Liver cirrhosis in cystic fibrosis – therapeutic implications and long term follow up

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Abstract

Experience gained from liver studies in 450 patients with cystic fibrosis, seen in a 38 year period from 1964 to 1992, is surveyed. Of these, 31 (7%) showed findings that indicated multilobular cirrhosis. There was a slight but not significant male predominance: 19 males against 12 females. Liver disease had its onset during childhood in most cases. The natural course of liver disease and of cirrhosis is protracted.

All patients were routinely evaluated by way of: (i) clinical examination, (ii) biochemical studies and specifically estimation of transaminases and γ glutamyltransferase, and (iii) liver imaging, ultrasonography, and computed tomography. The study aimed to detect early liver disease, that is multilobular cirrhosis and its complications, with a view to optimal introduction of treatment with ursodeoxycholic acid as this drug shows promise for preventing or stabilising the cirrhotic process.

Effects of surgical treatment on portal hypertension are surveyed. These include portacaval shunting, partial splenectomy (considered the procedure of choice), liver transplant in the event of liver failure, or a triple transplant (liver, lungs, and heart) if necessary. One triple transplant was successfully performed in a boy of 10 years with a 2 year follow up.

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Multilobular cirrhosis of the liver and its consequences are major complications of cystic fibrosis, second only to respiratory impairment. The rate of involvement of patients with cystic fibrosis ranges from 5% to 12% in reported series. The extension of focal biliary fibrosis, described by Bodian[1] and Di Sant Agnese and Blanc,[2] to most of the liver parenchyma results in the overall picture of multilobular cirrhosis.

This paper aims to: (i) outline the natural course of multilobular cirrhosis in patients with cystic fibrosis and (ii) discuss the consequences of cirrhosis, especially portal hypertension, and define the various medical and surgical measures that can be taken against liver impairment and the ensuing complications.

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Patients and methods

Thirty one patients with ascertained cystic fibrosis, 19 males and 12 females, were found to have multilobular cirrhosis after clinical examination, imaging, and evaluation of laboratory data. They were observed during a period of 28 years, between 1964 and 1992, and two subgroups followed up by two different specialists in the field were aggregated. The set of 31 patients was taken from a population of some 450 cystic fibrosis patients, both adults and children, of whom 300 were followed up as personal cases; 150 were referred for evaluation and advice. Some 10% of the personal, long term patients developed cirrhosis as opposed to 6·5% of the whole set; however, the latter figure probably underestimates the incidence of the condition.

All patients were evaluated at regular monthly or two monthly intervals as follows.

CLINICAL EXAMINATION

Clinical suspicion of multilobular cirrhosis was established whenever an enlarged and hard liver with nodules was perceptible: right lobe edge lowered down over 2 cm, left lobe over 3 cm. Splenomegaly, whenever ascertainable and confirmed on repeat examination, was considered as a criterion for portal hypertension.

BIOCHEMICAL INVESTIGATION

Laboratory data were collected at monthly or two monthly intervals. Investigations included complete blood count, prothrombin time, and measurement of aspartate aminotransferase, alanine aminotransferase, and γ glutamyltransferase.[3,4] The last three measurements were selected as basic routine tests for screening for liver abnormality because they properly reflect cytolytic and cholestatic activity and are easy to carry out. A sustained increase of more than 6 months' duration in these three enzymes suggested the onset of cirrhosis.

IMAGING

Images were obtained initially by scintiscan[5,6]

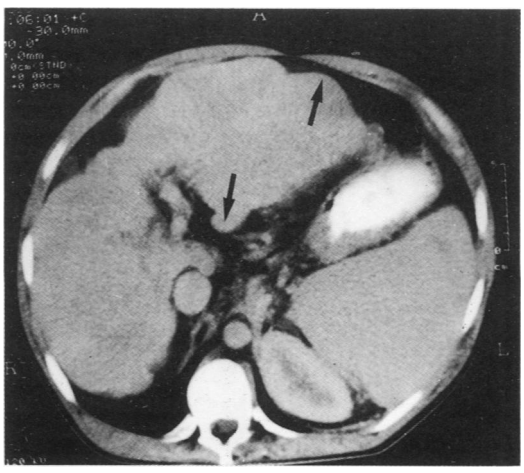

Figure 1 Hepatomegaly with irregular contours and a large spleen shown on computed tomography in patient 8.

