DECOMPENSATED CRYPTOGENIC AND ALCOHOLIC CIRRHOSIS IN SINGAPORE

A CLINICAL STUDY OF 100 PATIENTS

By Cheng Siang, Seah, M.D., M.R.C.P. (Ed.)
(Consultant Physician)
and
Chong Hai, Tay, M.B., B.S., M.R.C.P. (G.)
(Senior Registrar)
(Medical Unit, Thomson Road Hospital, Singapore.)

This paper describes the experiences encountered in the management of 100 consecutive patients suffering from cirrhosis of the liver, during a four year period (from 1961 through to end of 1964) from a medical unit of 180 beds (108 males, 72 females) at the Thomson Road General Hospital, Singapore. Excluded were cirrhosis from Wilson's disease, schistosomiasis, and biliary cirrhosis; also a few others where the clinical findings and laboratory results were inconclusive or patients labelled cirrhosis who died too soon for investigations to be done.

All the patients were poor with an average income below $300 (Malaysian) per mensem, with large families and with occupations involving unskilled labour. Except for a few, all were not educated. The majority were taxi drivers, trishaw-riders, hawkers, labourers in the City Council and Government Services, and some were unemployed. A number of them were already receiving aid from the Social Welfare Department prior to admission.

The report and discussion will be mainly of the clinicopathological features of the group as a whole but where pertinent an attempt will be made to compare the cryptogenic to the alcoholic group of cirrhosis. The latter was considered useful because patients of both groups, except for alcoholism, possessed similar social characteristics and shared common environmental conditions.

RACE, SEX AND AGE

All the patients were Asians, 73 of whom were Chinese (49 were immigrants), 20 Indians (14 from India) and 7 were Malays. 85 of the 100 patients were males, 3 of them below 20 years in age, 10 in the thirties, 36 in the forties, 24 in the fifties and the last 11 over 60 years old. Among the 15 females, 5 were over forty in years, 7 over fifty and 3 over sixty. (See Fig. 1)

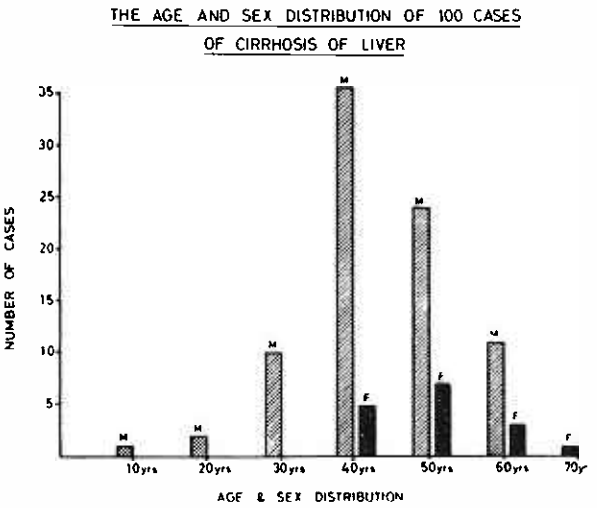

Fig. 1

DIAGNOSIS

Entry into this study was made only when the clinical diagnosis was obvious and there were the classical symptoms and signs of cirrhosis. In the less florid instances, there were biochemical and/or histological features for a firm diagnosis to be made. Histological confirmation was available in 24 successful needle biopsies (in same number of patients); in 8 others biopsies were obtained at operation (6 for laparotomies and 2 for "shunt" procedures), and in another 8 who died, autopsies were done.

Alcoholism was found to involve 53 patients, only 2 of whom were women. This was labelled only after careful interviews with the patient and relatives. The Almoner of the Unit helped also in these investigations. It might be asked, in view of the poor pecuniary circumstances, how could these patients afford to have their

drinks. The answer lay in the availability of cheap local wines easily obtainable in the small shops dotted in the city. 40 of the 53 alcoholics had been imbibing regularly from at least 15 years to over 30 years.

