Portal fibrosis in the livers of alcoholic patients

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SUMMARY Liver biopsies in nine of 70 male alcoholics seen during a 12 month period showed predominantly portal fibrosis with fatty change, but little or no alcoholic hepatitis. None of the 30 female alcoholics seen during the same period showed this appearance. The nine men were younger and of lower socioeconomic class than the other male alcoholics, but had a similar alcoholic history. Seven of the nine had chronic pancreatitis, diagnosed in six patients on the results of the pancreatic scan, Lundh meal and endoscopic retrograde pancreatography and in one because of pancreatic calcification and steatorrhoea. Serum tests for hepatitis B surface antigen were negative but five showed hepatitis B antibody. Four had serological evidence of previously treated or active syphilis compared with only one of the remaining 61 male alcoholics. Two had pulmonary tuberculosis and both had received isoniazid. Four of the other 61 alcoholics gave a history of tuberculosis similarly treated. At least one cause for the portal fibrosis other than primary alcoholic liver disease was found in all nine patients. Portal fibrosis in an alcoholic in the absence of severe alcoholic hepatitis should lead to a search for other causal factors. In particular, chronic pancreatitis should be excluded even if the patient is asymptomatic.

The nature of the liver lesion produced by alcohol and its natural history are well documented (Rubin, 1973). Alcohol does not characteristically produce portal and periportal fibrosis alone and the major pathway to cirrhosis is believed to be alcoholic hepatitis (Gerber and Popper, 1972).

Nine of 70 male alcoholics seen during one 12 month period had predominantly portal zone fibrosis on liver biopsy, with fat, but little or no alcoholic hepatitis. None of 30 female alcoholics seen during the same period showed this lesion. In all nine of these male alcoholics an alternative explanation for this lesion was sought and in none of them was alcoholic hepatitis thought to be responsible for the portal lesions. The nine patients are described in detail and compared and contrasted with the remaining 61 male alcoholics.

Methods

One hundred patients (70 males; 30 females), in whom there was a history of alcohol abuse and test results showing disturbed liver function, were

admitted to the medical unit at the Royal Free Hospital during one 12 month period. Personal details, including socioeconomic class, as defined by occupation and highest class achieved (Office of Population Censuses and Surveys, 1971), were documented and details of the drinking history taken as accurately as was possible. Particular note was made of the number of years of regular, heavy drinking and of the number of grams of ethanol consumed per day. A full medical history and clinical examination were undertaken. Biochemical and serological screening included measurement of the serum bilirubin, aspartate transaminase (AST), alkaline phosphatase (ALP) and amylase using routine laboratory techniques, the hepatitis B surface antigen (HBsAg) by radioimmunoassay and the *Treponema pallidum* haemagglutination assay (TPHA) by standard procedure. Percutaneous needle biopsy allowed histological diagnosis of the liver lesion.

In the nine male patients who had predominantly portal zone fibrosis on liver biopsy, additional investigations were undertaken. The serum hepatitis B surface antibody (HBsAb) was measured by radioimmunoassay and full HLA typing was carried out by a microcytotoxicity technique.

Pancreatic function was investigated by an oral glucose tolerance test (GTT) and measurement of

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faecal fat excretion in all nine patients. In eight patients pancreatic scanning with ^{75}Se -selenomethionine (Bouchier *et al.*, 1972) was combined with a standard Lundh test meal (James, 1973), and duodenal tryptic activity assessed by measurement of radioselenium in the duodenal aspirate (Youngs *et al.*, 1971), in addition to its routine chemical assessment. The biliary and pancreatic ducts were visualised by endoscopic retrograde cholangio-pancreatography (ERCP).

The diagnosis of chronic pancreatitis was established by the presence of two or more of the following abnormalities: (1) pancreatic calcification shown on anteroposterior and lateral plain radiographs of the abdomen (Sarles, 1974); (2) abnormalities of the pancreatic ducts characteristic of chronic pancreatitis (Kasugai *et al.*, 1972; 1973; Rohrmann *et al.*, 1974); (3) abnormal ^{75}Se -selenomethionine pancreatic scanning; (4) diminished duodenal tryptic activity after a standard Lundh test meal.

The radiology of the pancreas and the biliary tract was assessed blind by two experienced observers.

In six of the nine patients (2, 3, 5, 6, 7, 8), the liver biopsy was repeated when they had abstained from alcohol, or drastically reduced their daily intake, for a minimum of four months.

Results

Personal details of the nine male alcoholics with portal fibrosis are shown in Table 1. These nine male patients were younger—mean age 44 years—than the other 61 male alcoholics—mean age 50.4 years. All nine of them were designated to social classes III to VII, whereas only 48% (29/61) of the other male alcoholics belonged to these lower social classes. The length of drinking history was similar for the male alcoholics with portal fibrosis—18.6 years and those without, 20.4 years. The quantity

of alcohol consumed and the types of beverage favoured were similar for both groups. Patients 6 and 9 were practising homosexuals, one of whom (6) gave a history of acute viral hepatitis three years previously.

