Chronic liver disease associated with childhood ulcerative colitis

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Summary

In a series of 301 patients with ulcerative colitis forty-eight developed the disease before the age of 20. In this group of forty-eight patients there were four cases of serious chronic liver disease as compared with a total of seven cases of chronic liver disease in the whole series. The hepatic lesions in the patients developing colitis in childhood were unrelated to the extent, duration or severity of the colitis but colitis in very early life appeared to predispose to liver disease subsequently.

Introduction

Chronic liver disease is a well known and serious systemic complication of ulcerative colitis. The incidence of this complication varies enormously in reported series being dependent primarily on the degree of selection of the patients, but it is likely that it lies between 1 and 5% (Edwards and Truelove, 1963; Mistilis, 1965; Ross *et al.*, 1966). Conversely, in a review of patients with cirrhosis of the liver, Holdsworth *et al.* (1965) found 4% to be suffering from ulcerative colitis. More recently attention has been focused on the histological changes in the liver in patients with ulcerative colitis and it has become abundantly clear that histological abnormalities may be detected in the majority of colitics (Nedbal, Kudrman and Maratka, 1968; Eade, 1970; Perrett *et al.*, 1971). Unfortunately no clear relationship has been established between the cause of these lesions and the pattern of their possible progression to the more serious, irreversible forms of liver disease.

Although ulcerative colitis is relatively uncommon in children, a number of authors have commented on the more serious nature of the disease in childhood (Broberger and Lagercrantz, 1966; Watts *et al.*, 1966; Devroede *et al.*, 1971), and of the high risk of extra-colonic complications (Hijmans and Enzer, 1962; Grossmann and De Benedetti, 1970).

In the Nottingham series of 301 patients with ulcerative colitis we have seen forty-eight patients

who developed the disease before the age of 20, and of these four have progressed to serious liver disease. This high incidence of liver disease complicating childhood colitis has prompted us to report these cases and to compare our experience with that of others.

Patients and source of data

The patients described in this paper form part of a retrospective study of 301 patients with ulcerative colitis seen at the Nottingham Hospitals during the years 1961-1971. The area served by these hospitals is a fairly well defined one, with a population of approximately 800,000, and in this way the series was reasonably representative and unselected.

The criteria for the diagnosis of ulcerative colitis were similar to those of Jalan *et al.* (1970). The diagnosis was based on the following features:

- (1) rectal bleeding with or without diarrhoea;
 - (2) absence of pathogenic organisms in the stool;
 - (3) characteristic sigmoidoscopic appearances of hyperaemia, granularity, ulceration and friability and/or typical radiological appearances;
 - (4) histological changes consistent with the disease.
- Rectal biopsies were carried out in seventy-six patients and 101 patients had undergone proctocolectomy or ileo-rectal anastomosis.

The diagnosis of associated liver disease in patients with ulcerative colitis was established on a basis of clinical and biochemical criteria including recurrent jaundice, hepatomegaly, portal hypertension, stigmata of chronic liver disease and persistently abnormal liver function tests. The diagnosis of chronic liver disease was confirmed by hepatic biopsy but routine biopsies were not carried out in patients without definite evidence of hepatic dysfunction.

Results

The distribution of patients in this series with age at onset is shown in Fig. 1. The striking feature is the high incidence of liver disease in children and adolescents developing ulcerative colitis before the

FIG. 1. Patients with liver disease in 301 cases of ulcerative colitis. Hatched, male; solid, female.

age of 20. There were two patients with liver disease in the small group of five children developing colitis before the age of 9 and two patients with liver disease in forty-three starting colitis from the age of 10–19 years. In the remaining 253 older patients there were only three cases of chronic liver disease. A summary of the clinical features of the four children with colitis and associated liver disease is shown in Table 1, and their histories are detailed below. Liver function studies at the onset of their illnesses and when last examined are shown in Table 2.

