The association between primary biliary cirrhosis and coeliac disease: a study of relative prevalences

J G C Kingham, D R Parker

Abstract

Background—Coexistent primary biliary cirrhosis (PBC) and coeliac disease has been recorded but the association has not been systematically studied.

Aims—To determine relative prevalences of PBC and coeliac disease in a defined population over a 12 year period.

Patients and methods—All patients with PBC or coeliac disease in a stable population of 250 000 in South Wales were identified from a clinical register and laboratory records.

Results—Sixty seven patients with PBC and 143 patients with coeliac disease have been diagnosed and followed over a median of 86 (4–135) months; point prevalences in 1996 were 20 per 100 000 for PBC and 54 per 100 000 for coeliac disease. PBC in patients with coeliac disease was sought by investigating abnormal liver function tests. Ten (7%) had persistent abnormalities and three had PBC. Coeliac disease in patients with PBC was sought by investigating malabsorption, haematocrit deficiency, positive antigliadin antibody, or coeliac disease family history. Eleven patients underwent duodenal biopsy revealing one further coeliac disease case. Four patients (three women) have both conditions giving a point prevalence for patients with both conditions of 1.6 per 100 000 (95% confidence limits 0.44 to 4.1 per 100 000). Prevalence of PBC in patients with coeliac disease was 3% and of coeliac disease in patients with PBC was 6%.

Conclusion—A 12 year study of a stable 250 000 population revealed a relative prevalence of PBC in 3% of 143 patients with coeliac disease and of coeliac disease in 6% of 67 patients with PBC. PBC and coeliac disease are therefore associated. Screening for PBC in patients with coeliac disease using antimitochondrial antibody testing and screening for coeliac disease in patients with PBC with antigliadin antibody testing or duodenal biopsy are recommended.

(Gut 1998;42:120–122)

Keywords: primary biliary cirrhosis; coeliac disease; prevalence

Logan et al in 1978 reported four patients from Edinburgh and Dublin with coexistent coeliac disease and primary biliary cirrhosis (PBC), questioning whether this was a significant association. They did not attempt to assess the frequency of each disease relative to the other nor did they systematically review their respective patient populations for these diseases. There have been several subsequent reports of these two diseases coexisting with over 20 cases described but there have been no formal attempts to ascertain relative prevalence rates.

Methods

Since 1984 we have kept a register of all patients with specifically defined gastroenterological and liver diseases from a well circumscribed and stable population in South Wales. The register has been maintained prospectively by coding at the time of diagnosis (discharge summary or letter to referring doctor) all inpatients, outpatients, and day cases passing through the department of gastroenterology.

The population is defined by the Unitary Authority of Swansea as follows: city of Swansea (postcodes SA1–SA9) population 226 000; part of the surrounding rural area (postcodes SA14, 15, and 18) population 25 000. This population is predominantly of European ethnic origin (98.5%). The population is predominantly of European ethnic origin (98.5%). ONS figures for 1990–4 showed a 0.2% population growth with little migration or immigration.

Swansea is served by two district general hospitals with shared laboratory facilities and case notes giving ready access to records of histopathology, biochemistry, and serology results. We used the combined resources of our clinical register and computerised laboratory records to identify all cases of coeliac disease and all of PBC resident in this area. The clinical case notes were obtained after establishing any of the following:

Recorded clinical diagnosis of PBC or of coeliac disease.
- Histology record of partial or subtotal villous atrophy on small intestinal biopsy.
- Histology record of typical or probable PBC on liver biopsy.
- Positive antimitochondrial antibody of titre 1/40 or greater.