PRESENTING COMPLAINTS

These, shown in Table 1, were the common symptoms of cirrhosis of the liver.

TABLE I

THE PRESENTING COMPLAINTS

1.	Abdominal swelling	41
2.	Oedema legs	37
3.	Abdominal pains	22
4.	Infections	22
5.	Jaundice or dark urine	14
6.	Loose stools and or vomiting	12
7.	Vomiting blood or melaena	8
8.	Mental change	7
9.	Loss of weight	6
10.	Inability to walk	5
11.	Bleeding gums	3
12.	Shortness of breath	3

Of interest are abdominal swelling and oedema of the legs. These symptoms and their incidences were under rated by the patients. Thus ascites was obviously present in more than 50 patients although only 41 complained of it and tibial oedema was found in 70 patients but only 37 noted its presence. An increased pigmented hue of the extremities was detectable in 40 instances but this was "missed" by the patients none of whom complained of a darkening of skin colour.

Abdominal pain was severe enough and together with abdominal distension caused 3 patients to be subjected to emergency laparotomy. one of whom was found to be suffering from a chronic duodenal ulcer as well.

Inability to walk was found to be due to peripheral neuropathy in 2 alcoholics. In the other 3 a generalised muscle wasting was the cause. One wondered on the possibility of a "cirrhotic myopathy" but muscle biopsy in 2 of them revealed no unusual histological changes.

The subject of gastrointestinal haemorrhage and hepatic coma will be dealt with later.

THE PERIPHERAL SIGNS

The most frequently seen were oedema, jaundice and pallor, as can be seen in Table II. Anaemia will be discussed later. Overt haemorrhage was only responsible for a small proportion of the anaemic patients.

TABLE II

1.	Oedema legs	70
2.	Jaundice	61
3.	Pallor	55
4.	Naevi	48
5.	Pigmentation	40
6.	Liver palms	36
7.	Digital clubbing	17
8.	Ecchymosis or purpura	14

There were no significant differences in incidence among these signs between the cryptogenic and alcoholic patients with the exception of naevi. These were, however, more prominent and in numbers, in some of the alcoholic patients.

ASCITES AND HEPATOSPLENOMEGALY

There were 56 patients with ascites.

Ascites was found more frequently in the cryptogenic (64%), than in the alcoholic patient (49%) with cirrhosis. This finding is different to that of Baggenstoss and Stauffer (1952). Gross ascites with abdominal wall oedema occurred in 12 cryptogenic cirrhotic patients but was present in only 1 of the alcoholics.

That the liver in the alcoholic is more often than not large rather than shrunken was borne out also by this study. In 40 (75%) of the 53 alcoholic patients, the liver could be easily felt, 7 of them being definitely nodular. These nodular livers were thought to be malignant at first but follow-up examinations did not confirm this. That nodular hyperplasia is not the sole property of posthepatitic cirrhosis is now increasingly recognised (Rubin et al 1962). Among the 47 patients with cryptogenic cirrhosis 25 (52%) enlarged livers were felt, only 2 of which were with palpable nodules.

Splenomegaly, on the other hand, was definitely more indicative of cryptogenic rather than alcoholic cirrhosis. Thus it was found in 47% of the former compared to a 17% incidence in the latter. This is in keeping with the findings of Summerskill et al (1960).

HEPATIC COMA

This had to be energetically dealt with on 52 occasions during the 4 years of this study. Recovery from this was achieved in 23 instances. The alcoholics were more prone to this dreaded complication (33 out of 52 episodes). This had been the experience of Summerskill et al (1960).

The precipitating causes were difficult to pin-point and were no doubt multifactorial in some cases *e.g.* infection, hypokalaemia, dehydration. However, a massive upper gastrointestinal haemorrhage was definitely the cause in nine of the fatal outcomes. (See Fig. 2.)

