

Recognition of alcoholic liver disease in a district general hospital

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SUMMARY Two-hundred-and-two patients with alcoholic liver disease whose investigations included a liver biopsy were seen in a district general hospital over a seven year period. Thirty-five per cent presented with general gastrointestinal symptoms rather than with overt liver disease or previously recognised excess consumption of alcohol. Recognition of the alcohol problem was assisted by the finding of a raised mean corpuscular volume (MCV) and/or gammaglutamyl transpeptidase (GGTP). The use of these methods of detection is discussed in relation to the rapid rise in alcohol consumption in the United Kingdom, and the high mortality of cirrhosis reported from special centres. Twenty-two per cent of the patients were found to have an established cirrhosis, and there was some evidence that the women were more susceptible to some of the toxic effects of alcohol. Early detection can be enhanced by a high level of suspicion, wider recognition of the significance of a high MCV, and the greater use of GGTP estimations.

Recent studies have emphasised the increased importance of alcohol in the aetiology of liver disease seen in special referral units (Morgan and Sherlock, 1977; Krasner *et al.*, 1977). As the mortality of established cirrhosis is high and alcohol consumption is increasing rapidly (Spring and Buss, 1977) the early recognition and treatment of alcoholic liver disease becomes particularly important in the United Kingdom at this time.

Many patients present to a district general hospital with digestive symptoms not previously recognised as being related to alcohol. In this paper the detection and recognition of alcoholic liver disease in 202 patients seen in a new district general hospital over seven years is described, together with their haematological, biochemical, and histological abnormalities.

Methods

PATIENTS

Northwick Park Hospital is a district general hospital serving a population of approximately 200 000 in, and around, the London borough of Harrow. We have included in the study all patients with alcoholic liver disease for whom liver histology was available, and who presented between 1 January 1971 and 31 December 1977. All patients had clinical or biochemical evidence of liver disease together with a

known or strongly suspected high intake of alcohol, and subsequent investigations showed no other cause of the abnormalities.

All patients were thought to have drunk more than 80 g of alcohol daily for at least one year, and, where sufficiently reliable information was available, they were divided into those drinking more, or less, than 160 g/day.

Liver function tests were performed by standard laboratory methods, and serum gammaglutamyl transpeptidase (GGTP) was measured by the method of Rosalki *et al.* (1970) in 146 patients. Mean corpuscular volume (MCV) was measured by a Coulter Counter Model S set so that the haematocrit excluded trapped plasma (England *et al.*, 1972). Comparative values of MCV were obtained from 2296 people taking part in a prospective study of cardiovascular disease in a working population, and from 80 patients with non-alcoholic liver disease.

The appearances on liver histology were classified according to the following six categories: (1) normal (including four patients with minor non-specific infiltrates of mononuclear cells); (2) fatty change; (3) hepatofibrosis with or without fatty change; (4) alcoholic hepatitis characterised by extensive polymorphonuclear leucocyte infiltration, liver cell necrosis, and sometimes the presence of alcoholic hyaline; (5) cirrhosis; (6) cirrhosis and alcoholic hepatitis. One patient with cholestasis

secondary to chronic alcoholic pancreatitis was excluded together with another with coexisting acute viral hepatitis.

Data were analysed using $2 \times 2 \chi^2$ or t tests, and, as the values for aspartate transaminase (AST) and GGTP showed a log normal distribution, logarithmic conversion was carried out before statistical calculations.

Results

One-hundred-and-forty-four men and 58 women were included giving a sex ratio of 2.5:1. There was no significant difference between the ages at presentation of the men (52.8 years standard deviation 11.2) and the women (54.0 \pm 11.6 years).

ALCOHOL CONSUMPTION

All patients had been drinking more than 80 g/day of alcohol which is equivalent to approximately 4½ pints of beer, two-thirds of a bottle of sherry, or one-third of a bottle of spirits. Over 90% of the patients had been actively drinking up until at least two weeks before admission and most were steady rather than 'spree' drinkers. Of the 168 patients whose consumption was thought to be reliably assessed, 56 of 127 men consumed more than 160 g/day compared with only 11 out of 41 women ($\chi^2 = 3.85$, $P < 0.05$). The mean duration of heavy alcohol consumption was significantly longer for the men (16.5 \pm 9.1 years) than for the women (8.9 \pm 5.6 years, $P < 0.001$). There was also a sex difference in the types of alcoholic beverage consumed. Just over 90% of the women predominantly drank sherry, wine, or spirits rather than beer or cider, while only 60% of the men came into this category.

