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Review Article

Celiac disease-related hepatic injury: Insights into associated conditions and underlying pathomechanisms☆

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ABSTRACT

Background: Celiac disease (CD) is the most common autoimmune enteropathy. Clinical manifestations may range from a typical malabsorption syndrome to several apparently unrelated extra-intestinal symptoms.
Aim: Here we specifically focus on the spectrum of CD-related liver disorders and the underlying pathomechanisms.
Methods: A computer-based search up to August 2015 was completed using appropriate keywords. References from selected papers were also reviewed and used if relevant.
Results: An unexplained hypertransaminasemia with nonspecific histologic hepatic changes is the most common hepatic presentation. CD however can coexist with a number of liver disorders such as Autoimmune Hepatitis, Autoimmune Cholangitis, Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis requiring a specific treatment in addition to gluten-free diet. CD has also been associated with Viral Hepatitis, Fatty Liver, Non-Alcoholic Steatohepatitis and some severe cryptogenic hepatopaties in the liver transplantation list. Pathomechanisms underlying hepatic injury in CD are multiple, appear still not completely defined and may probably co-occur.
Conclusions: An ever-increasing number of CD-related liver injuries exist, probably representing a continuum of a same disorder where genetic predisposition, timing, and duration of previous gluten exposure might influence the reversibility of liver damage. Evidences, although not conclusive, support therefore testing for CD also in cryptogenic hepatobiliary conditions where the relationship with CD has not yet been fully investigated.

1. Introduction

Celiac disease (CD) is the most common food intolerance in the world, affecting at least 1% of the Caucasian population [1]. It is a chronic autoimmune enteropathy, elicited by the ingestion of gluten and other related prolamines in genetically predisposed individuals, that results in an immune-mediated damage to small intestine characterized by villous atrophy, crypt hyperplasia and intraepithelial lymphocytic infiltrate. All these modifications improve considerably with gluten free diet (GFD) and relapse after its reintroduction [2]. More than 90% of patients share specific human leucocyte antigen (HLA) class II such as HLA DR3, particularly the HLA-DQ2 molecule, while the fewer remaining patients carry HLA DQ8 haplotypes [3].

Diagnosis of CD in adults on gluten containing diet is based on the presence of duodenal histology diagnostic for CD and high levels of serum auto-antibodies, including anti-endomysium antibodies (EMA) or sensitive and specific Immunoglobulin A (IgA) anti-tissue transglutaminase antibodies (IgA anti-tTGase titre >7 U/mL) [4]. tTGase is a calcium dependent enzyme, ubiquitously expressed, that plays a vast array of biological functions. It is considered the "auto-antigen" of CD as gluten intake induces secretion of IgA-class autoantibodies that target tTGase [5]. Another class of autoantibodies, described in 90.3% paediatric and 59.6% adult patients with active CD and very damaged mucosa, is the anti-filamentous actin antibodies (A-FAA) which has therefore been considered by some authors an additional CD diagnostic tool [6,7].

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In genetically predisposed children who are symptomatic and have anti-tTGase levels at least 10 times greater than the upper limit of normal, positive EMAs and good response to a GFD, recent new ESPGHAN guidelines established that small intestine biopsy may not be necessary [2].

Diagnostic challenge depends on the fact that CD may arise at any age and its clinical manifestations are highly variable, ranging from a typical intestinal malabsorption syndrome to isolated extra-intestinal symptoms such as hepatobiliary diseases, iron deficiency anaemia, infertility, osteoporosis, dermatitis herpetiformis, autoimmune myocarditis and neurological dysfunctions [8,9], which may even remain the only presenting sign for a long period. Here we will specifically focus on the hepatic injury and CD.

Search strategy. We reviewed the literature (search engines: PUB MED and GOOGLE SCHOLAR) up to August 2015 by using individually or in combination the following key words: celiac disease, liver, hepatobiliary. We selected and reviewed those related to old and novel associations, mainly focusing on emerging pathogenic mechanisms. Pertinent articles quoted into the references of selected literature were examined as well, and included when necessary.

2. Types of liver disorders associated with Celiac disease

In the absence of other causes, silent CD accounts for 6–9% of patients with unexplained liver enzyme elevation [10,11]. The classical association between CD and liver disorders was first described almost forty years ago by *Hagander* who reported that 30 of 74 adults with CD presented with an unexplained hypertransaminasemia (HTS) (aspartate aminotransferase, AST and/or alanine aminotransferase, ALT), which generally normalized after 6–12 months of GFD adherence [12]. In the same year Pollock published data on chronic hepatitis in adults with CD [13]. Subsequently, in 1978, Lindberg et al. showed a liver damage in CD and other food intolerances in childhood [14]. Bonamico et al. in the early eighties reported HTS in 56.9% of Italian children with active CD [15]. In the early nineties, the phenomenon was better characterized both in adults [16] and in children [17]. Recent data from the US also confirmed this trend: 40% of adult CD individuals will have gluten dependent elevated transaminase at diagnosis [18].