Case 1

This patient developed diarrhoea with 5–6 bowel actions daily at the age of $2\frac{1}{2}$, and a few months after this had an attack of jaundice lasting a few weeks. By the time he was 5 he was passing gross blood and mucus with his stools and had abnormal liver function tests. The diarrhoea continued on and off until he was 9 and at this time the liver became palpable 9 cm below the costal margin, liver palms were noted, and his jaundice fluctuated. Following two haematemeses from oesophageal varices a porto-caval shunt was performed. At operation the liver was noted to be enlarged and finely nodular, and the portal pressure recorded at 300 mm water. The operative wedge liver biopsy was reported as showing marked fibrosis of the portal tracts extending in some areas in bands towards the centres of lobules. There was proliferation of the ducts and ductules and a moderate mononuclear and plasma cell infiltration of the portal tracts.

Over the next 4 years he improved greatly, his diarrhoea lessened and there was no further gastrointestinal bleeding. A rectal biopsy at the age of 12 showed the mucosa to be infiltrated with chronic inflammatory cells but there was no ulceration. The sub-mucosa showed slight inflammatory cell infiltration and oedema. When he was 24 a small tuberculous lesion in the lung was detected and he began chemotherapy with INAH and PAS. His hepatic status is unchanged, with the liver enlarged 9 cm below the right costal margin, and he continues to have bouts of mild bloody diarrhoea.

Case 2

At the age of 3 she had bouts of bloody diarrhoea extending over a number of months. The diarrhoea recurred when she was 7 and at this time splenomegaly was noted. From the age of 10–15 she remained in fair health apart from mild bouts of diarrhoea and the development of an iron deficiency anaemia. When aged 15 she became jaundiced for the first time. The liver was palpated 5 cm below the costal margin and the spleen 3 cm below the costal margin. Liver function tests were as shown in Table 2. During the subsequent weeks she had a series of severe haematemeses from oesophageal varices necessitating a porto-caval shunt; an end to side anastomosis was performed. An operative liver biopsy showed cirrhosis (Fig. 2). At about the time of this operation she began to suffer increasingly troublesome bouts of diarrhoea with blood and mucus which responded only partially to steroid therapy. Barium enema examinations over this

TABLE 1. Clinical features of the four patients

Case	Sex Present age	Age at onset of colitis	Progress of ulcerative colitis	Age at onset of liver disease	Progress of liver disease	Liver histology
1	M (27)	2½	Mild relapsing colitis	9	Bleeding varices and porto-caval shunting aged 11. Hepatic status recently unchanged	Fibrosis
2	F (36)	3	Total procto-colectomy aged 27	15	Bleeding varices and porto-caval shunting aged 15	Cirrhosis on open biopsy aged 15
3	M (29)	12	Total procto-colectomy aged 22	24	Bouts of fever and jaundice. Steroid therapy. Stones removed from bile duct aged 29	? sclerosing cholangitis on biopsy at age 29
4	F (43)	13	Colectomy and ileo-rectal anastomosis aged 25	37	Recurrent jaundice, steroid therapy	Pericholangitis

TABLE 2. Liver function tests at onset of hepatic complications and when last seen

	Case 1		Case 2		Case 3		Case 4	
	Age 9	Age 27	Age 15	Age 36	Age 24	Age 29	Age 29	Age 43
Bilirubin (mg/100 ml)	8.7	1.3	3.7	1.8	2.9	2.4	7.6	8.7
Alkaline Phosphatase K.A. units	82		35.5					
International units		445		323	281	199	550	780
Total plasma								
Proteins (g/100 ml)	8.1	6.6	9.0	6.6	8.9	8.2	8.8	7.5
Albumin (g/100 ml)	2.3	2.2	3.8	3.3	—	4.3	3.7	3.4
Globulin (g/100 ml)	5.8	3.4	5.2	3.3	—	3.9	5.1	4.1

FIG. 2. Case 2. Operative liver biopsy showing regeneration nodules and broad bands of fibrous tissue. (H & E $\times 50$.)

period showed typical changes of ulcerative colitis extending throughout the whole colon. After considerable deterioration in general health a total procto-colectomy and ileostomy was carried out at the age of 27. Following this procto-colectomy her general health has improved greatly though there was an episode of haematemesis and bleeding from the ileostomy after 2 years. She is now leading a full life as a health visitor and dog-breeder. There have been no further episodes of jaundice; there is no evidence of liver failure. A recent needle liver biopsy taken at the age of 36 was fragmented but showed surprisingly good preservation of the hepatic architecture with increased fibrosis but no definite evidence of cirrhosis. Most portal tracts were normal but a few were oedematous with a mild infiltrate of inflammatory cells (Fig. 3).