PRESENTATION

This is shown in Table 1. Only 29% of the patients presented because of known excessive drinking, and 35% had gastrointestinal symptoms not previously recognised as being alcohol related. Proportionately more women than men presented with gastrointestinal complaints such as dyspepsia, nausea, vomiting or diarrhoea but this difference just failed to reach statistical significance ($\chi^2 = 3.34$ $0.1 > P > 0.05$).

MEAN CORPUSCULAR VOLUME

The MCV at presentation is shown in Table 2 together with the results from a large working population and a group of hospital patients with non-alcoholic liver disease. There was a highly significant increase in MCV of both sexes in the alcoholic groups. Also the mean MCV in the women (102.9 fl) was significantly higher than in the men

Table 1 Presentation of 202 patients with alcoholic liver disease

	Men		Women		Total	
	No.	%	No.	%	No.	%
Gastrointestinal	45	31.3	26	44.8	71	35.1
Alcoholism	44	30.6	14	24.1	58	28.7
Overt liver disease	16	11.1	6	10.3	22	10.9
Other	39	27.0	12	20.7	51	25.3
Number	144		58		202	

Table 2 Mean corpuscular volume (MCV)

	Men		Women	
	No.	Mean MCV \pm SD	No.	Mean MCV \pm SD
Working population	1588	86.2 \pm 3.91	708	86.1 \pm 4.39
Non-alcoholic liver disease	38	86.0 \pm 4.30	42	87.2 \pm 3.72
Alcoholic liver disease	140	*97.4 \pm 7.87	58	*102.9 \pm 8.32

*For both men and women the MCV was significantly higher than in normal subjects ($P \ll 0.001$), and MCV in women with alcoholic liver disease was higher than in the men ($P < 0.001$).

(97.4 fl, $P < 0.001$). The rise in MCV seems to be largely due to recent alcohol consumption, as 10 of the patients who had not been drinking for at least one month before admission had a much lower MCV of 88.0 \pm 4.5 fl.

LIVER FUNCTION TESTS

The results for AST and GGTP at presentation are shown in Table 3. GGTP values were more frequently raised than the AST, and the percentage increase above the reference range was much greater for GGTP. There was considerable overlap in the enzyme values found in the various histological groups, and although mean GGTP levels were highest in patients with alcoholic hepatitis this was not statistically significant after logarithmic transformation. The group with normal histology had a significantly lower mean AST and GGTP ($P < 0.001$) than other categories. In women the mean GGTP was higher than in the men (204.4 cf. 138.4 IU/l, $P < 0.05$). This sex difference was not observed with AST. No significant correlation was found between MCV and GGTP for either men ($r = 0.062$) or women ($r = 0.0035$).

LIVER HISTOLOGY

This is shown in Table 4. Twenty-two per cent of the total had an established cirrhosis with or without associated alcoholic hepatitis. Although a larger percentage of the women were cirrhotic (25.8% cf. 20.1%) this failed to reach statistical significance. When the pattern of alcoholic liver damage was

Table 3 Comparison of AST and GGTP values at presentation

	AST	GGTP
	Reference range 0-35 IU/l	Reference range 0-60 IU/l
Number of patients	202	146
% of results abnormal	68.8	87.7
% increase in mean AST and GGTP above upper limit of normal	90	303.3

Table 4 Liver histology in relation to sex and age

Histological category	Men %	Women %	Total %	Age at presentation (%)	
				≤55	>55
				Normal	17.4
Fatty change	38.9	48.3	41.6	49.2	30.5
Hepatofibrosis ± fat	16.0	10.4	14.4	10.8	19.5
Alcoholic hepatitis	7.6	5.2	6.9	7.5	6.1
Cirrhosis	17.3	24.1	19.3	14.2	26.8
Cirrhosis + alcoholic hepatitis	2.8	1.7	2.5	1.6	3.7
Number	144	58	202	120	82

analysed according to age, fatty change was found significantly more frequently in the younger patients ($P < 0.01$), and cirrhosis was more common in the over 55 year old group ($P < 0.02$). In the male patients those with normal histology or fatty change had shorter mean durations of heavy drinking (16.2 and 13 years respectively) compared with a mean duration of 22.1 years in the cirrhotic group (normal, $P < 0.05$; fatty change, $P < 0.001$). Alcoholic hepatitis was found in only 9.4% of the patients and was not found more frequently in the women.

Discussion

Over the period 1965-75 the amount of wine consumed in the United Kingdom more than doubled, and total alcohol consumption increased by approximately 30% (National Council on Alcoholism, 1976). Recent figures show that the average daily intake for each adult is approaching 20 g/day. Epidemiological studies from France (Pequignot *et al.*, 1974; Pequignot and Tuyns, 1975) suggest that the prevalence of cirrhosis is increased in men who regularly drink more than 60 g/day, and in women after 20 g/day. The mortality of established cirrhosis is high, especially if drinking continues (Brunt *et al.*,

1974; Krasner *et al.*, 1977). Early detection of alcoholic liver disease therefore appears to be crucial to prevent an epidemic of death from alcoholic cirrhosis.

