LATENT CIRRHOSIS IN SINGAPORE
A MORPHOLOGICAL AND AETIOLOGICAL STUDY

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SYNOPSIS

This is an analysis of 29 cases (21.5%) of latent and 106 cases of symptomatic hepatic cirrhosis from a total of 2098 consecutive autopsies. The relative proportion of latent to symptomatic cirrhosis tends to be greater in the older age group, in Chinese than Indians, and in females than males. Among the latent cirrhosis a history of excessive alcohol consumption, micronodular cirrhosis and the presence of alcoholic hyalin in the liver cells are distinctly uncommon. It is concluded that while alcohol plays an important role in the pathogenesis of symptomatic cirrhosis especially among the Indians, it is not an important aetiological factor in the pathogenesis of latent cirrhosis in Singapore. On the other hand, the high orcein positivity rate together with the predominance of macronodular type of cirrhosis and the frequent history of previous surgery or transfusion among the latent cirrhosis suggest that hepatitis B infection plays an important role in its pathogenesis in Singapore. A great majority of latent cirrhosis are early and not severely active. It is suggested that latent cirrhosis may represent the preclinical stage of a recent cirrhosis or a protracted cirrhosis of low activity.

INTRODUCTION

Cirrhosis is a common liver disease in Singapore (Lee Y.S. (a)). Its true incidence however is difficult to establish as a significant proportion are asymptomatic or latent (McCartney 1933). Autopsy offers the only means whereby this aspect of the disease can be investigated. Most of the studies on latent cirrhosis of the liver were done on Western populations (McCartney 1933, Ricketts and Kirsner 1951, Hallen and Norden 1964, Ludwig et al 1970). Singapore is a multi-racial society comprising of Chinese 76%, Indians 7%, Malays 15% and others 2% (Census 1970). Significant differences have been demonstrated in the aetiology and morphology

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of cirrhosis between the Chinese and Indian ethnic groups in Singapore (Lee Y.S. (b)). How much of these differences are seen in latent cirrhosis is unknown. This study is an attempt to examine the autopsy prevalence, age, sex and racial distribution, morphological features and the relative importance of alcohol and hepatitis B infection in the pathogenesis of latent cirrhosis in Singapore.

MATERIAL AND METHOD

A total of 2098 necropsies over a 5½-year period were reviewed. Stillbirths, neonates and cases where liver tissue were not available such as limited necropsies of the skull were excluded. Otherwise the series was consecutive.

The autopsy protocol of all cases and clinical notes of cirrhotic cases were available for analysis. At least one liver slide was available for histological examination. All the slides were stained with haematoxylin and eosin. Cirrhotic livers were also stained with Masson trichrome for fibrous tissue, Wilder's for reticulin, orcein stain (Shikata et al 1974) for hepatitis B antigen and Sudan III and IV for fat whenever unprocessed liver tissue was available. Special stains for alcoholic hyalin (Tock 1969) were also done.

Definition

Cirrhosis: Defined as a chronic liver disease with diffuse fibrosis, nodular parenchymal regeneration and disruption of the lobular architecture. Conditions such as fibrosis without regeneration, or nodular regeneration without fibrosis are excluded.

Portal cirrhosis: Included in this category are all cirrhoses which had variously been described as atrophic, hypertrophic, Laennec's, alcoholic, fatty, nutritional, toxic, postnecrotic, post-collapsed, posthepatic, septal, pigmentary or non-specific except biliary and cardiac cirrhosis.

Latent cirrhosis: This is an asymptomatic portal cirrhosis found incidentally at autopsy and the cause of death is not due to the cirrhotic process.

Micronodular cirrhosis: This is a portal cirrhosis in which more than 50% of the area of the sections is occupied by micronodules i.e. nodules with only one or no portal tract.

Macronodular cirrhosis: This is a portal cirrhosis in which more than 50% of the area of the sections is occupied by macronodules i.e. nodules with two or more portal tracts.

Mixed-nodular cirrhosis: This is a portal cirrhosis in which the area of the sections is equally shared between micronodules and macronodules.

Stage of cirrhosis: This denotes the degree or extent of the cirrhotic process. It is arbitarily divided into early, intermediate and advanced.

Activity of cirrhotic process: This is judged by the amount and extent of inflammatory infiltration, piecemeal necrosis and ductular proliferation. It is arbitarily divided into mild, moderate and severe.

