Introduction

A wide range of diseases of the liver and biliary system, especially of inflammatory nature, can complicate the clinical course of coeliac disease (CD). \(^1\)

In general, a distinction can be made between:

- **coeliac hepatitis** \(^2\): which develops in both patients presenting with intestinal symptoms and subjects with asymptomatic coeliac disease. This benign and clinically silent condition, probably mediated by an immune response, is the most frequent type and can be resolved by a gluten-free diet;

- **autoimmune chronic liver inflammation**: it usually presents itself in the form of autoimmune hepatitis or, sometimes, primary biliary cirrhosis and/or primary sclerosing cholangitis. These, less frequent, disorders require a specific immunosuppressive therapy, as a gluten-free diet (GFD) has not proved to be very effective \(^3\);

- occasionally, other types of hepatic lesions can appear, such as nodular regenerative hyperplasia and hepatocellular carcinoma \(^4\).

Clinical and epidemiological aspects

The first report of a liver complication in CD dates back to 1977 when hypertransaminasaemia, at CD diagnosis, was found in 30 out of 75 (40%) untreated coeliac patients. \(^5\) In most cases it can be reversed by introducing a gluten-free diet. Ten years later, an increase in aminotransferase activity was also described in 39 out of 65 (60%) children with gluten intolerance and gastrointestinal symptoms. \(^6\) In the same year, the case of a young girl was reported. She presented with a persistent and cryptogenic elevation of serum aminotransferases and a mild inflammation of the portal tract. In this case, CD diagnosis was suggested by the considerable presence of anti-reticulin antibodies, which was evidence of the fact that this disease can develop atypically as a cryptogenic liver disorder \(^7\). Two successive retrospective studies confirmed this hypothesis, by showing that more than 9% of patients characterised by a persistent and cryptogenic elevation of serum aminotransferase activity resulted to be affected by asymptomatic coeliac disease. \(^8,9\) This condition, today known as coeliac hepatitis \(^2,3\), is characterized by:

- Absence of hepatomegalia, splenomegalia or any clinical sign suggesting a chronic liver disease;

- Absence of hypergammaglobulinaemia and serum antibodies (with the exception of CD-specific anti-transglutaminases);

- Presence of a mild inflammation in the globular and portal tracts, which can be reversed by GFD.

An alternative diagnosis is to be taken into consideration, if there is no response after a 12-month GDF treatment \(^10\). Hyper-transaminasaemia can conceal severe liver damage \(^5,11\). In these cases, the histological tests may highlight an autoimmune liver disorder characterised by primary biliary cirrhosis (PBC) and/or primary sclerosing cholangitis (PSC) and autoimmune hepatitis \(^10\).

A study \(^12\) carried out on 4732 adult coeliac patients showed a three times higher risk of developing PBC and PSC in comparison with healthy subjects.
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- Furthermore, two cases of nodular regenerative hyperplasia (NRH)\(^{(13)}\) have been recently described in patients with gluten-sensitive enteropathy who presented with IgA anticardiolipin antibodies (aCL). The T-help cells deriving from gluten-specific T-cells have been suggested to trigger an IgA response directed against both transglutaminase and the protein/phospholipid complexes, thereby leading to the formation of IgA aCL. The above-mentioned complexes bring about thrombosis in the small radicles of the vena porta, thereby causing hyperplasia in the surrounding tissue\(^{(13)}\).

- Table 1 reports the most significant data obtained by a number of studies concerning the association between coeliac disease and liver disorders:

<table>
<thead>
<tr>
<th>Author</th>
<th>Liver disorder</th>
<th>N° patients</th>
<th>N° patients with CD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardella et al. (1999)(^{(9)})</td>
<td>Hypertransaminasaemia</td>
<td>200</td>
<td>9.3</td>
</tr>
<tr>
<td>Volta et al. (2001)(^{(16)})</td>
<td>Hypertransaminasaemia</td>
<td>110</td>
<td>9.1</td>
</tr>
<tr>
<td>Gillette et al. (2000)(^{(17)})</td>
<td>Primary biliary cirrhosis</td>
<td>378</td>
<td>2.6</td>
</tr>
<tr>
<td>Volta et al. (2002)(^{(18)})</td>
<td>Primary biliary cirrhosis</td>
<td>173</td>
<td>4</td>
</tr>
<tr>
<td>Francavilla et al. (2001)(^{(19)})</td>
<td>Autoimmune hepatitis</td>
<td>96</td>
<td>3.4</td>
</tr>
<tr>
<td>Villalta et al. (2005)(^{(20)})</td>
<td>Autoimmune hepatitis</td>
<td>47</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Pathogenesis

The pathogenetic mechanism underlying liver damage in coeliac patients is still unclear. The different types of diseases described above may represent a wide spectrum of the same disease in which individual factors, such as genetic predisposition and the duration to gluten exposure, can influence the reversibility of liver damage\(^{(4)}\). Autoimmune liver disorders and coeliac disease do share class-II HLA haplotypes. In the Caucasian population, two haplotypes have been identified as markers predisposing to autoimmune hepatitis: complex HLA A1 B8 DR3 and HLA DR4. Similarly, specific class-II HLA antigens such as HLA-DR3, in particular molecules HLA-DQ2 and HLA DR4, confer genetic predisposition to coeliac disease\(^{(3,1)}\). Furthermore, coeliac patients present with increased intestinal permeability which can facilitate the absorption of antigens from the bowel. In genetically predisposed subjects, increased permeability to antigens may induce an immune response against both the antigens sharing common epitopes with the very liver proteins and/or cryptic antigens unmasked by gliadin reaction\(^{(4)}\). Novacek\(^{(14)}\) et al. have found a close correlation between the intestinal permeability index and the serum transaminase levels. Finally, it is common knowledge that mucosal damage in coeliac patients leads to the exposure of enzyme tissue transglutaminase, the target antigen recognised by the anti-endomysium antibodies. The hypothesis that this antibody can play a role in extraintestinal CD manifestations, particularly in liver disorders, is corroborated by a recent discovery of extracellular accumulation of IgA-class anti-tissue transglutaminase antibodies in the liver biopsies of two patients with coeliac disease in the active phase\(^{(15)}\).

Conclusions

The close association between coeliac disease and liver disorders calls for an effective screening effort and strict surveillance for CD. The number of coeliac patients who are undiagnosed or untreated is still large and gluten-sensitive enteropathy, complicated by subclinical liver disorders, can in most cases lead to more severe liver damage. As a number of these changes are reversible, much importance has been attached to a timely diagnosis and the adoption of an appropriate gluten-free diet.
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Essential bibliography