The commonest mode of presentation of patients was with ill-defined gastrointestinal symptoms, and less than one-third were seen because of known excessive alcohol consumption. As only a small percentage of patients with alcoholic liver disease presenting to a district general hospital have overt liver disease (jaundice, ascites, hepatic encephalopathy, or variceal bleeding) we have studied the use of red cell indices and liver enzymes in the detection of patients without overt liver disease.

We have previously shown (Wu *et al.*, 1974) that 85% of a group of patients regularly drinking more than 80 g/day of alcohol had a rise in mean corpuscular volume as measured by a Coulter Counter. This macrocytosis of alcoholism is often unrelated to folate deficiency and appears to be due to a direct toxic effect on the developing erythroblast (Wu *et al.*, 1975). The present study confirms that MCV is significantly raised in patients who are ultimately found to be drinking more than 80 g/day, and the macrocytosis was more marked than in patients with non-alcoholic liver disease. Other causes of macrocytosis, such as B₁₂ deficiency or thyroid disease, were excluded by appropriate tests. The rise in MCV appears to be primarily related to a high alcohol intake as patients who were not actively drinking showed a much lower MCV. We have also observed that MCV falls towards normal levels after alcohol withdrawal even in cirrhotic patients, and can be used as an indicator of continued abstinence or of heavy drinking. The explanation of the significantly higher MCV in the female alcoholics is not clear from this analysis, but it suggests that women may be more susceptible to the macrocytosis of alcoholism.

Our findings confirm previous work (Zein and Discombe, 1970; Rosalki and Rau, 1972; Dragosits *et al.*, 1976) which has shown that GGTP is a more sensitive indicator of alcohol induced liver injury than AST; in this study it was found to be abnormal in 88% of patients. Although there is some relationship between GGTP and the extent of liver cell necrosis (Wu *et al.*, 1976), and the values were higher in these series for patients with alcoholic hepatitis, there was considerable overlap between the various histological groups. GGTP seems to be most useful for detection of alcohol related liver damage rather than estimation of liver cell necrosis, although in an individual the degree of damage and the presence of cirrhosis cannot be predicted from the level.

The pattern of histological liver damage showed marked differences from that recently reported by

special referral centres. Both Morgan and Sherlock (1977) and Krasner *et al.* (1977) reported that 57% and 58% respectively of their patients had cirrhosis with or without alcoholic hepatitis, compared with only 22% in this series. We found alcoholic hepatitis in just under 10% and only one patient was found to have a hepatoma. Unlike Glover *et al.* (1977) we found no patients with 'acute alcoholic cholestasis' in the absence of alcoholic hepatitis, cirrhosis, or extrahepatic obstruction. Our findings are similar to the results of Eghöje and Juhl (1973) who found cirrhosis in 18% of a consecutive series of 347 chronic alcoholics. Like them, we have also shown a clear relationship between the prevalence of cirrhosis and the length of drinking history.

This series also lends some support to the suggestion that women are more susceptible to alcoholic liver disease (Spain, 1945; Wilkinson *et al.*, 1969; Pequignot *et al.*, 1974; Ashley *et al.*, 1977; Krasner *et al.*, 1977; Morgan and Sherlock, 1977). Although the greater prevalence of cirrhosis among female patients did not reach statistical significance, and alcoholic hepatitis was not more frequent, it is interesting that GGTP levels were higher in the women. The women also tended to drink smaller amounts of alcohol and they had a much shorter mean duration of excessive drinking. It has been argued that women might tend to underestimate their consumption to a greater extent than men (Hamlyn, 1977), but some corroboration of alcohol intake was obtained from relatives of the majority of women in the series. Women therefore appear to develop alcoholic liver disease of equivalent or greater severity to men in spite of having consumed smaller quantities of alcohol.

As the pattern of alcohol consumption in a drinking population shows a logarithmic normal distribution (Rankin *et al.*, 1975) the recent increase in per capita consumption in the United Kingdom (Spring and Buss, 1977) is likely to result in a disproportionate rise in the numbers at risk of developing alcoholic liver disease. Our experience suggests that identification of these patients will be aided by a high degree of suspicion (especially in women with undiagnosed gastrointestinal symptoms), investigation of any unexplained macrocytosis, and the greater use of GGTP estimations in the assessment of liver function.

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