RESULTS

Autopsy prevalence

In 2098 consecutive autopsies, 135 (6.4%) cases of portal cirrhosis were encountered of which 29 (1.4%) cases were latent (Table 1).

Age distribution

The mean age in latent cirrhosis was 57.8 years (range 33-81 years) compared to 50.7 years (range 7-81 years) in symptomatic cases. There was a greater proportion of latent cirrhosis among the older age groups (Table 1).

Table 1. Latent Cirrhosis: Frequency and age distribution

Age (years)	No. autopsies	No. portal cirrhosis	No. latent cirrhosis
30	711	10 (1.4%)	0
30-39	168	11 (6.5%)	2 (1.2%)
40-49	199	31 (15.6%)	4 (2.0%)
50-59	356	40 (11.2%)	8 (2.2%)
60-69	406	31 (7.6%)	10 (2.4%)
70+	244	12 (4.9%)	5 (2.0%)
Unknown	14	0	0
Total	2098	135 (6.4%)	29 (1.4%)

Table 2. Latent Cirrhosis: Race and sex distribution

Race	Male			Female			All Cases		
	No. autopsy	No. latent cirrhosis	No. portal cirrhosis	No. autopsy	No. portal cirrhosis	No. latent cirrhosis	No. autopsy	No. portal cirrhosis	No. latent cirrhosis
Chinese	1149	87 (7.6%)	19 (1.7%)	669	15 (2.2%)	5 (0.7%)	1818	102 (5.6%)	24 (1.3%)
Indian	164	26 (15.9%)	3 (1.8%)	41	5 (12.2%)	2 (4.9%)	205	31 (15.1%)	5 (2.4%)
Others	54	2 (3.7%)	0	21	0	0	75	2 (2.7%)	0
Total	1367	115 (8.4%)	22 (1.6%)	731	20 (2.7%)	7 (1.0%)	2098	135 (6.4%)	29 (1.4%)

Table 3. Latent and Symptomatic Cirrhosis: Distribution by types of cirrhosis

Types of cirrhosis	Latent cirrhosis	Symptomatic cirrhosis
Micronodular	4 (13.8%)	42 (29.6%)
Mixed-nodular	4 (13.8%)	9 (8.5%)
Macronodular	21 (72.4%)	55 (51.9%)
Total	29 (100.0%)	106 (100.0%)

Table 4. Latent and Symptomatic Cirrhosis:

Stage of cirrhosis	Latent cirrhosis	Symptomatic cirrhosis
Early	20 (69.0%)	22 (20.8%)
Intermediate	4 (13.8%)	34 (32.1%)
Advanced	5 (17.2%)	50 (47.2%)
Total	29 (100.0%)	106 (100.0%)

Race and sex distribution

The relative proportion of latent cirrhosis to symptomatic cirrhosis tended to be greater among the Chinese (23.5%) than the Indians (16.1%) and among the females (35.0%) than the males (19.1%). On the other hand, symptomatic cirrhosis among the Indians (12.7%) was significantly more common than the Chinese (4.3%) ($p < 0.001$) and among the males (6.8%) than the females (1.8%) ($p < 0.001$).

Type of cirrhosis

Of the 29 cases of latent cirrhosis, there were 4 (13.8%) micronodular, 4 (13.8%) mixed-nodular and 21 (72.4%) macronodular cirrhosis. Macronodular cirrhosis was significantly more common ($p < 0.05$) and micronodular cirrhosis less common ($p < 0.01$) among the latent cirrhosis than among the symptomatic cirrhosis (Table 3).

Stage of cirrhosis

69.0% of latent cirrhosis was considered "early" compared to only 20.8% of symptomatic cirrhosis ($p < 0.001$). On the other hand, 47.2% of symptomatic cirrhosis was considered "advanced" compared to only 17.2% of latent cirrhosis ($p < 0.005$) (Table 4).

Activity of cirrhotic process

Activity in the great majority of latent cirrhosis was either mild (44.8%) or moderate (48.3%). Only 6.9% had severe activity compared to 53.8% of symptomatic cirrhosis ($p < 0.001$) (Table 5)

History of excessive alcohol consumption

47 (45.2%) out of 104 cases of symptomatic cirrhosis gave a history of excessive alcohol consumption compared to only 1 (3.2%) out of 29 cases of latent cirrhosis ($p < 0.001$) (Table 6).