After scrutiny of the case notes and subsequent re-evaluation and investigation we found 143 patients (105 women, 38 men) with coeliac disease and 67 patients (57 women, 10 men) with PBC who had been diagnosed and followed regularly over the period 1984–96. The diagnostic criteria for coeliac disease were partial or subtotal villous atrophy, with or without evidence of malabsorption, responsive to gluten withdrawal. The criteria for PBC were positive antimitochondrial antibody, cholestatic biochemistry, and liver biopsy consistent with...
Table 1  Liver function abnormalities in 35/143 patients with coeliac disease

<table>
<thead>
<tr>
<th>Pattern of liver function transaminases</th>
<th>No abnormal at any time</th>
<th>No persistently abnormal</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin↑, AST↑, AP↑, γ-GT↑</td>
<td>2</td>
<td>2</td>
<td>PBC</td>
</tr>
<tr>
<td>AST↑, AP↑, γ-GT↑</td>
<td>12</td>
<td>4</td>
<td>PBC</td>
</tr>
<tr>
<td>AST↑</td>
<td>8</td>
<td>2</td>
<td>Fatty liver</td>
</tr>
<tr>
<td>AP↑, γ-GT↑</td>
<td>10</td>
<td>2</td>
<td>Secondary lymphoma</td>
</tr>
<tr>
<td>γ-GT↑</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Case histories of the four patients with both PBC and coeliac disease

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Symptoms and signs</th>
<th>Initial investigations</th>
<th>Subsequent investigations and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>F</td>
<td>Diarrhoea, pruritus, weight loss, pigmentation, steatorrhoea</td>
<td>Hb 11.3 g/dl; MCV 76 fl; ferritin &lt; 5 μg/l; folate 1.6 mg/ml; AP 1813 U/l; bilirubin 18 μmol/l; AST 89 U/l; γ-GT 582 U/l; albumin 35 g/l; AMA 1/1000; ANF 1/40; liver biopsy: PBC, grade 4 cirrhosis; duodenal biopsies: subtotal villous atrophy</td>
<td>Gluten exclusion led to rapid resolution of diarrhoea and weight gain, repeat duodenal biopsy at 9/12: minimal partial villous atrophy, liver disease progressed: liver transplant at three years after initial presentation, currently well</td>
</tr>
<tr>
<td>57</td>
<td>F</td>
<td>Diarrhoea, abdominal pain, weight loss, hepatosplenomegaly</td>
<td>Hb 8.8 g/dl; MCV 76 fl; vitamin B₁₂ 130 ng/ml; folate 2.3 mg/ml; ferritin 6 ng/ml; facsal fat 30 g/day; AP 36.5 KA units; AST 164 U/l; AMA 1/2560; liver biopsy: PBC, grade 3 cirrhosis; duodenal biopsies: subtotal villous atrophy</td>
<td>Repeat LFTs: AP 540 U/l; AST 47 U/l; albumin 31 g/l, multiple transfusions required for hypersplenism, died of pneumonia 15 years after initial presentation</td>
</tr>
<tr>
<td>32</td>
<td>F</td>
<td>Pruritus, anorexia, weight loss</td>
<td>Hb 8 g/dl; MCV 66 fl; AP 794 U/l; AST 85 U/l; bilirubin 17 μmol/l; albumin 34 g/l; duodenal biopsy: subtotal villous atrophy; liver biopsy: non-specific inflammation</td>
<td>Gluten exclusion and haematinic deficiencies resulted in weight gain, pruritus persisted; LFTs remained abnormal, started oral contraceptive: developed jaundice, resolved on stopping, LFTs remained abnormal; repeat duodenal biopsy: good response to gluten exclusion, AMA 1/1024, review of previous liver biopsy: PBC, four years after initial presentation: Xanthelasma, spider naevi, jaundice, hepatosplenomegaly, started on ursooxydsalic acid: LFTs improved, currently asymptomatic</td>
</tr>
<tr>
<td>51</td>
<td>M</td>
<td>Osteoporosis</td>
<td>AP 1131 U/l; AST 77 U/l; γ-GT 904 U/l; liver biopsy: minimal portal tract inflammation only</td>
<td>No diagnosis at first, over next 10 years developed pruritus, weight loss, pigmentation, splenomegaly, LFTs worsened, endoscopy revealed varices, repeat liver biopsy: PBC, grade 4, ERCP: consistent with cirrhosis, AMA still negative, iron deficiency anaemia developed, low vitamin B₁₂, duodenal biopsies: subtotal villous atrophy, antireticulin antibodies positive, gluten exclusion resulted in improved well being, repeat duodenal biopsy: mild partial villous atrophy only; LFTs did not change after gluten exclusion</td>
</tr>
</tbody>
</table>

Hb, haemoglobin; MCV, mean cell volume; AP, alkaline phosphatase; AST, aspartate aminotransferase; γ-GT, γ-glutamyltransferase; AMA, antimitochondrial antibody; ANF, antinuclear factor; LFT, liver function test; PBC, primary biliary cirrhosis; ERCP, endoscopic retrograde cholangiopancreatography.