Details of the clinical history including the mode of presentation and the major clinical findings are shown in Table 2. Although all nine patients had hepatomegaly, they otherwise had very few stigmata of chronic liver disease. One patient (2) had received several courses of drugs including isoniazid for pulmonary tuberculosis. One other patient (3) was taking isoniazid at the time of the study. Four of the other 61 patients had had tuberculosis and had received isoniazid. One of these had only fatty change on liver biopsy with no evidence of portal fibrosis, and the other three patients had established cirrhosis.

Table 3 contains details of the biochemical and serological findings in the nine patients. Patient 6 had been HBsAg negative during his episode of acute hepatitis, but has subsequently become HBsAb positive. Four other patients (3, 4, 5, 9) were also HBsAb positive but gave no history of hepatitis. Patient 9 was homosexual, but no potential route for infection by the hepatitis B virus could be identified in the other three. The incidence of positive HBsAb in the serum in these nine patients is 58% (5/9), compared with an expected incidence in British alcoholics with fatty liver of 20% (Pennington and Kay, personal communication, 1977). In four of the patients the TPHA was positive. Three of them (4, 6, 9) had been treated previously for secondary syphilis and the TPHA titres were consistent with adequately treated, inactive, disease. In patient 3 the TPHA titre indicated active infection, though the patient was clinically asymptomatic. Only one of the other 61 male patients had positive serology with a titre consistent with treated syphilis. Liver biopsy in this patient showed alcoholic cirrhosis and hepatitis.

Table 1 *Personal details of nine male alcoholics with portal fibrosis*

Patient	Age (yr)	Social Class (I → VII)	History of alcohol abuse (yr)	Quantity of ethanol per day (g)
1	33	IV	14	197
2	48	VI	20	344
3	40	VI	12	345
4	54	V	15	238
5	41	VI	27	422
6	41	VI	20	340
7	53	VI	25	184
8	46	III	22	183
9	40	III	20	152

Table 2 Clinical details of nine male alcoholics with portal fibrosis

Patient	Mode of presentation	Clinical findings		
		Stigmata of chronic liver disease	Liver size (cm below costal margin)	Others
1	Epigastric pain, diarrhoea, weight loss		4 cm enlarged, firm, tender	
2	Hepatomegaly	Parotid enlargement	4 cm enlarged, firm, non-tender	Inactive pulmonary TB
3	R. hypochondrial pain	Jaundiced	5 cm enlarged, soft, tender	Diabetes, active pulmonary TB
4	Knee injury, hepatomegaly	Spider naevi, palmar erythema, testicular atrophy	8 cm enlarged, soft, non-tender	
5	Epigastric pain, vomiting	Spider naevi	4 cm enlarged, firm, tender	
6	Delirium tremens after accident		5 cm enlarged, firm, tender	Peripheral neuropathy
7	Anorexia, weight loss	Jaundiced	1 cm enlarged, firm, non-tender	Peripheral neuropathy
8	Ataxia		6 cm enlarged, firm, tender	Cerebellar ataxia, peripheral neuropathy
9	Hepatomegaly		8 cm enlarged, firm, non-tender	

TB: tuberculosis.

Table 3 Biochemical and serological data in nine male alcoholics with portal fibrosis

Patient	Serum						
	Bilirubin ($\mu\text{mol/l}$) (n.r. 5-17*)	Alkaline phosphatase (KA U/dl) (n.r. 3-13)	Aspartate transaminase (IU/l) (n.r. 4-15)	Amylase IU/l (n.r. 150-350)	HBsAg	HBsAb (Titre $\times$ NHS)	TPHA (titre)
1	18.8	9.0	34	240	—	—	—
2	10.0	15.0	24	160	—	—	—
3	24.0	13.0	22	195	—	+ $\times$ 41	+ 1/1280
4	14.8	5.0	31	225	—	+ $\times$ 5.5	+ 1/160
5	7.0	5.0	31	250	—	+ $\times$ 142	—
6	12.0	4.0	61	180	—	+ $\times$ 3.2	+ 1/160
7	44.4	17.0	49	340	—	—	—
8	13.0	6.0	23	300	—	—	—
9	13.0	6.0	38	260	—	+ $\times$ 283	+ 1/160

* Normal range values.

NHS: normal human serum.

