REVIEW

Coeliac disease and liver dysfunction

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The spectrum and pathogenesis of liver dysfunction in coeliac disease (CD) is reviewed. CD and liver disease share common risk factors, and consequences of CD may cause liver dysfunction. Liver dysfunction should be sought in CD, and its aetiology explored when abnormalities persist after gluten exclusion. CD should be excluded in patients with unexplained liver dysfunction before being labelled "cryptogenic".

The aim of this paper is to review the spectrum and pathogenesis of liver dysfunction that occurs in coeliac disease (CD), and consider the need for screening for CD in patients with liver dysfunction and for liver disease in patients with CD.

The occurrence of liver dysfunction in patients with CD is well established. Initial reports in the 1970s observed that hepatic aminotransferase enzymes were frequently raised at the time of diagnosis in both adults and children, and usually normalised following gluten exclusion.^{1,2} Since that time, there has been considerable progress unravelling the pathogenesis of CD. The recognition of an autoimmune component to CD has led to its association with other autoimmune disorders being established, including autoimmune liver disease.

The availability of serological markers such as endomysial and antigliadin antibodies has allowed a diagnosis of CD to be more easily explored, although confirmation continues to rest on the typical histological appearance of a proximal small bowel biopsy.³ Use of serology to screen populations has led to recognition of an increased prevalence in the general population (as high as 1/184 in Italian children⁴), in children with other associated disorders including insulin dependent diabetes mellitus (IDDM), and in asymptomatic first degree relatives. Furthermore, the use of serology has contributed to an expanding spectrum of atypical manifestations now being attributed to CD, including liver dysfunction and disease.

SPECTRUM OF LIVER DISEASE

Three types of liver disease are described in CD. These may not necessarily be discrete entities with differing pathogeneses, but may represent a spectrum of the same disease where inherited factors and duration of gluten exposure may influence the severity and pattern of liver dysfunction.

Mild liver dysfunction

At the time of diagnosis of CD, a mild disturbance of liver function, characterised by raised hepatic

transaminase enzymes (aspartate aminotransferase (AST)/alanine aminotransferase (ALT)) with normal bilirubin and gamma glutamyl transferase (γ GT) is reported in up to 42% of adults^{5–7} and 54% of children.⁸ In most cases, liver enzymes normalise within 12 months of gluten exclusion. In cases where liver biopsy has been performed, histological changes are often mild and non-specific and include Kupffer cell hyperplasia, mononuclear cell infiltration, steatosis, and mild fibrosis.^{7,9–12}

It is also evident that some patients being investigated because of liver dysfunction have asymptomatic CD. In a study of 55 adults being investigated for raised transaminases, the prevalence of CD was 9%.¹¹ All were symptom free, and normalisation of transaminases occurred with adherence to gluten exclusion. Similarly Bardella and colleagues¹² reported a prevalence of CD of 9.3% in adults with unexplained raised transaminases, compared to a background prevalence of 0.5%. In children, asymptomatic raised hepatic enzymes have been reported as the sole manifestation of CD, with normalisation on a gluten free diet (GFD).^{9,13}

Mild hepatic steatosis is a frequent histological finding in patients with CD who undergo biopsy. In others it is more severe, attributed to the presence of malnutrition, and responds to GFD.¹⁴ A recent report described steatosis in an obese child with untreated CD,¹⁵ which did not resolve until GFD was implemented.

Chronic liver disease

Severe histological disease including chronic hepatitis, severe fibrosis, and cirrhosis has been reported in adults and children.^{1,13,16} Even in the presence of these changes, biochemical response to GFD is described. Furthermore, Kaukinen and colleagues¹⁷ report four adults being assessed for liver transplantation because of chronic liver disease (three with cryptogenic hepatitis and one with congenital hepatic fibrosis) in whom CD was diagnosed following serological screening. Gluten withdrawal led to improvement of hepatic function, and transplantation was avoided. In patients with chronic liver disease of established aetiology, development of CD may precipitate deterioration: in two patients with primary biliary cirrhosis

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Abbreviations: AILD, autoimmune liver disease; AIH, autoimmune hepatitis; AISC, autoimmune sclerosing cholangitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, coeliac disease; GFT, gluten free diet; γ GT, gamma glutamyl transferase; HCV, hepatitis C virus; HSV, herpes simplex virus; IDDM, insulin dependent diabetes mellitus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis

(PBC) described by Neuberger,¹⁸ deterioration in liver function as a result of CD responded to GFD. An association between hepatitis C virus (HCV) infection and CD in adults has been reported,¹⁹ and suggested to be the most common liver disease associated with CD.

Autoimmune liver disease

In children, autoimmune liver disease (AILD) encompasses autoimmune hepatitis, primary sclerosing cholangitis, and autoimmune sclerosing cholangitis. A diagnosis of autoimmune hepatitis (AIH) usually comprises the typical histological appearance of mononuclear portal tract infiltration in the presence of characteristic circulating autoantibodies (antinuclear, antismooth muscle, and antiliver kidney microsomal (LKM1) antibodies).