Primary biliary cirrhosis and coeliac disease

PBC. Sixty seven were classified as having definite (56 patients) or probable (11 patients) PBC. Confidence intervals were calculated using a Poisson distribution.

Results
The catchment population from which these patients were drawn is approximately 250 000. In 1995, 136/143 patients with coeliac disease and 51/67 patients with PBC were alive. In that year all four patients with both conditions were still living, though in one coeliac disease had yet to be diagnosed; this came to light after investigation in 1996. Thus the point prevalence in this population in 1995 and 1996 of coeliac disease was 54 per 100 000 and of PBC was 20 per 100 000. (The corresponding figures for women for 1996 are 77 per 100 000 for coeliac disease and 34 per 100 000 for PBC.)

Four patients were identified on clinical, histological, biochemical, and serological grounds as suffering from both conditions with a point prevalence of 1.6 per 100 000 (95% confidence limits 0.44 to 4.1 per 100 000). In patients with coeliac disease evidence of PBC was sought by identifying abnormal liver function tests. Twenty four per cent (35/143) had an abnormality of at least one liver function test at some point (table 1). Of these, most were transient and not specifically cholestatic. Ten patients had persistent abnormalities of liver function tests and were fully evaluated. Four had PBC, one macronodular cirrhosis, one focal nodular hyperplasia, one non-specific reactive hepatitis, one fatty liver, and two secondary cancer.

Of the 67 patients with PBC, one was simultaneously diagnosed as having coeliac disease; in two the diagnosis of coeliac disease was made first. In the remaining 64 patients with PBC evidence of possible coeliac disease was sought by features suggestive of malabsorption (in seven), a family history of coeliac disease (in one), the presence of antireticulin antibody (in one), or the finding of otherwise unexplained haematin deficiency anaemia (in six). Eleven
patients underwent duodenal biopsy and one further case of coeliac disease came to light. Table 2 presents the case histories of the four patients with both PBC and coeliac disease.

Discussion

In a stable catchment population of approximately 250 000, the point prevalence in 1995 and 1996 of coeliac disease was 54 per 100 000 and of PBC was 20 per 100 000. These figures are comparable with others published from the United Kingdom. The prevalence of coeliac disease in England and Wales based on Coeliac Society membership was estimated at 27 per 100 000 whereas a higher figure of 61 per 100 000 has been recorded in south east Scotland. Recent reports from north east England on the epidemiology of PBC give prevalence figures increasing from 1.8 per 100 000 in 1976 to 12.8 per 100 000 in 1987 and 22.6 per 100 000 in 1994. From our figures over a 12 year period with a median follow up of seven years, approximately 3% of patients with coeliac disease (4/143) might develop PBC while around 6% of patients with PBC (4/67) might have underlying coeliac disease. There is no suggestion from these clinical and biochemical data, nor from those previously published, of a causative association between the two diseases nor that the activity of one influences the course of the other. The association presumably represents a shared susceptibility of biliary and small bowel epithelium to attack by autoimmune mechanisms.

This study probably underestimates the relative frequency of these two diseases as no attempt has been made to search for antimitochondrial antibodies in the entire group of coeliac patients nor has every patient with PBC been subjected to duodenal biopsy. Despite these deficiencies we believe prevalence figures of the order demonstrated in this study would be applicable to the rest of the United Kingdom and that the association proposed by Logan et al 20 years ago can be considered established. Given this association, screening for possible PBC in patients with coeliac disease using antimitochondrial antibody tests is recommended; similarly, screening for coeliac disease in patients with PBC could be readily performed with antigliadin antibody testing or duodenal biopsy when the presence of varices is being assessed.

We wish to thank Dr J Hywel Jones and Professor J G Williams for allowing us to study patients under their care and Dr Tim Peters and Miss Maria Lena Trivella of the University of Bristol Department of Social Medicine for statistical advice. This work has previously been published in abstract form (Hepatology 1996;24:533A).

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