Table 5. Latent and Symptomatic Cirrhosis: Activity of cirrhotic process

Activity	Latent cirrhosis	Symptomatic cirrhosis
Mild	13 (44.8%)	26 (24.5%)
Moderate	14 (48.3%)	23 (21.7%)
Severe	2 (6.9%)	57 (53.8%)
Total	29 (100.0%)	106 (100.0%)

Table 6. Latent and Symptomatic Cirrhosis: Differences in history and morphology

History and morphology	Latent cirrhosis (29 cases)	Symptomatic cirrhosis (106 cases)	X^2 test
History of alcohol	1 (3.2%)	47 (45.2%)	$p < 0.001$
History of previous surgery/transfusion	6 (19.4%)	5 (4.8%)	$p < 0.01$
Fatty change (>25% of hepatocytes)	5 (16.1%)	28 (26.9%)	N.S.
Alcoholic hyalin	4 (12.9%)	34 (32.7%)	$p < 0.05$
Orcein positivity	15 (51.7%)	44 (41.5%)	N.S.

History of previous surgery/transfusion

6 (19.4%) cases of latent cirrhosis had a history of previous surgery or transfusion while only 5 (4.8%) cases of symptomatic cirrhosis had a positive history ($p < 0.01$).

Alcoholic hyalin and fatty change

While fatty change showed no significant differences in frequency and extent between latent and symptomatic cirrhosis, alcoholic hyalin was distinctly less common in latent cirrhosis ($p < 0.05$).

Orcein positivity

Orcein positivity of the liver cells was common in both latent (51.7%) and symptomatic (41.5%) cirrhosis. There was also no difference in the extent and severity of the involvement.

DISCUSSION

Latent cirrhosis is common in Singapore. It accounts for 21.5% of portal cirrhosis at necropsy. It tends to be more prevalent in the older age groups, in Chinese than Indians and in females than males. The finding of a greater tendency of latent cirrhosis among females is at variance with previous reports (Spain 1945, McCartney 1933, Ludwig 1970).

There are ethnic differences in the morphology and causative factors in the pathogenesis of cirrhosis in Singapore (Lee Y.S. (b)). The cirrhoses among the Indians are predominantly of the micronodular variety often associated with a history of excessive alcohol consumption, fatty change and alcoholic hyalin. Alcohol is considered an important aetiological factor. Majority of these cases are symptomatic. On the other hand, micronodular cirrhosis and alcoholic hyalin are distinctly uncommon among the latent cirrhosis; and a history of excessive alcohol consumption is rarely obtained. It is concluded that while alcohol plays an important role in the pathogenesis of symptomatic cirrhosis especially among the Indians, it is not an important aetiological factor in the pathogenesis of latent cirrhosis in Singapore.

While only about 4% of normal liver at autopsy is orcein-positive (Tan et al 1977), more than 40% of both latent and symptomatic portal cirrhosis are positive. This high orcein positivity rate together with the predominance of macronodular type of cirrhosis and the frequent history of previous surgery or transfusion among the latent cirrhosis suggest that hepatitis B infection plays an important role in its pathogenesis in Singapore.

The degree and extent of the involvement of the liver in cirrhosis depends on the duration and activity of the cirrhotic process. Latency occurs when the liver cell mass is adequate and the anatomical and pathophysiological derrangements insufficient to produce symptoms. This occurs when the cirrhotic process is early and recent. However, the same "early" picture may also be present over a long period of time if the activity of the cirrhotic process is unusually slow. This may occur in individuals whose constitution (genetic or immunological) permits only a weak but prolonged reaction to the causative agent(s) responsible for the cirrhotic process. This is in keeping with observations that the cirrhotic process in latent cirrhosis is often "early" and lacks severe activity. Ludwig et al (1970) suggested that old age might be a factor responsible for the slowing down of the cirrhotic process, as a greater proportion of cirrhosis among the older age groups was latent. A non-specific reactive hepatitis of unknown cause had also been observed among the aged and infirm people (Schaffmer and Popper 1959). McCartney (1933), however, was unable to demonstrate among the latent cirrhosis more advanced degrees of cirrhosis in the older patients and concluded that latent cirrhosis did not tend to progress to the active or clinical form, in which more severe degrees of cirrhosis were often seen. On the other hand, on occasions where liver function tests were done incidentally, mild impairment was demonstrated in some of the cases (Ludwig et al 1970). It appears therefore that functional derrangements do occur in latent cirrhosis and may represent the preclinical stage of the disease.

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