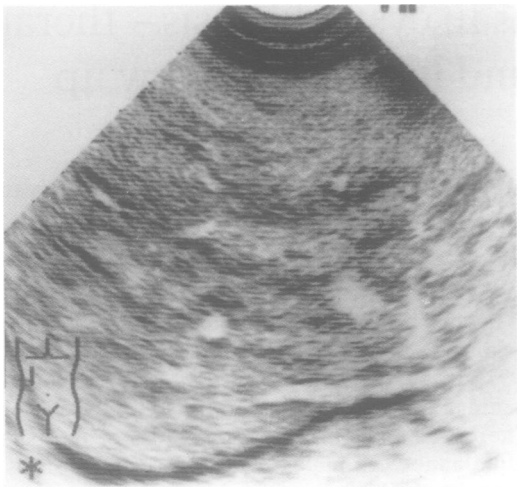

Figure 2 Heterogeneous liver parenchyma shown on ultrasonography in patient 19.

and, since they became available, by ultrasonography and computed tomography.[7,8] The morphological abnormalities observed and considered as indications for cirrhosis were an enlarged liver volume with irregular contours (fig 1), heterogeneous parenchyma (fig 2), regenerative nodules visualised, and attenuation of ultrasound transmission. Splenomegaly, dilated portal veins (fig 3), and dilated collateral veins were considered diagnostic for portal hypertension.

Findings on imaging were usually detected later than biochemical changes, except in two cases. Patients with isolated liver enlargement ascertained on clinical examination and confirmed by ultrasonography were not included, nor were patients with a transient increase in enzyme activities and no further symptoms of multilobular cirrhosis. Patients with steatosis, recognisable on computed tomography and ultrasonography, were also ruled out.

FIBROSCOPY

Within the last decade, all patients who had indications on clinical examination, laboratory investigation, or imaging that were suggestive of liver disease underwent systematic fibroscopy once or twice a year to detect portal hypertension.

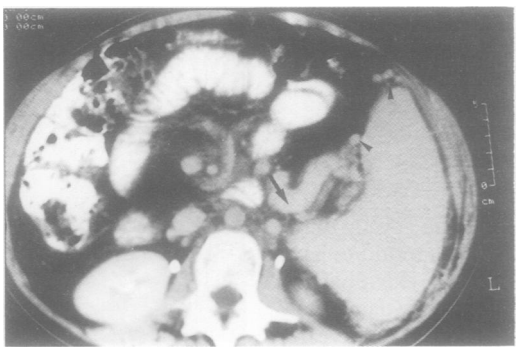

Figure 3 Splenomegaly, dilated portal veins, and diffuse varices shown on computed tomography in patient 18.

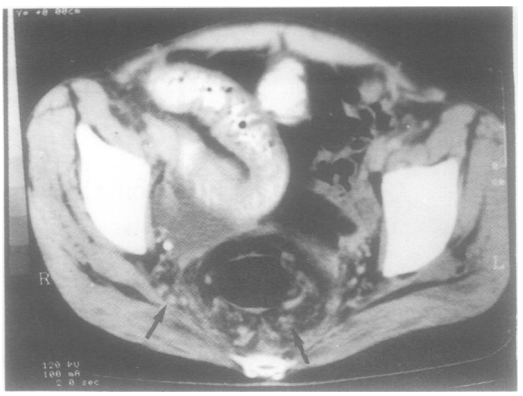

Figure 4 Pelvic varices shown on computed tomography in patient 18.

