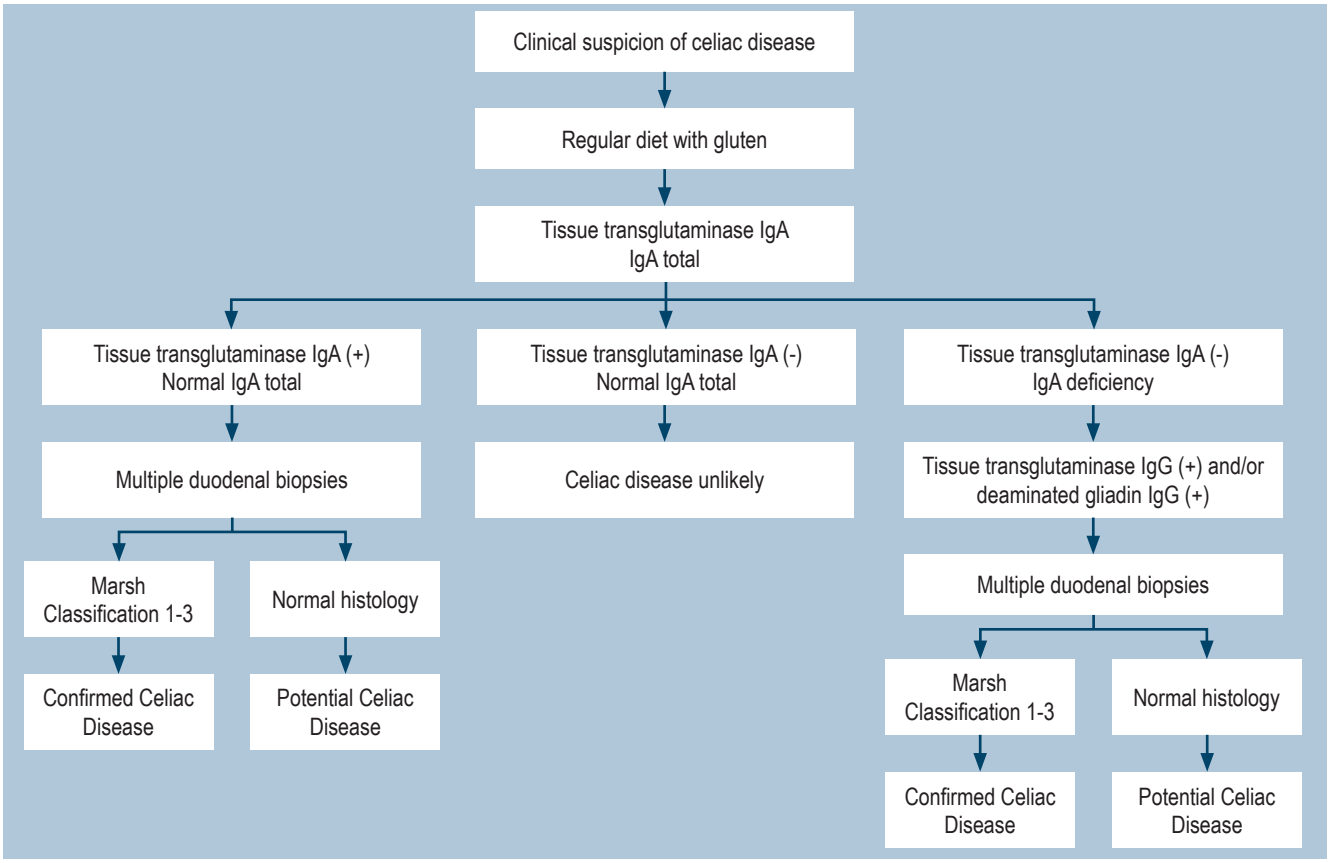

Figure 1. Diagnostic algorithm for celiac disease.

non-cirrhotic portal hypertension, cryptogenic cirrhosis, and in the context of liver transplant[8,9]. Apart from these scenarios, due to the high global prevalence of hepatitis B[10], this study aims to review articles in the literature that deal with a potential association between hepatitis B and CD and determine the particularities of the vaccination against hepatitis B in celiac patients.

MATERIALS AND METHODS

The PubMed database was searched in October 2022 to identify articles for this review using two search strategies. In the first strategy (Search A), the descriptor "CD + hepatitis B" was used, and in the second (Search B), "CD + HBV"; only English terms were employed. Additionally, manual searches were carried out in the articles' references. We included articles on CD and hepatitis B with a clearly described methodology, published in English-language journals without date restrictions, and selected by affinity with the objective. A full-text version of selected articles was obtained to confirm eligibility.