Since then, CD-associated liver injuries appeared to include two main different forms of liver damage on the basis of their response to a GFD:

- *"Cryptogenic" liver disorders*, ranging from a mild to severe liver dysfunction, characterized by an isolated increase of hepatic aminotransferases. Liver histology generally shows a preserved liver architecture with a mild mononuclear infiltrate of the portal and/or lobular tract and a slight hyperplasia of the Kupffer cells, which are typical of nonspecific reactive hepatitis, also known as "celiac hepatitis". After 1 year of GFD most patients achieve the disappearance of these hepatic histological features [17,19,20].
- *Autoimmune liver diseases (AILDs)* that include Autoimmune Hepatitis (AIH) and Autoimmune Cholangitis. The typical histological picture is a mononuclear and eosinophilic infiltration of the portal tract in the presence of characteristic circulating autoantibodies (antinuclear ANA, anti-smooth muscle SMA, anti-liver kidney microsomal antibodies LKM1 or anti-liver cytosol type 1 LC1) [19,20].

Generally, CD-associated AILDs do not improve after the institution of GFD, but require a specific immunosuppressive therapy in addition to diet alone [17,19–22].

Primary Biliary Cirrhosis (*PBC*) and *Primary Sclerosing Cholangitis* (*PSC*) are other closely related immune mediated CD-associated hepatobiliary conditions (see next section).

Currently, it remains unclear whether these two forms of liver disease (cryptogenic and autoimmune) have a different pathogenesis or if they are an expression of the same disorder, where different genetic predisposition, immunological factors and/or duration of gluten exposure may influence the severity, reversibility and pattern of liver injury [23–25].

2.1. "Cryptogenic" liver disease

Several studies have shown a positive correlation between liver diseases and CD. A large adult Swedish population study ($n = 13{,}818$) has shown that CD patients were 2–6 times more susceptible to develop liver disease during their life than healthy controls. Similarly, patients with liver disease were 4–6 times more susceptible to develop CD than patients without hepatic involvement [26]. Two recent meta-analysis, have reported the prevalence of CD and cryptogenic HTS in adults [11] and children [20]. In details, in adults the prevalence of CD in patients with cryptogenic HTS ranged from 4% to 6%, while the prevalence of HTS in patients with newly diagnosed CD was 4 times more [11].

In children, our group has shown that the pooled prevalence of CD in patients with cryptogenic HTS and vice versa was 12% and 36%, respectively [20].

2.2. Autoimmune hepatitis (AIH)

A possible genetic link between CD and AIH is not surprising because both disorders express selected combinations of genes coding for class II HLA molecules on chromosome 6 [27]. AIH is a progressive liver disease that, according to the nature of the serum autoantibodies, can be recognized in two different forms: AIH type 1 (AIH-1) and AIH type 2 (AIH-2). AIH-1 is characterized by the positivity for ANA and/or ASMA [28], while AIH-2 is defined by the positivity for anti-LKM1 [29] or anti-LC1 [30].

Of note, F-actin is the predominant, if not the sole, target of AIH-1-specific SMA reactivity [7]. We believe that a diagnostic problem may therefore arise if a CD patient with positive A-FAA due to a severe degree of villous atrophy has also liver damage. In fact one might erroneously consider anti-actin positivity as a marker of AIH-1 rather than of a simple reactive hepatitis. On the other hand, its pathogenic role for an AIH has not been hitherto well studied.

The prevalence of AIH in adult CD pts is 1.6% [31] whereas CD in patients with AIH is ten times more seroprevalent than in the general population [32]. In children it has been reported a similar trend [20,33,34].

The clinical impact of a GFD on the outcome of the liver disorder in patients with AIH remains to be clarified [19,20]. However, it was suggested a probable long-term beneficial effect of a GFD because patients with AIH and CD appear less prone to relapse after immunosuppressive withdrawal as compared to patients with AIH unrelated to CD [35].

2.3. Primary Biliary Cirrhosis (PBC)

The relationship between CD and PBC is well documented, and it was first described in 1978 [36]. Several more recent epidemiological studies on Danish and Swedish cohorts [37], in United Kingdom [38] and in Canada [39] indicate that EMAs were positive in about 1 out of 10 adult patients with PBC, more than the expected prevalence of CD and PBC (6% and 3%, respectively).

Differently from EMAs, the titre of anti-mitochondrial autoantibodies (AMAs), which are the serological hallmark of PBC remains elevated after withdrawal of gluten from the diet. This evidence suggests that, probably, PBC and CD share the same etiological factor(s) but independent pathologic processes [40]. A reciprocal