Case 3

At the age of 12 he developed diarrhoea with up to 6 bowel actions per day. His general health remained fairly good but by the age of 16 radio-

FIG. 3. Case 2. Needle liver biopsy showing fibrosis with oedema and mild inflammatory infiltrate in the portal tracts. (H & E $\times 126$.)

logical examination showed whole colon involvement with ulcerative colitis. A marked deterioration in his condition occurred at the age of 24 (with more frequent bowel actions, abdominal pain, the passage of blood and mucus and loss of weight). Total procto-colectomy and ileostomy was performed with gratifying improvement in his general condition. Pathological examination of the excised colon, rectum and anus confirmed the typical features of ulcerative colitis with diffuse shallow ulceration extending to the ascending colon.

Six months later he became jaundiced with fever, and over the next 2 years he had a series of attacks of jaundice, often with fever. A laparotomy, 2½ years after the procto-colectomy, revealed a narrow, thick walled common bile duct which was irregular throughout its whole length. The gallbladder was removed and a cholangiogram performed through the cystic duct. This confirmed marked reduction in width and irregularity of the common bile duct and the absence of stones. These features were considered to be those of a sclerosing cholangitis.

For 5 years he was maintained on steroid therapy with bouts of fever, jaundice and abdominal pain. A further laparotomy has recently been carried out when duodenostomy and sphincterotomy were performed. Multiple calculi were found in the hepatic ducts. Wedge liver biopsy showed a normal pattern with both double and normal plates in the liver in which most of the portal tracts showed mild fibrosis and infiltration with lymphocytes and plasma cells, without ductule proliferation. In one tract there was concentric fibrosis around a bile duct; although many of the changes could be related to repeated cholangitis the appearances favoured sclerosing cholangitis.

Case 4

This gypsy girl presented at the age of 13 with diarrhoea and iron deficiency anaemia. For the next 10 years she continued with bouts of intermittent diarrhoea passing blood and mucus per rectum. At the age of 24 she showed typical radiological changes of whole colon involvement with ulcerative colitis. A total colectomy and ileo-rectal anastomosis was performed and histological examination confirmed the diagnosis. The spleen was noted to be enlarged at operation. Subsequently her diarrhoea continued to a lesser degree and she remained mildly anaemic. Steroid therapy brought about considerable clinical improvement and proctoscopy 10 years after operation revealed a granular friable mucosa. She persistently refused to accept rectal excision and an ileostomy.

The first bout of cholestatic type jaundice occurred when she was 29. Her liver biopsy a month after onset of jaundice showed expansion of the portal tracts by fibrosis with bile duct proliferation and a mixed inflammatory cell infiltrate. In one area concentric periductal fibrosis was a feature. There was prominent periportal cholestasis (Figs. 4 and 5). Since then her health has been poor and there was only marginal clinical improvement on steroids. When last seen 3 years ago she was still jaundiced with grossly abnormal liver function tests. Unfortunately, in view of her gypsy habits she has been lost to follow-up.

Discussion

In this present series the onset of ulcerative colitis in childhood has apparently carried a con-

FIG. 4. Case 4. Liver biopsy showing cholestatic and cholangitic features. (H & E $\times 126$.)

FIG. 5. Case 4. Liver biopsy showing pericholangitis. (H & E $\times 250$.)

siderable risk of subsequent serious liver disease. This is in broad agreement with the findings of Holdsworth *et al.* (1965) who found that 80% of their patients with colitis and chronic liver disease developed the first symptoms of colitis below the age of 30. Similarly Mistilis (1965) found that nine of his twenty-four patients with pericholangitis had symptoms of colitis before the age of 20, and Stauffer *et al.* (1965) reported twelve of their thirty patients with both ulcerative colitis and hepatic disease as having bowel symptoms before the age of 20. Other authors have commented that the combination of ulcerative colitis and cirrhosis was almost

confined to patients under the age of 40 (Wilcox and Isselbacher, 1961) and similar conclusions have been reached in earlier papers (Jones, Baggenstross and Bargaen, 1951; Boden *et al.*, 1959).

