Colitis-associated sclerosing cholangitis in children: A single centre experience

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Abstract

Objective: Sclerosing cholangitis (SC) is an important immune-mediated extra-intestinal manifestation of inflammatory bowel disease (IBD), primarily affecting patients with ulcerative colitis (UC). The reported prevalence of SC in adults and children with UC is low at between 2 and 7%. We present findings from a hepatological work-up in children with inflammatory colitis and elevated liver function tests (LFT) from a tertiary paediatric gastroenterology unit.

Design: This study is designed as a retrospective review of the medical records of 17 children and adolescents with inflammatory colitis and abnormal LFTs who presented to our IBD service between April 2004 and April 2012.

Results: Over the eight year period a total of 52 patients were diagnosed with inflammatory colitis (ulcerative colitis and unclassified colitis). Seventeen of the 52 patients had abnormal liver function tests and underwent liver biopsy and cholangiography. All 17 patients (32.6%) were diagnosed with hepato-biliary disease.

Conclusion: This is one of the largest reported series of children with inflammatory colitis and associated hepato-biliary disease. The data from this patient group indicate that the prevalence of IBD-associated hepato-biliary disease in children with abnormal LFTs is much higher than previously reported. As the diagnosis of IBD-associated hepato-biliary disease affects patient management, we recommend liver biopsy and cholangiography in all children with inflammatory colitis and abnormal liver function tests.

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1. Introduction

Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are frequently associated
with extra-intestinal, autoimmune manifestations. Sclerosing cholangitis (SC), a condition characterized by progressive inflammation and obliterative fibrosis of medium- and large-sized bile ducts may develop in the liver, particularly in patients with UC. The reported prevalence of SC in children with UC is relatively low (2–7%). However liver disease may be missed as elevated liver enzymes in IBD patients may not be investigated further, on the assumption that they are transiently elevated, possibly secondary to the acute inflammation of the gut or medications.

Here we present data from a large retrospective case-series on children diagnosed with UC or inflammatory bowel disease, unclassified (IBDU) and abnormal liver function tests (LFTs). The hepatological work-up included serological immune markers, liver biopsy and cholangiographic [magnetic resonance cholangio-pancreatography (MRCP)] changes.

2. Methods

2.1. Patient cohort and diagnostic workup

We retrospectively reviewed the hepatic biochemical investigations of 52 children with a diagnosis of UC/IBDU who presented to our IBD service between April 2004 and April 2012.

According to our current personal practice patients with elevated alanine transaminase (ALT) and/or gamma glutamyl-transpeptidase (GGT) levels of at least twice the upper limit of normal (ULN) at initial presentation, or patients with a known diagnosis of UC/IBDU and a subsequent sustained elevation in ALT and/or GGT for at least 3 months had further hepatological investigations. Seventeen of the 52 patients met the above criteria and underwent additional hepatological tests including serum auto-antibody screening (anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-smooth muscle antibody, anti-liver–kidney-microsomal antibody and anti-tissue transglutaminase antibodies), measurement of serum IgG levels, percutaneous liver biopsy and MRCP.

2.2. Diagnostic criteria and classification of liver disease

The histopathological diagnoses of liver disease were made by one of two paediatric histopathologists experienced in paediatric liver disease. All biopsies were assessed for changes seen in chronic cholangiopathies (bile ductular proliferation, diminution or absence of interlobular bile ducts, peri-ductular fibrosis, positive orcein stain) and features of auto-immune hepatitis (characterized by mononuclear and plasma cell infiltration of the portal areas with expansion into the liver lobule, interface hepatitis and bridging collapse). Biopsies with features of both, auto-immune hepatitis (AIH) and biliary changes, were classified as ‘auto-immune hepatitis/sclerosing cholangitis overlap syndrome’ (AIH/SC Overlap Sy). For the purposes of this study, four degrees of fibrosis were recognized: none; mild, with fibrosis confined to portal areas; moderate, with fibrosis bridging the neighbouring portal areas; and severe, with pseudo-lobule formation, representative of cirrhosis.

2.3. Classification of cholangiographic findings

Cholangiography was performed in all children using MRCP and reported by a radiologist experienced in paediatric MR imaging. Typical cholangiographic findings of large duct sclerosing cholangitis included irregularity of the bile duct wall, areas of mild dilatation, with intermittent strictures giving the bile ducts a “beaded” appearance, formation of saucclations and pseudodiverticuli.

A final hepatological diagnosis was made following MRCP. Patients were classified as follows: a) SC with auto-immune features (abnormal MRCP with histological features of cholangiopathy and additional histological or serological features of auto-immunity), b) SC (abnormal MRCP with histological features of cholangiopathy but no additional histological or serological features of associated auto-immunity), c) small duct SC with auto-immune features (normal MRCP with histological features of cholangiopathy and additional histological or serological features of auto-immunity) and d) small duct SC (normal MRCP with histological features of cholangiopathy but no additional histological or serological features of auto-immunity).