Results

The average age at onset of liver disease in the 31 patients with cirrhosis was 7 years. One case of neonatal cirrhosis was observed with an onset characterised by prolonged jaundice and a hard liver edge with a progression to portal hypertension and fatal hepatic failure at 5 years (patient number 3). In 28 cases, cirrhosis appeared before the age of 14, before puberty; puberty is usually delayed in patients with cystic fibrosis. In the three older cases, the onset was noted at age 17, during puberty. We did not observe the onset of cirrhosis in 107 adults aged over 18 years. In all the cirrhotic adults of our series, onset of hepatic disease occurred in childhood or adolescence.

We did not observe any instances of familial occurrence, as has been previously reported.[9] Portal hypertension, when carefully looked for by imaging, could be observed precociously generally about a year after the rise of the enzyme activities (tables 1 and 2).

Like Scott-Jupp *et al* we found a slight male predominance[10]: 19 males against 12 females, but this could not be considered as significant because of the small sample. Nor could the overall history of meconium ileus for the same reason. This was found in six cirrhotic patients (20%), which was twice the expected incidence in the overall population with cystic fibrosis.[11] The number of microgallbladders was also slightly, but not significantly, higher than expected.[12] Two cases of lithiasis were detected in 31 cirrhotic patients against 12 in 150 non-cirrhotic patients with cystic fibrosis who were all explored by ultrasonography with that specific aim. Scintiscans of the main biliary tract were performed in two cirrhotic patients (numbers 8 and 12), but failed to show any noticeable abnormality, and strictures were not demonstrated at necropsy when performed. On fibroscopy, oesophageal varices were seen in 20 out of the 31 cases; all patients with varices also had splenomegaly.

Out of 16 deaths observed, 10 followed respiratory complications and six were a result of liver complications. Two of these patients died of liver failure and four of ruptured varices. Necropsy in one patient showed rupture of duodenal varices and not of oesophageal varices. Diffuse pelvic varices, readily visible, were reported on tomodensitometric evaluation of patient number 18, aged 22 years (fig 4).

Table 1 Details of the 16 cirrhotic patients who died

Patient No	Sex	Year of birth	Age (years) at death	Cause of death	Meconium ileus	Micro-gall-bladder	Pulmonary condition*	Age of occurrence (years)			Surgical treatment
								Hepatomegaly	Rise in liver enzymes	Portal hypertension	
1	F	1962	11	Pulmonary complications			0	7	8	10	
2	F	1965	7	Hepatic insufficiency	+	+	2	5	6	6	
3	M	1964	5	Hepatic insufficiency	+	+	1	Neonatal	3	3	
4	M	1966	5	Hyponatraemia		+	1	2	5	5	
5	M	1962	11	Portal hypertension		+	0	5	7	7	
6	F	1959	13	Portal hypertension		+	2	8	11	12	
7	M	1969	12	Pulmonary complications			1	4	5	8	Portacaval shunt
9	M	1971	11	Pulmonary complications		+	0	0·3	7	7	
10	F	1973	10	Pulmonary complications			1	6	?	8	
11	M	1948	23	Portal hypertension			1	17	17	19	
12	M	1972	19	Pulmonary complications		+	1	9	9	9	
13	M	1968	22	Pulmonary complications			0	3	3	4	Portacaval shunt
14	M	1982	5	Pulmonary complications		+	0	2	3	3	
15	F	1981	6	Pulmonary complications	+		2	3	6	6	
23	F	1971	18	Pulmonary complications			0				Portacaval shunt
29	M	1977	9	Portal hypertension		+	0	6	6	6	

*Pulmonary condition: 0=very bad, 1=bad, 2=moderate.