HEPATITIS B AND CD

Some authors have investigated the prevalence of CD in patients with hepatitis B; these findings are summarized in **Table 1**[11–14]. The prevalence of CD varied between 3.3% and 17.2%[6–8]. Leonardi et al.[11] demonstrated a high prevalence of CD in patients with hepatitis B. Although limited by the small size of the patients studied, this study is interesting because it may represent what has been observed in Italy[15]. The prevalence of hepatitis B virus (HBV) in Italy is higher than in the rest of Europe[16], and a high prevalence of CD is also estimated[17]. Concerning the study by Nau et al., southwest Brazil is also a region with a high prevalence of hepatitis B, where the majority of inhabitants are descendants of Portuguese, Italian, and German immigrants[18].

Despite the limited sample size of their hepatitis B cohorts, which requires conservative interpretation, the studies still provide intriguing data. Soto Iglesias et al.[19] presented two patients who developed CD after resolving an acute HBV infection. Reactive serological tests and the presence of typical histopathological findings confirmed

the diagnosis of CD. The same authors suggested that developing the immune response for clearance of HBV triggers the intestinal tissue damage observed in CD in genetically predisposed individuals. One hypothesis in the field of liver disorders is that a deregulated immune process would induce liver damage due to autoantibodies. Another hypothesis suggests that liver damage results from increased intestinal permeability, resulting in toxins or autoantigens from the liver through the portal vein[12]. Although the role of HBV infection in the development of autoimmune diseases has been widely discussed in the literature, it remains a controversial topic.

Bardela et al. found the opposite: The prevalence of HBV among 158 individuals with CD was 4.5%[20]. Other studies that evaluated the prevalence of HBV in celiac patients are summarized in **Table 1**[21–23]. After all these years, there is no clinical evidence of an association between CD and hepatitis infection, and the appearance of these two diseases in a patient may be a chance finding. Still, despite the findings described in this review, it is not possible to make a specific recommendation for CD screening in people with hepatitis B or vice versa[24].

INTERFERON α

Interferon α and its pegylated form have been used for more than thirty years to treat chronic hepatitis B with the advantages of a finite duration of treatment and a loss of hepatitis B surface antigen (HBsAg) with antibody seroconversion against the sustained hepatitis B virus surface antigen (anti-HBsAg); however, efficacy is limited since seroconversion is achieved in a small proportion of treated patients, and side effects are frequent[24]. Leonardi et al.[11] evaluated 15 of 60 patients who had used interferon α therapy for 12 months at a dose of 5 million units (5 MU). As mentioned above, it demonstrated a high prevalence of hepatitis B among celiac patients but did not compare the prevalence of hepatitis B according to interferon α use. Sima et al.[12] investigated 88 patients with chronic hepatitis B. They observed that 26 patients who had previously used interferon α had celiac antibodies compared to 6 patients without treatment with interferon α ($p < 0.05$). Some reports indicate autoimmune disorders such as insulin-dependent diabetes mellitus and CD that may develop during treatment with interferon α for viral hepatitis because this drug has immunomodulatory properties that can induce a silent autoimmune disorder such as CD[25–29].

Interferon α therapy may trigger CD in susceptible patients, and it has been hypothesized that the most likely pathogenesis of this process could be a dysregulation of the balance between the need to recognize antigens of pathogenic microorganisms and the need to prevent inappropriate immune responses to foods and normal flora[12]. These findings suggest that CD should be sought before interferon therapy for early diagnosis and prevention of CD complications. However, there is still insufficient evidence that interferon α can activate CD.

Table 1. Prevalence of celiac disease in patients with hepatitis B and vice versa

Author	Year	Country	Patients	Total	N	Prevalence
CD in patients with hepatitis B						
- Leonardi et al.[11]	2010	Italy	Patients with hepatitis B	35	6	17.2%
- Sima et al.[12]	2010	Iran	Patients with hepatitis B	88	8	9.1%
- Nau et al.[13]	2013	Brazil	Patients with hepatitis B	50	6	12%
- Sood et al.[14]	2017	India	Patients with hepatitis B	30	1	3.3%
Hepatitis B in patients with CD						
- Bardella et al.[20]	1995	Italy	Patients with CD and elevated aminotransferases	67	3	4.5%
- Novacek et al.[21]	1999	Austria	Patients with CD	178	1	0.6%
- Moghaddam et al.[22]	2013	United Kingdom	Patients with CD	98	1	1%
- Tanwar et al.[23]	2020	India	Patients with CD and portal hypertension	42	2	4.8%

HBV VACCINE

The success of a vaccination program depends on the availability of safe and highly effective vaccines and the implementation of appropriate vaccination strategies. After a complete vaccination cycle with the classic schedule of three vaccine doses administered at 0, 1, and 6 months, anti-HBsAg seroprotection rates at a concentration equal to or greater than 10 mIU/mL (the antibody threshold considered protective) are close to 100% in healthy children and almost 95% in healthy adults[30,31].