2.4. Diagnostic criteria for inflammatory colitis

The diagnosis of UC was made on the basis of clinical, endoscopic and histological findings in accordance with the Porto criteria.

The term “inflammatory bowel disease, type unclassified” (IBDU) was used for patients in whom there was evidence on clinical and endoscopic grounds for chronic inflammatory bowel disease affecting the colon, without small bowel involvement, but no definitive histological or other evidence to favour a diagnosis of either CD or UC.

3. Results

3.1. Prevalence of hepato-biliary disease in patients with inflammatory colitis and abnormal liver biochemistry

Of the 177 children currently on our IBD register, a total of 52 patients had an initial diagnosis of UC or IBDU (i.e. not Crohn’s colitis). Seventeen of these 52 patients (32.6%) had elevated LFTs and proceeded to liver biopsy and MRCP. Our patients were aged 9 to 16 years (median 13 years) at presentation and the majority were male (11/17; 65%). In 82% (14/17), liver function tests were elevated at initial presentation and the liver biopsy and colonoscopy were performed under the same general anaesthesia. In 3 patients the LFTs became abnormal after the diagnosis of colitis (from 3 weeks to 4 months later). All 17 patients were diagnosed with associated hepatobiliary disease (Table 1).

3.2. Laboratory results at the time of liver biopsy

The GGT was the most sensitive biochemical marker and was elevated in all patients ranging from 83 U/L to 1401 U/L with a median value of 245 U/L (normal range 6–25 U/L). The ALT was also elevated in all patients ranging from 51 to...
Table 1  Patient demographics, and biochemical, histological and radiological findings.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at Dx (years)</th>
<th>GGT (NR 6–25 U/L)</th>
<th>ALT (NR 0–50 U/L)</th>
<th>IgG (NR 6–13 g/L)</th>
<th>Auto-antibody positive</th>
<th>GI histology</th>
<th>Liver biopsy histology</th>
<th>Liver fibrosis</th>
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<td>Small duct SC with auto-immune features</td>
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<td>SC with auto-immune features</td>
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</tbody>
</table>

a Patients on immunosuppressive therapy at time of liver biopsy.
1435 U/L (normal range 0–50 U/L), with a median of 124 U/L. Serological auto-immune markers were present in all treatment naïve patients with one or more positive auto-antibody and elevated IgG levels, ranging from 17.1 to 27.5 g/L with a median of 23.8 g/L (normal range 6–13 g/L) (Table 1).

3.3. Histological and radiological findings

The histology findings of the liver were interpreted with the histopathologist aware of the diagnosis of inflammatory colitis, the abnormal LFTs and serological auto-immune markers. The majority of patients (10/17; 59%) had non-specific biliary changes in keeping with cholangiopathy and none had classical peri-ductal fibrosis of PSC as seen in adult patients. The remaining 7 patients had histological features of AIH/SC overlap syndrome (41.2%) (Table 1).

The MRCP demonstrated beading of medium and large sized intrahepatic bile ducts, suggestive of SC, in the majority of patients (12/17; 71%) (Table 1). All 12 patients with abnormal MRCP findings had additional features of auto-immunity. In the remaining 5 patients the MRCP was normal (small duct SC) but 4 of these patients had either serological evidence of auto-immunity (patients 1, 3 and 15) or histological changes suggesting an overlap syndrome (patient 12).

3.4. Management of the liver disease and outcome

All patients reported in this series received induction therapy with oral prednisolone (induction dose of 2 mg/kg/day up to a maximum of 40 mg/day for 2 weeks) as treatment for their hepatic and gastro-intestinal inflammation. In contrast to children with IBD alone, those with associated liver disease were maintained on low dose prednisolone maintenance (5 mg/day) and long term treatment with ursodeoxycholic acid (10–20 mg/kg/day). These children also received regular follow up in the Paediatric Hepatology Clinic. Biochemical remission with normalization of LFTs was achieved in all patients after a median of 6 months (range, 3 to 10) from the diagnosis. Eight of the patients (47%) have subsequently been commenced on maintenance treatment with azathioprine (2.0 to 2.5 mg/kg/day). In 6 of the 8 children azathioprine was started for relapsing colitis, in the other 2 for a flare up of the liver disease.

All 17 patients are currently clinically well and 15 of them (88%) have normal LFTs at a median follow up of 3.0 years (range, 3 months to 8 years) from diagnosis of the liver disease. Two adolescent patients have developed elevated LFTs following non-adherence to the medications. Three patients were considered for withdrawal of maintenance immunosuppression and underwent a second liver biopsy 2 years (patient 1) and 6 years (patients 5 and 10) after the first biopsy. All three had normal LFTs and no inflammatory activity in the repeated liver biopsy and have been successfully weaned off steroid maintenance therapy, but were kept on UDCA treatment. No patient has developed a clinically progressive disease or required liver transplantation to date.

