Coeliac disease and liver dysfunction

S Davison

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. 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. 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 children), 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 (γGT) is reported in up to 42% of adults and 54% of children. 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.

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%. All were symptom free, and normalisation of transaminases occurred with adherence to gluten exclusion. Similarly Bardella and colleagues 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).

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. A recent report described steatosis in an obese child with untreated CD, 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. Even in the presence of these changes, biochemical response to GFD is described. Furthermore, Kaukinen and colleagues 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...

**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; γGT, gamma glutamyl transferase; HCV, hepatitis C virus; HSV, herpes simplex virus; IDDM, insulin dependent diabetes mellitus; PSC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis
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. 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 colleagues 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 colleagues 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’ study 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 autoimmune diseases. In 909 children with CD, a high prevalence of autoantibodies (islet cell or anti-insulin 11.1%; antithyreoperoxydase 14.4%) was evident at time of diagnosis. 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. 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 3 enzyme (Tg) in the endomysium that is the autoantigen recognised by endomysial IgA antibody. Anti-TG IgA antibodies are being explored as having a pathogenic role in CD and as a risk factor for other autoimmune diseases.

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.

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. The major HLA risk factors for AHI are specific loci in the HLA DR region, including B8/DR3 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 protein gliadin. However, what triggers the abnormal mucosal response to gliadin is not known. Postulated triggers include viruses, which may have aminoacid sequences homologous to...
SCREENING PATIENTS WITH LIVER DYSFUNCTION FOR COELLIAC 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 \(\alpha\), antitrypsin deficiency and Wilson’s disease, and furthermore is readily treated.

SCREENING PATIENTS WITH COELLIAC 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%.\(^{11}\) 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,\(^{11}\) 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 endomyseum 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.

REFERENCES