UPPER GASTROINTESTINAL HAEMORRHAGE

Haemetemesis and or melaena was encountered 47 times, including the above mentioned nine occasions preceding hepatic coma. The incidence of haemorrhage, in this study, was found to be higher among the alcoholics (37%—in 20 of the 53 patients) compared to the other group (12%—6 out of 47 patients).

This increased incidence of upper gastrointestinal haemorrhage among alcoholics is compatible with the observations of Baggenstoss and Stauffer (1952) but in contradistinction to that of Summerskill et al (1960).

LABORATORY FINDINGS

Haematological results

Anaemia (less than 12 Gms% Haldane) was by far the commonest finding in this series and was recorded in 69 patients, 26 only of whom could be accounted for by overt haemorrhage. In 18 others, a low serum iron (< 100 micro gm%) was found. In one patient a definite haemolytic anaemia with a positive Coomb's test (direct) was detected. This association is the subject of a paper by Zieve, (1958). Increased haemolysis was responsible for two others with anaemia, one with Thalassaemia—E disease and in the other a G6PD deficiency.

Anaemia was not associated with a megaloblastic erythropoiesis in any case.

Leucocytosis was more often met with in the alcoholic, only one of whom was definitely leucopenic. Pancytopenia, probably from "hypersplenism", occurred in 8 patients with cryptogenic cirrhosis but none of the alcoholics showed this feature.

Serum albumin and gammaglobulin

Relatively severe hypoalbuminaemia was the feature in these patients. Serum electrophoresis from 81 patients was carried out, (normal range: serum albumin 4.6 to 6.6 Gm% and gammaglobulin 0.5 to 1.4 Gm%). 49 patients had levels of serum albumin below 3 Gm%. Among them 7 patients were severely affected, with an albumin content of below 2 Gm%.

The gammaglobulin was raised to more than 2 Gm% in 45 patients and in 8 others there was no separation of the beta and gamma fractions of globulin. No significant differences could be detected in comparison between the alcoholic and cryptogenic cirrhotic patients.

HEPATIC COMA AND GASTROINTESTINAL HAEMORRHAGE

INCIDENCES IN CIRRHOSIS

	EPISODES WITH RECOVERY		EPISODES ENDING FATALLY	
	ALCOHOLIC	CRYPTOGENIC	ALCOHOLIC	CRYPTOGENIC
Hepatic coma	8	6	11	9
Hepatic coma precipitated by gastrointestinal haemorrhage	7	2	7	2
Gastrointestinal haemorrhage	19	14	3	2

Fig. 2

Serum transaminases

The serum glutamic-oxaloacetic (S.G.O.T.) and glutamic-pyruvic transaminase (S.G.P.T.) were studied in 45 patients. The S.G.O.T. was raised to twice the normal (120 King units) in 38 patients and the S.G.P.T. (normal 110 King units) similarly elevated in 21 instances. In two patients who subsequently developed hepatocellular carcinoma, serial readings, in a matter of two weeks, showed a threefold rise of the S.G.O.T. This was significant.

MANAGEMENT

With so many variables, no attempt was made in this study to evaluate the different therapeutic agents which may be of use in the treatment of cirrhosis. Whenever not contraindicated the patient was given a generous hospital diet; similarly prednisolone was administered to 13 patients and testosterone by injection to 11 others. Vitamin supplements were given to the majority of the group and abstinence advised to the alcoholics. This was not always heeded.

Diuretic agents were used with care. In refractory patients, aldactone was made available—to 17 patients. Chemotherapy was also used whenever indicated, *e.g.* in infections and impending or during hepatic failure.

FOLLOW-UP, READMISSIONS AND SURVIVORS

After discharge from hospital every patient was asked to report regularly for further management, as an outpatient in the follow-up Clinic of the Unit. Readmissions were made whenever indicated. Thus there were a total of 120 readmissions for the whole series, during the four year period.

14 of the 100 patients defaulted after a follow-up period of more than 3 months but less than a year's duration.

42 deaths were recorded.

Among the 44 survivors, who are still under treatment 22 have lived for more than a year since the first admission, six among whom are in their fourth year of follow-up.