Table 2 Details of the 15 cirrhotic patients still alive

Patient No	Sex	Age in 1992 (years)	Mutation	Meconium ileus	Microgall-bladder	Pulmonary condition*	Age of occurrence (years)			Surgical treatment
							Hepatomegaly	Rise in liver enzymes	Portal hypertension	
8	M	22	508/508	+		0	5	8	8	
16	M	11	508/N1303K			1	5	6	7	
17	M	20	508/508		+ Lithiasis	2	17	17	18	Partial splenctomy
18	F	20	508/G542Y			1	14	14	14	
18	M	9	508/X		+	1	7	5	–	
20	F	12	Q1313Xexon21		+	1	9	9	–	
21	M	14	508/X			0	12	12	–	Portacaval shunt
22	F	22	508/508		+	0	17	17	18	
24	M	18	508/X		+ Lithiasis	2	14	14	16	
25	F	18	508/508	+		2	10	10	10	
26	M	15	508/508			1	8	8	8	Portacaval shunt
27	F	19	508/X			1	8	10	10	
28	M	8	508/508			1	3	3	–	
30	F	22	508/508			0	9	6	6	
31	M	12	508/508			2	1·5	1·3	1·5	Triple transplant: heart, lungs, liver

*Pulmonary condition: 0=very bad, 1=bad, 2=modertate.

Mean duration of survival, after the development of liver disease, was 4·5 years in patients who died of cirrhosis, that is with liver failure and ruptured varices. In cirrhotic patients, mean age of death caused by respiratory failure was 12 years, but the figures are affected by the fact that patients seen in the 1970–8 period could not benefit from the more recently developed antibiotic treatment against *Pseudomonas aeruginosa*. In the more recently seen patients, five with cirrhosis have a survival of more than 10 years after the onset of liver disease and are still alive. Fifteen patients with multilobular cirrhosis received ursodeoxycholic acid; one, an advanced case with respiratory and liver failure, died (number 23).

SPECIFIC CLINICAL FEATURES

One patient developed neonatal cirrhosis as mentioned above; three patients developed ascites in the course of the disease and, in one of these, ascites coincided with the terminal stage.

More than 30% of patients with cystic fibrosis followed up were found to have a transient moderate increase in circulating enzymes without developing multilobular cirrhosis. Their serology for hepatitis was always negative. Histological examination, when samples were available from necropsy or liver biopsy done during the pulmonary operation, showed focal biliary fibrosis. Follow up enzyme studies enabled us to recognise four cases of viral hepatitis; one was anicteric and confirmed by serology. Their enzyme activities were unequivocally raised (table 3). In three non-cirrhotic patients, hepatitis was not the starting point for cirrhosis, and in one cirrhotic patient (number 4), it did not aggravate the course of the disease.

Table 3 Differential diagnosis in various liver conditions in cystic fibrosis

Condition	Increase in enzyme activities	Imaging
Focal biliary fibrosis	Transient, moderate	Normal
Viral hepatitis	Transient, raised	Hepatomegaly
Steatosis	Transient, moderate, or prolonged	Increased echogencity on ultrasonography, hypodense liver on computed tomography
Multilobular cirrhosis	Prolonged, moderate	Bosselated, heterogeneous, hepatomegaly, portal hypertension

PATHOLOGY

Needle biopsies of the liver were not systematically done: in biliary fibrosis the lesion is focal and can be missed, and the results of anatomical data are not necessary for a decision about treatment. Currently the increase in enzymes is sufficient to start treatment with ursodeoxycholic acid.[13] When performed, biopsy samples were taken before or during surgical procedures in seven patients. Necropsies performed in four cases confirmed multilobular cirrhosis.

GENETIC ASPECTS

Incomplete data on the type of underlying mutation did not allow us to state whether there was a correlation between mutation types and the incidence of liver changes. Deletion F508 is as common in the cirrhosis group as in other forms of cystic fibrosis. Cirrhosis may be seen in patients heterozygous for δ F508 as it may occur in patients who do not carry this mutation (tables 1 and 2).

Treatment

In the past two years, 15 cirrhotic patients received prolonged treatment with ursodeoxycholic acid at a daily dose of 20 mg/kg. Except patient number 23, who died of pulmonary failure, there was in all other cases a normalisation of the three enzymes and to some extent a stabilisation of signs seen clinically and on imaging.

Five patients had their oesophageal varices sclerosed with a short to average three year follow up. All patients except one had a recurrence of bleeding, but there were no obvious respiratory consequences of repeated anaesthesia for the two or three scleroses per patient.