3.5. Histological changes in the large bowel mucosa

The histology findings were interpreted in the context of the clinical presentation and the macroscopic findings. The majority of patients (12/17; 71%) had pan-colitis. There was no apparent association between the severity of the colitis and the liver disease; of the 8 children who required maintenance treatment with azathioprine for relapsing colitis, only one had advanced fibrosis and of the three children who underwent subsequent colectomy for treatment resistant active colitis, none had advanced liver fibrosis (Table 1).

4. Discussion

We report here that about one-third of our patients with UC and IBDU-colitis were found to have chronic liver disease. The true prevalence of liver disease among patients with inflammatory colitis is difficult to assess as reported data is often based on patient groups with a diagnosis of SC, of whom only a proportion also have IBD. Literature which reports on the incidence of liver dysfunction in patients with IBD is very sparse. Twenty-seven years ago a study by Wee et al. reported a high incidence of liver disease in adults with UC and biochemical evidence of liver disease. Out of 107 patients, 81 (75%) were found to have histological evidence of advanced hepatobiliary disease with a subsequently poor outcome. Similar to the reported incidence in our study, Grzybowska-Chlebowczyk et al. describe a high incidence of abnormal liver function in 16 out of 48 children with UC (33%) who were all found to have SC on MRCP. The nomenclature for cholangiopathies in the paediatric population is still not clearly defined with ongoing debate on whether paediatric cholangiopathy is a different immune-mediated process altogether and not simply an earlier stage of typical adult PSC. In contrast to adults, SC in children commonly presents with significant auto-immune features e.g. positive serum auto-antibodies and elevated IgG. This observation is confirmed in our series where the commonest liver condition was SC with auto-immune features, diagnosed in 16 of the 17 patients (94%). All the patients with large duct SC (12 patients) had additional auto-immune features and 4 of 5 patients had small duct SC; we may hypothesize that the hepatobiliary disease in these 4 patients could represent an earlier stage within a spectrum of small and large duct immune mediated SC.

The diagnosis of large duct SC is confirmed by cholangiography which commonly shows typical bile duct changes. Wider application of MRCP, a diagnostic test which is non-invasive and increasingly comparable with direct cholangiography has allowed better definition of the liver impairment observed in IBD. Small duct SC is a recognized variant with histological features of cholangiopathy but normal MRCP and may represent an earlier stage of the disease with a better prognosis.

The medical management of SC includes immunosuppression and treatment with choleretics such as bile acids. Ursodeoxycholic acid, a hydrophilic bile acid, has been shown to improve the biochemical markers of many cholestatic liver diseases, including chronic cholangiopathies, but has not been proven to modify the natural history and outcome in adults with PSC. Up to 40% of adult patients progress to end stage liver disease and require liver transplantation 10 years from diagnosis.

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Most studies which report long term paediatric outcome are in patients with SC, of whom only a proportion also have IBD.28-30 Miloh et al. report the outcome of a group of 47 children with SC from a tertiary hepatology centre. 59% of the children were also diagnosed with IBD. Nine of the 47 children (19%) required liver transplantation after a median time of 7 years from diagnosis.7 Batres et al. report long term follow-up data on the disease progression in 20 children with a diagnosis of SC (of whom 50% also had IBD).18 The majority of children (13/20) presented with advanced liver disease (bridging fibrosis or cirrhosis) and 7/13 went on to develop a hepatic decompensation. Only 2 of 7 children (28.5%) with earlier stages of liver disease progressed to liver failure. The median time to transplantation was 7.7 years from diagnosis. The success of liver transplantation in this group of patients is limited by disease recurrence in 10–40% of transplant recipients.19,20

There are no evidence-based guidelines on how to further investigate the hepatic involvement in IBD in children. The important question of whether early diagnosis and medical treatment of auto-immune mediated SC will improve long term outcome remains. The good response to immunosuppression in AIH makes an improvement in other forms of immune-mediated hepato-biliary disease conceivable.13,21 The majority of patients in our series were diagnosed at presentation of their IBD and have subsequently achieved excellent medium term outcomes. We therefore recommend that assessment for chronic liver disease should be a part of the routine diagnostic workup in children presenting with symptoms of inflammatory colitis. In the presence of abnormal liver biochemistry, further specific investigations including extended auto-antibody screen, liver biopsy and MRCP are indicated. This may require the involvement of / referral to a unit with hepatology expertise.

In this series we have demonstrated that the prevalence of liver disease in childhood inflammatory colitis (UC and IBDU) is higher than previously reported. The relatively small number of subjects within a selected patient group may potentially lead to an overestimation of the incidence rate.

There is clearly an urgent need for longer prospective multi-centre studies in this patient group in order to improve our understanding of this important disease and collect evidence for improvement in its long term management.

Conflict of interest

The authors declare that there is no conflict of interest.

References