CAUSES OF DEATH

Of the 42 deaths (22 alcoholics), 16 occurred during the first admission to hospital and 3 were taken home to die (confirmed) when they were critically ill, according to Chinese rites, to be near all the relatives at the hour of demise. The rest of the 23 patients survived for varying periods and died in hospital after readmission for a complication (see Fig. 3). 11 of these patients had survived for more than a year and up to four years.

MORTALITY RATE OF CRYPTOGENIC AND ALCOHOLIC CIRRHOSIS

42 deaths in 100 patients in 4 years study.

22 alcoholic
20 cryptogenic

Period of survival from date of first admission.

	MONTHS								
	<3	6	12	18	24	30	36	42	48
ALCOHOLIC	8	7	1	2	1	2	0	0	1
CRYPTOGENIC	11	5	2	0	0	1	1	0	0

Fig. 3

The immediate causes of death are summarised in Table III.

TABLE III

1. Liver failure (hepatic coma)	20*
2. Liver failure preceded by gastrointestinal haemorrhage	9
3. Massive gastrointestinal haemorrhage	5
4. Terminal cirrhosis (wasting, ascites etc.)	4
5. Generalised haemorrhagic phenomena	2
6. Heart failure	2
Total	42

(* including 2 cases developing hepatocellular carcinoma)

Consent for autopsy was obtained in 8 cases. There were some interesting findings arising from these autopsies. The cirrhosis was of the portal type (Laennec's) in 5 patients and the remaining three were of the coarse nodular (postnecrotic) type, one of whom was a chronic alcoholic. (The pathogenesis of this variety in alcoholics is discussed by Popper et al 1960 and Rubin et al in 1962). This liver had, in addition, malignant nodules of hepatocellular carcinoma.

One patient was found to have haemorrhagic effusions in the pleural, pericardial and abdominal cavities. In another who died quite suddenly of abdominal pain there was seen a grossly haemorrhagic bladder mucosa, and with ecchymoses over the mesentery and mesocolon.

Histological examination of the kidneys revealed pyelonephritis in two patients and in two others there were changes similar to the "cirrhotic glomerulosclerosis" described by Bloodworth and Sommers (1959).

ASSOCIATED DISORDERS

Malignant change

Subsequently, during follow-up, two of the hundred patients developed hepatomas which contributed to their deaths.

Diabetes mellitus and haemochromatosis

Diabetes mellitus, unrelated to the primary disorder of cirrhosis, was met with in two patients but a fully developed clinical picture of haemochromatosis occurred in three others. In all these three patients histological confirmation was obtained—one at autopsy and the other two by needle biopsy.

Desferrioxamine was administered to two of the patients with haemochromatosis but death intervened too soon for an assessment to be made.

Renal disease

Chronic pyelonephritis was demonstrated in 4 patients, and a haemorrhagic cystitis in two others at autopsy.

Recurrent microscopic haematuria and albuminuria was a feature in 11 patients, 2 of whom had small renal calculi. However, the cause was obscure in the others. Glomerulonephritis complicating cirrhosis has been reported on by Patek et al (1951), and a "cirrhotic" glomerular sclerosis by Bloodworth and Sommers (1959).

Duodenal ulcer

This was demonstrated radiologically in 4 patients, and seen at operation in a fifth one. The presence of this can cause real difficulty in the management of a brisk upper gastrointestinal bleed in a cirrhotic.

Congestive heart failure

This was the cause of death in two patients. Of interest was the absence of ischaemic patterns in the E.C.G. The aetiology was obscure.

Active pulmonary tuberculosis

Pulmonary tuberculosis complicating cirrhosis was of a high incidence in this series, 12 of whom had an active infection requiring immediate treatment. 13 others had apical infiltrations seen in the X-ray films of the chest which were ajudged inactive after investigations.

DISCUSSION ON MORTALITY

The chief characteristic of this series was severe decompensated hepatic cirrhosis.