When unselected series of children with colitis are considered (Table 3) the incidence of chronic liver disease is considerably less; this presumably reflects a several-year latent period of colitis before the development of hepatic complications. Thus Platt, Schlesinger and Beeson (1960) found only one definite case of liver disease in sixty-two children starting colitis under the age of 15; Bargaen and Kennedy (1955) reported two in 139 children under 15; Patterson, Castiglioni and Sampson (1971) one case in twenty-three children and teenagers; and Handley and Roy (1968) found no cases in their series of children starting colitis under the age of 16 years. In a long follow-up of 134 children with ulcerative colitis Lagercrantz (1955) detected two patients with cirrhosis.

The question of the relation of the liver disease to the duration and severity of the colitis remains unanswered. Whilst it is unusual for clinical liver disease to precede the colitis occasional examples do occur (Mistilis, 1965; Holdsworth *et al.*, 1965). When liver disease follows the colitis, as is usual, there has been an extremely variable duration of bowel symptoms. In an analysis of patients from series in which adequate details are available (Mistilis, 1965; Stauffer *et al.*, 1965; Holdsworth *et al.*, 1965) it can be shown that liver disease took approximately 10 years to develop after the onset of colitis in adult life which was similar to those patients who developed colitis in childhood. Information about

TABLE 3. Series of children with ulcerative colitis

Author	Children with ulcerative colitis	Children with ulcerative colitis and liver disease	Details
Bargaen and Kennedy (1955)	139 (onset under 15 years of age)	2	1 with liver failure after ileostomy 1 with liver failure after ileostomy
Lagercrantz (1955)	134 (follow-up study)	2	Both with cirrhosis
Platt, Schlesinger and Beeson (1960)	62 (onset under 15 years of age)	1	1 with cirrhosis Hepatomegaly noted in three
Hijmans and Enzer (1962)	43 (onset under 16 years of age)	1	1 with cirrhosis 2 with possible hepatitis 3 with hepato-splenomegaly 4 with hepatomegaly
Handley and Roy (1968)	31 (onset under 15 years of age)	0	
Grossman and De Benedetti (1970)	32 (onset under 18 years of age)	1	Cirrhosis
Patterson, Castiglioni and Sampson (1971)	43 (onset under 20 years of age)	1	1 with cirrhosis 1 with possible hepatitis

the degree and type of liver damage in relation to the severity of the colitis is similarly conflicting. Mistilis, Skyring and Goulston (1965) have indicated that pericholangitis may progress to fibrosis and Eade (1970) has pointed out that severe long standing colitis may be associated with fibrosis. Regression of liver lesions after colectomy has been reported by Nedbal *et al.* (1968) and Eade, Cooke and Brooke (1970) but Bagen and Kennedy (1955) have described progression of liver lesions after excision of the diseased bowel.

The liver lesions of childhood colitis follow a similar histo-pathological pattern to those seen in adult colitis. A spectrum of liver disease has been described including fatty infiltration, pericholangitis, active chronic hepatitis, macronodular cirrhosis and a few examples of biliary cirrhosis. Sclerosing cholangitis following childhood colitis is extremely rare and there may be doubt about the diagnosis of this disorder in our patient owing to the recent finding of calculi in the duct system. The two cases of portal hypertension in our series who underwent porto-caval anastomosis represent an unusual complication of colitis and their long survival is encouraging. This topic has been well reviewed by McCarthy and Read (1962) who noticed improvement in the colitis after porto-caval shunting as was found in Case 1 of this series.

The four cases described here underline the complexities of liver disease in relation to ulcerative colitis. The various theories which have been put forward to explain the liver lesion in ulcerative colitis have recently been reviewed (Perrett *et al.*, 1971). There seems little support for previous viral hepatitis or drug therapy as having an important relationship. The concept of portal bacteraemia in colitis is an attractive one (Brooke, Dykes and Walker, 1961) and the pathological lesion of pericholangitis is sited correctly on anatomical grounds. Many authors have favoured an immunological theory of aetiology particularly as younger patients with colitis are prone to hepatic complications, but it is impossible to relate auto-antibody studies to the liability to develop systemic complications (Wright and Truelove, 1966). The possibility that colitis associated with liver disease represents a distinct disease entity has also been canvassed (Medical Staff Conference, 1967). Further prospective studies may clarify the situation.

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