In primary sclerosing cholangitis (PSC) no characteristic autoantibody has been established. The diagnosis rests on showing the characteristic biliary lesion in biopsy tissue or appearance of the intra and extrahepatic biliary tree by cholangiography. Autoimmune sclerosing cholangitis (AISC) describes patients with PSC who have positive autoantibodies and may have histological features that overlap with those seen in AIH ("overlap syndrome"). In adults, an additional form of AILD, PBC is encountered, characterised by the presence of antimitochondrial antibody.

It is possible that the disturbance of liver function and architecture described as transaminitis or chronic liver disease in patients with CD may be caused by an autoimmune process: there is histological overlap and furthermore, up to 20% of patients with AIH may not have typical autoantibodies at presentation.²⁰ The first report of an association between AILD and CD appeared in 1978: Logan *et al* reported four adults in whom PBC and CD were diagnosed simultaneously.²¹ This association has been so strengthened over subsequent decades, with the estimated CD prevalence of 2–7% in patients with PBC,^{22–24} that screening of patients with PBC for CD has been recommended.^{18 22 24} Evidence supporting an association of CD with PSC,^{25 26} and AISC²⁷ in adults has also emerged, and in patients with AIH, the estimated prevalence of CD is as high as 3–5%.^{28 29}

In children PSC and AISC are described in particular in association with inflammatory bowel disease, but an association with CD has not been reported. The association of CD with AIH has been investigated in Italy by two multicentre studies.^{30 31} The first investigated the risk of autoimmune disorders including AIH in 909 children and young adults with CD.³⁰ AIH occurred in 1.1%, with no cases occurring in either the healthy control group or in the control group with Crohn's disease. A subsequent study³¹ evaluated the clinical features of 14 children in whom both AILD and CD were present. Nine presented with gastrointestinal symptoms: seven had liver disease evident at diagnosis, while two developed hepatic dysfunction within three months of CD diagnosis but following implementation of GFD. Five presented with liver disease, three of whom had symptoms suggestive of CD, while the remaining two were asymptomatic and diagnosed following antibody screening. Of the 14, 12 had one or more characteristic autoantibody, but two were seronegative. Histological changes included moderate or severe hepatic fibrosis in all cases. The final diagnoses were: 11 AIH (two seronegative), one AISC, and two overlap syndrome. All children achieved biochemical remission with immunosuppression and GFD. Two patients who recommenced gluten had a biochemical relapse.

PATHOGENESIS OF LIVER DYSFUNCTION

Two mechanisms must be considered in the pathogenesis of liver dysfunction associated with CD. Firstly, that the presence of one disease leads directly to the development of the other, and secondly that both disorders share the same inherited

predisposition and/or environmental triggers. Both of these mechanisms may coexist.

Liver dysfunction caused by coeliac disease

Patients with enteropathy caused by CD have impaired gut mucosal integrity leading to malabsorption and increased permeability. Malnutrition of any cause is associated with hepatic dysfunction and may give rise to steatosis. The role of increased intestinal permeability in the pathogenesis of liver dysfunction in CD was explored by Novacek and colleagues.⁷ Of 178 adults with CD, intestinal permeability (determined by oral lactulose/mannitol absorption test) was significantly higher in those with abnormal hepatic aminotransferase enzymes. Furthermore, Lindberg and colleagues² observed that liver dysfunction occurred in children not only with CD but also cows' milk protein induced enteropathy, suggesting that it is not gluten itself but rather the ensuing mucosal damage that leads to hepatic dysfunction. Brazier and colleagues²⁶ postulated that in PSC altered permeability of the small bowel may allow toxic or infective agents access to the biliary epithelial cells, leading to an immunologically mediated disease. In Bardella and colleagues' study⁵ of 158 adults with CD however, neither body mass index nor severity of intestinal histology correlated with liver dysfunction.

CD has been shown to be associated with the generation of a variety of autoantibodies. In 90 children with CD, a high prevalence of autoantibodies (islet cell or anti-insulin 11.1%; antithyroperoxidase 14.4%) was evident at time of diagnosis.³² In the majority, after a period of gluten exclusion these antibodies became undetectable. No child had abnormal glucose tolerance or thyroid function.

The role of gluten exposure in relation to manifest autoimmune disease has also been investigated.³⁰ Prevalence of IDDM and autoimmune thyroiditis in patients with CD was related to duration of gluten exposure, and in 77.5% of children with both an autoimmune disease and CD, the autoimmune disorder appeared first—that is, during gluten exposure. Furthermore, patients with CD subsequently exposed to gluten during a gluten challenge were more likely to develop autoimmune disease than those without further exposure.