There were the clinical features of failure of hepatocellular function with 70% having oedema, 61% with jaundice and more than 50% with ascites, on presentation. Anaemia, hypoalbuminaemia (Sherlock, 1963) and a poor nutritional status made prognosis worse. Thus 19 of the 42 deaths occurred within three months of hospitalisation, failing to respond to treatment. It may be significant to point out here that MacDonald and Mallory (1958), found that in two-thirds of (postnecrotic) cirrhotic patients, death ensued in two months, after decompensation.

Wells (1960) published a report on the use of prednisolone and testosterone propionate in cirrhosis, in a trial of nearly 2 years (86 weeks) carried out in another medical unit in Singapore. Of his 80 patients, 30 (37.5%) had died during that period. This is slightly lower than the 42% in this series which, however, were observed for a longer (four year) period. In his group of prednisolone treated patients the mortality rate was reduced to 26%.

SUMMARY

1. Described above are some of the observations encountered in the management of 100 patients suffering from decompensated cirrhosis of the liver (40 with histological confirmation).
2. All the patients were of poor social circumstances, 53 of them being chronic alcoholics.
3. Gastrointestinal haemorrhage, complicating this disorder, occurred more often in the alcoholic than in the cryptogenic group, in

contradistinction to the experience of the West.

4. During the 4 years of study, 42 died (with an average survival period of 8-7 month), 19 at the first hospitalisation and 23 others subsequently after readmission for a complication. Of these 23, 10 died within six months, 2 within a year and the other 11 survived from one to four years.
5. Of 44 still alive, 22 have lived for more than a year, 6 of whom are in their fourth year of follow-up.
6. The remaining 14 patients have defaulted from attendance.
7. Hepatic coma preceded 20 of the 42 deaths.
8. Hepatic coma was encountered on 53 occasions.
9. Interesting associated disorders are described also.

REFERENCES

1. Bloodworth, J.M.B. and Sommers, S.C. (1959) "Cirrhotic Glomerulosclerosis" a renal lesion associated with hepatic cirrhosis. Lab. Investig., 8, 962-978.
2. Baggenstoss, A.H. and Stauffer, M.H. (1952) Posthepatitic and Alcoholic Cirrhosis: Clinicopathologic study of 43 cases of each. Gastroenterol., 22, 157-180.
3. MacDonald, R.A. and Mallory, G.K. (1958) The Natural History of Postnecrotic Cirrhosis. A study of 221 autopsy cases. Amer. J. of Med., 24, 334-357.
4. Popper H., Rubin, E., Krus, F. and Schaffner, F. (1960) Postnecrotic Cirrhosis in Alcoholics. Gastroenterol., 39, 669-686.
5. Ratnoff, O.D. and Patek, A.J. (1942) Natural History of Laennec's Cirrhosis: Analysis of 386 cases. Medicine, 21, 207-268.
6. Rubin, E., Krus, S. and Popper, H. (1962) Pathogenesis of Postnecrotic Cirrhosis in Alcoholics. Arch. Path., 73, 288-299.
7. Sherlock, S. (1963) Diseases of the Liver and Biliary System p.338 3rd Ed., Blackwell Scientific Publications, Oxford.
8. Summerskill, W.H.J., Davidson, C.S., Dible, H.D., Mallory, G.K., Sherlock, S., Turner, M.D. and Wolfe, S.J. (1960) Cirrhosis of the Liver, a study of alcoholic and Non-alcoholic Patients in Boston and London. New Eng. J. Med., 262, 1-9.
9. Wells, R. (1960) Prednisolone and Testosterone propionate in Cirrhosis of the Liver—A controlled trial. Lancet, ii. 1416-1419.
10. Zieve, L. (1958) Jaundice, Hyperlipemia and Haemolytic Anemia: A heretofore unrecognised syndrome associated with alcoholic fatty liver and Cirrhosis. Ann. Int. Med., 48, 471-496.