Table 4 Pancreatic investigations in nine male alcoholics with portal fibrosis

Patient	Oral glucose tolerance test	Faecal fat excretion (mmol/day) (normal < 18)	Abnormal pancreatic scan (0 $\rightarrow$ +++)	Duodenal aspirate tryptic activity	ERCP
1	Flat	74.0			
2	Normal	14.0	+++	Nil	Normal main pancreatic duct; poor filling 2° radicles; CBD—long intrapapillary segment
3	Moderately severely diabetic	10.8	+	Nil	Stricture main pancreatic duct; abnormal 2° radicles
4	Normal	10.8	+	Normal	Normal
5	Normal	8.6	+++	Low	Long stricture main pancreatic duct in body of gland
6	Normal	8.0	++	Low	Abnormal 2° radicles
7	Normal	16.0	++	Nil	Minimal changes main pancreatic duct; stricture distal CBD
8	Flat	13.4	++	Nil	Dilated main pancreatic duct; cystic changes in 2° radicles
9	Normal	11.5	0	Normal	Normal.

CBD: common bile duct.

Full HLA typing was carried out on all nine patients. No phenotype showed an unusually high incidence.

Table 4 contains details of the pancreatic investigations. Seven of the nine patients (1, 2, 3, 5, 6, 7, 8) were thought to have chronic pancreatitis. In patient 1 this was suspected from the history of epigastric pain, weight loss, and diarrhoea and confirmed to an extent by the increased faecal fat excretion and the presence of pancreatic calcification on plain abdominal radiographs. The patient, however, refused further investigation, but it was felt that there was sufficient evidence to diagnose pancreatitis, even though he did not fulfil the exact criteria laid out earlier. In patient 3 the diagnosis was suggested when overt diabetes developed, and in patient 7 because of an episode of painless cholestasis. Patients 2, 5, 6, and 8 were, however, asymptomatic. Figure 1 shows the changes on ERCP in patient 3 in whom the diagnosis was suspected and Fig. 2 the changes on ERCP in patient 8 in whom it was not. Of the other 61 male alcoholics, 10 (16%) had symptomatic, proven

Fig. 1 ERCP in patient 3 showing a stricture in the main pancreatic duct (arrowed) and abnormalities of the secondary radicles.

Fig. 2 ERCP in patient 8 showing a dilated main pancreatic duct and cystic changes in the secondary radicles.

chronic pancreatitis, but the incidence of asymptomatic disease in the remainder is not known.

The histological findings on liver biopsy are summarised in Table 5. The common finding in all nine patients was fibrosis involving the portal tracts and often, the immediately periportal zones. Some portal tracts were linked by fibrous tissue (Fig. 3). The fibrotic areas contained proliferated bile ducts and a variable inflammatory infiltrate which usually included both acute and chronic inflammatory cells. The liver cells contained fat vacuoles but alcoholic hepatitis as defined by a combination of liver-cell swelling, Mallory bodies, a neutrophil leucocytic reaction, and pericellular fibrosis was seen in only one patient (6) and was then only very mild. In one other biopsy (8) there was a slight increase in pericellular collagen near central veins. Giant mitochondria were sometimes visible in the liver cells under the light microscope. Cholestasis was found in only two patients (2, 8) and was not severe. A small or moderate amount of stainable iron was commonly seen in liver cells and Kupffer cells.

Electron microscopy was carried out on biopsies from six patients. Giant mitochondria, as typically seen in alcoholic patients, were found in the liver cells. There was a variable degree of proliferation of the endoplasmic reticulum and fat vacuoles were present. Mallory bodies were not demonstrated; lipocytes were prominent.

Table 5 Main liver biopsy findings in nine alcoholics with portal fibrosis

Case	Fibrosis*		Fat*	Liver-cell siderosis*	Cholestasis*	Duct proliferation*	Alcoholic hepatitis*	Possible causes†
	Portal	Intralobular						
1	+	—	++	+	—	+	—	P
2	+	—	+	—	+	+	—	PT
3	++	—	++	+	—	+	—	PHS
4	++	+	++	—	—	+	—	HS
5	++	—	+	+	—	+	—	PH
6	+	+	+++	+	—	+	±	PHS
7	++	+	++	++	—	++	—	P
8	++	+	++	++	+	++	—	P
9	+	—	+++	—	—	—	—	HS

† Graded 0 to +++ according to the maximum change found in any one biopsy.

* P: chronic pancreatitis. H: hepatitis B. S: syphilis. T: antituberculous treatment.

Fig. 3 Patient 4. Liver biopsy showing fatty change and fibrosis. An inflamed septum links two portal tracts. Haematoxylin and eosin (H and E), $\times 155$ (original magnification).