Along with host-related factors (i.e., age, sex, immunocompetence, genetics, and co-infections), vaccine and vaccination-related factors have also been found to affect the response to vaccination. Among these, the dose and vaccination schedule, the injection site, and the route of administration are critical factors in achieving an optimal immune response[32].

Addressing the issue of CD and hepatitis B is mainly related to immunization against hepatitis B in people with CD. The CD is more common in individuals with HLA-DQ2 and HLA-DQ8, and the literature has shown that these individuals have a lower response rate to HBV vaccination than the general population[33–36]. In particular, the immune response to the HBV vaccine is primarily determined by immunogenetic peptides through the HLA-DR and DQ molecules, and the DR3-DQ2 and DR7-DQ2 haplotypes generally have a lower response rate[37–39].

The correlation between CD activity (by measuring serum anti-transglutaminase titers) and the development of an antibody response to the HBV vaccine has been previously demonstrated[34]. Trovato et al.[40] evaluated 96 children with CD; 41.7% (n = 40) showed non-protective or absent antibody titers against HBV. Elevated tTG-IgA values ($p = 0.023$) and older age at diagnosis ($p < 0.001$) were associated with a lack of seroconversion to the HBV vaccine. They hypothesize that competition between gluten and the HBV surface antigen could explain this phenomenon. Therefore, we can speculate that in patients with CD, the immune system may focus on the non-self antigen that occurs most frequently in these patients (dietary gluten) and may polarize its activity in this direction rather than toward the antigen HBV surface antigen with massive production of tTG autoantibodies, but suboptimal production of antibodies against HBV surface antigens.

A lack of response has also been correlated with age, smoking, obesity, and male sex[39]. However, when children with CD follow a gluten-free diet, the immune response to the HBV vaccine is similar to that of the general population. This suggests that treatment adherence may improve the lack of response to the HBV vaccine in celiac children[41]. Lastly, the lack of response to the hepatitis B vaccine should be considered a sign of possible undiagnosed CD[33]. Nemes et al.[34] evaluated 128 children and adolescents with CD and 113 age-matched controls: 22 patients with CD were prospectively immunized after diagnosis during dietary treatment (Group 1) and a total of 106 celiac children, and the control subjects received vaccination by mass immunization regardless of diet status (Group 2). Diet compliance and CD activity were monitored by measuring tTG and anti-endomysial antibodies (EmA). The vaccine response rate for Group 1 was 95.5% compared to 50.9% for Group 2. The response rate among 27 undiagnosed and untreated CD patients was 25.9%, significantly lower than that in control subjects of 75.2% ($p < 0.001$).

Some strategies can be followed when vaccinating against hepatitis B in CD patients. One possibility would be administering the three usual doses, giving booster doses to non-responders, and performing serology to assess the response after each dose[42]. The intradermal route for the booster dose of the hepatitis B vaccine in celiac patients is a better option to obtain a higher titer of antibodies against HBV[43]. Furthermore, the intradermal route allows for a better cost-effectiveness ratio since the cost reduction exceeds 50% (2 µg per dose) compared to standard intramuscular vaccination (10 µg per dose)[44]. A third strategy would be to revaccinate celiac patients intramuscularly in treatment with a gluten-free diet after the decrease in celiac-specific antibodies[34]. The intradermal route is preferable for revaccination of these patients[45].

The prevalence of seroprotective levels of anti-HBsAg detected 11 years after primary immunization and the frequency of response to a booster dose of the vaccine are lower in celiac patients than in healthy controls[46]. Therefore, a booster dose of the vaccine should be administered every ten years to all celiac patients to protect non-responding celiacs from HBV infection[45].

CONCLUSION

Despite the coexistence of both diseases, a clear association between hepatitis B and CD has not been demonstrated, so routine screening for CD in HBV carriers cannot be recommended; however, hepatitis B should be investigated in the setting of elevated aminotransferases in celiac patients. Due to the poor response to vaccination against HBV, particular strategies should be implemented in celiac patients, such as the intradermal route and revaccination.

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Hepatitis B y enfermedad celíaca: ¿un motivo de preocupación?

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