Mucosal inflammation in CD leads to exposure of the tissue transglutaminase enzyme (tTg) in the endomysium that is the autoantigen recognised by endomysial IgA antibody.³³ Anti-tTg IgA antibodies are being explored as having a pathogenic role in CD and as a risk factor for other autoimmune diseases.³⁴

These studies suggest that introduction of GFD may prevent autoimmune disease becoming manifest, and that duration of gluten exposure may be a risk factor for autoimmune disease. In patients with CD and AILD, both immunosuppression and GFD are usually implemented. The potential for AILD to respond to gluten exclusion has not been widely explored, however histological response to GFD alone has been reported in one patient with PSC.²⁶

Common predisposition/trigger

A shared inherited predisposition for AILD and CD occurs in patients who possess certain HLA class II molecules and haplotypes. HLA molecules DR3 and DQ2 both confer susceptibility to CD, with the haplotype DR3/DQ2 having the strongest association.³⁵ The major HLA risk factors for AIH are specific loci in the HLA DR region, including B8DR3³⁶ which is in close linkage disequilibrium with HLA DQ. Furthermore, in patients with PSC and IBD, the haplotype HLA-B8/DR3 is found with increased frequency. In PBC however no close association with HLA phenotype has been established.

The trigger for the inflammatory process in CD is the dietary peptide gliadin. However, what initiates the abnormal mucosal response to gliadin is not known. Postulated triggers include viruses, which may have aminoacid sequences homologous to

Figure 1 Investigation of biochemical liver dysfunction in children with coeliac disease.

the toxic epitopes in gliadin. Similarly, the trigger which activates an autoimmune response in the liver is not known. Again, numerous reports of possible viral triggers exist, including measles, Epstein-Barr virus, herpes simplex virus type 1 (HSV-1), and HCV. Both HCV and HSV-1 share homologous amino acid sequences with the target of anti LKM-1 antibodies. In adults, there is an established relation between HCV infection and AIH, with antiviral treatment rather than immunosuppression being primary therapy. The potential role of HCV in predisposing to CD by triggering an autoimmune reaction was considered by Fine and colleagues.¹⁹ Adults with HCV or AILD were more likely to have CD (prevalence being 1.2% and 3.4% respectively) than those with other gastrointestinal disease, other liver disease, or the healthy population.

SCREENING PATIENTS WITH LIVER DYSFUNCTION FOR COELIAC DISEASE

Screening children considered to be at increased risk of CD is becoming well established. This includes children with IDDM (CD prevalence 1–17%³⁷), Down's syndrome (CD prevalence 4–17%^{38–42}), as well as first degree relatives (CD prevalence 10%). Potential consequences of untreated CD include impaired fertility and reduced bone density as well as an increased risk of gastrointestinal malignancy. Should children with either AILD or cryptogenic liver dysfunction undergo serological screening for CD?

The prevalence of CD in children with AILD is not known. Treatment of AILD, in particular AIH, involves immunosuppression with its attendant side effects. CD and its symptoms may be masked by treatment and remain undiagnosed. Furthermore, if gluten exclusion contributes to amelioration of hepatic inflammation, as in those with liver disease of unknown cause or transaminitis, prompt diagnosis of CD would be beneficial. Serological screening should therefore be carried out in this population.

All children with cryptogenic liver disease should undergo serological screening for CD. As indicated by Bardella and colleagues,¹² the prevalence of CD is much higher than other disorders routinely screened for, including α_1 antitrypsin deficiency and Wilson's disease, and furthermore is readily treated.

SCREENING PATIENTS WITH COELIAC DISEASE FOR AUTOIMMUNE LIVER DISEASE

This is less clear. The prevalence of AIH in children with CD is less well studied, but in the Italian study of children/young adults was 1.1%.³⁰ It is not clear whether the risk of AILD is only increased in untreated patients with CD, and whether after gluten exclusion a continued increased risk would be expected. Of 14 children with both CD and AILD, 12 had liver dysfunction during gluten exposure: in only two did it develop after gluten exclusion,³¹ suggesting that GFD may be protective. As liver dysfunction is common in CD and may not always be attributable to AILD, a proposed algorithm for investigation is outlined in fig 1.

WHICH TEST?

The presence of IgA antibodies to both gliadin and endomysium has a sensitivity, specificity, positive, and negative predictive value of approximately 95% in the diagnosis of CD. In patients with chronic liver disease however, the positive predictive value of IgA gliadin is reduced.^{12 19 29} Serological screening should therefore incorporate endomysial IgA and not rely on gliadin antibodies alone.

SUMMARY

Coeliac disease is becoming increasingly described in asymptomatic patients and those with atypical symptoms. There may be considerable benefit derived from early treatment, even in the absence of symptoms. Cryptogenic liver disease is the diagnostic label applied to a significant but diminishing proportion of patients with liver disease in whom recognised diagnoses have been excluded. CD should also be excluded before this label is applied. CD and liver disease may share common risk factors, and the consequences of CD may themselves predispose to liver dysfunction. Liver dysfunction should therefore be sought in patients with CD at the time of diagnosis, and its aetiology explored in those with persistent abnormalities after gluten exclusion.

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