Six of the nine patients reduced their alcohol consumption dramatically or were able to abstain from alcohol completely. These patients had a

second biopsy. Patient 2 had abstained completely and the second biopsy was similar to the first, but without cholestasis. Patient 6 reduced his intake and the second biopsy eight months later was similar to the first. This patient had had a liver biopsy three years previously which showed an acute hepatitis of viral type on light microscopy together with excess fat. Patients 3, 5, and 7 abstained from alcohol completely and in all three the portal fibrosis appeared to decrease. This is illustrated by Figs. 4 and 5, which show the first and second liver biopsies in patient 7. Patient 8 reduced his intake considerably and on repeat biopsy fatty change and siderosis were mild and cholestasis absent, although the portal fibrosis, infiltration with inflammatory cells, and bile duct proliferation were as before.

Patient 6 was known to have had viral hepatitis, but in the other patients the histological appearance did not suggest a definitive cause for the portal lesion. However, the combination of portal fibrosis, bile duct proliferation and a mixed inflammatory infiltrate often suggested the possibility of disease involving the distal extrahepatic biliary tree, such as chronic pancreatitis.

Discussion

Portal fibrosis is not a recognised feature of the spectrum of alcohol-related liver injury in the absence of severe alcoholic hepatitis. It may develop as a result of septum formation between portal and central areas (Gerber and Popper, 1972) but such septa were not seen in our patients. The occurrence of predominantly portal fibrosis in nine of the 70 male alcoholics reviewed during a 12 month period therefore led to a search for causal factors.

Pennington and Kay (personal communication, 1977) have shown an incidence of HBsAb measured by radioimmunoassay of 8.8% in the general

Fig. 4 Patient 7. First liver biopsy showing extensive fibrosis in and around a portal tract. Many liver cells contain fat vacuoles. H and E, $\times 155$ (original magnification).

population and an incidence of 20% in patients with alcoholic fatty liver. The incidence of positive HBsAb in our patients with portal fibrosis was 56% (5/9) which is considerably higher. Only one of these (6) had had a documented attack of hepatitis. Although the portal inflammatory infiltrate in acute hepatitis is normally slight to moderate, in some patients a more extensive portal reaction develops (Bianchi *et al.*, 1971) and may leave residual scarring.

Liver disease in the form of fibrosis, gumma, and hepar lobatum is often found in the later stages of syphilis. Fehér *et al.* (1975) have recently described an early, asymptomatic syphilitic hepatitis occurring with secondary syphilis in the early latent stages. After treatment with penicillin the syphilitic hepatitis healed with accumulation of collagen in the walls of sinusoids and in the spaces between the liver cells.

Three of our patients (4, 6, 9) had had secondary syphilis and a previous syphilitic hepatitis may have contributed to the portal fibrosis. A fourth patient (3) had active syphilis at the time of the study.

Isoniazid can produce liver injury which is indistinguishable from viral hepatitis (Mitchell *et al.*, 1976). In 12-20% of recipients, isoniazid produces subclinical hepatic injury which may become chronic (Black *et al.*, 1975). Isoniazid injury may have contributed to the portal fibrosis seen in one of our patients (2) who had received several courses of the drug. Patient 3 was currently receiving isoniazid but was known to have the portal lesion beforehand.

Seven of our nine patients were shown to have chronic pancreatitis on investigation. One patient (7) had had an episode of cholestasis and ERCP showed narrowing of the distal common bile duct.

Fig. 5 Patient 7. Second liver biopsy; fibrosis is less and fatty change very mild. A centrilobular vein (above right) appears normal. H and E, $\times 155$ (original magnification).

He was therefore similar to 11 of the 38 patients with non-gallstone chronic pancreatitis recently described by Scott *et al.* (1977). Two other patients (1, 3) had clinical features suggestive of pancreatitis but the remaining four were asymptomatic. Mezey *et al.* (1970) found that abnormalities of pancreatic function commonly occur in alcoholics with no history suggestive of pancreatic disease. The flat GTT seen in two of the patients (2, 7) may have resulted from intestinal malabsorption, which can occur in alcoholics even with normal jejunal histology (Mezey *et al.*, 1970).

The portal zone fibrosis seen on liver biopsy in the seven patients with chronic pancreatitis may have resulted from subclinical cholangitis or obstruction to the bile duct in its intrapancreatic course due to oedema and swelling of the pancreas. The absence of histological cholestasis suggests, however, that the ducts were not seriously obstructed at the time of biopsy. Of all the possible causes of portal zone fibrosis in this group of patients, disease of the pancreatobiliary system appears the most likely.

In all nine patients at least one possible cause for the portal zone fibrosis seen on liver biopsy was suggested. Alcohol was not thought to be responsible. If portal zone fibrosis is identified in an alcoholic in the absence of severe alcoholic hepatitis a search should be made for other causal factors. In particular, chronic pancreatitis should be excluded whenever possible even in the asymptomatic patient.

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