Five other patients were successfully given portacaval shunts (numbers 7, 13, 21, 23, and 26). The longest survival was nine years; outcome in these patients was temporarily satisfactory.

One patient (number 16) underwent partial splenectomy at age 9 years: oesophageal varices disappeared three months after surgery without recurrence in three years.[14]

One cirrhotic patient (number 31), who was developing terminal pulmonary changes with ensuing heart failure, received a successful triple transplant of the lungs, heart, and liver two years ago at 10 years of age. He is alive but has some symptoms of obliterative bronchiolitis.

Discussion

Onset of liver disease followed by multilobular cirrhosis, was, as a rule, seen in the first decade or in the beginning of the second decade. Incidence does not increase beyond the age of childhood despite increasing prolonged survival of patients with cystic fibrosis. We did not find any correlation between the pulmonary condition at the onset of cirrhosis or during the evolution of liver complications. It would seem that both liver and lungs have their independent evolution, at least until the preterminal stage of the disease. The fact that the onset of cirrhosis is rare after puberty suggests the existence of a self stabilising factor responsible for the initial triggering of cirrhosis. As respiratory complications are being treated with greater efficiency, we might well eventually witness greater numbers of adolescents with cirrhosis who have survived respiratory or other complications of cystic fibrosis, and see more deaths from cirrhosis, the onset of which still occurs in childhood according to our experience.

A comparison of cases of cirrhosis seen in our original series between 1964 and 1970 with our recent cases reflects changes in the field. While the underlying mechanism is still thought to be the same,[1,2] in focal biliary cirrhosis and its extension to most of liver parenchyma,[15] other factors, for example immunological,[16] toxic,[17,18] or secondary to impaired nutrition,[19] may play a part. But there is as yet no satisfactory theory to account for the development of the liver disease. Nevertheless, enzyme surveillance studies and imaging techniques enable us to identify focal biliary fibrosis characterised by transient moderate enzyme activities on one hand and steatosis of the liver and increased echogenicity on ultrasonography and hypodensity on computed tomography on the other hand with some accuracy and to differentiate these from hepatitis and multilobular cirrhosis (table 3).

The early results of ursodeoxycholic acid on enzyme activities show it is effective and promising,[13] but we still need to verify whether it can stabilise an already existing cirrhosis and whether it can stop its development at the stage of focal biliary fibrosis.

The recurrence of bleeding after sclerosis of oesophageal varices, the presence of duodenal veins that necropsy showed had caused the death of one patient (number 6), and the presence of pelvirectal varices in another (number 18, figs 2 and 3), led us to be more cautious in performing sclerosis of the oesophageal varices as they may be followed by bleeding in inaccessible areas.

Surgical portacaval shunting has been performed for many years[9] and is unquestionably effective, but it is major surgery. The surgical strategy has been the object of a sustained debate: should the procedure be applied prophylactically when varices are demonstrated or only in the aftermath of bleeding?

Partial splenectomy,[14] undergone by patient number 16 at the age of 9 years, has the advantage of being much simpler to perform than shunting. The immunological function of the spleen is preserved. Another major advantage is that liver transplant, should this become necessary in the later course of the disease, is not compromised; five other patients have been operated on, successfully, by the same surgical team. If transplantation is considered there is the difficult choice between a single organ transplant, that is liver, or a triple organ transplant, that is lungs, heart, and liver.[20-22] The outstanding findings published by Starzl *et al* show that when cirrhosis of the liver is considered severe and life threatening, while the pulmonary situation is under control, there is no particular danger in limiting the procedure to the sole liver transplant.[20,21] Reciprocally, if the cardiac and pulmonary lesions are severe, a multiple organ transplant may be considered, and our patient number 31 is an example. But it appears in this particular case that the liver transplantation did not protect the pulmonary transplant.

Multilobular cirrhosis in cystic fibrosis is a life threatening complication. However, current medical and surgical means are available, allowing today a comfortable life and a prolonged and reasonable life expectancy for these patients. New developments are pending.

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