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The Relationship between Cognitive Function and Liver Function in Alcoholism

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Summary: Thirty alcoholic patients were investigated for evidence of impaired hepatic function and deficits in cognitive functioning, to see if there was any significant relationship between these two complications of alcoholism. Forty-seven per cent had abnormal γ-glutamyl transpeptidase levels, and 63 per cent had abnormal results on the Category test. Only one significant correlation coefficient was found, between one parameter of hepatic function and one of cognitive function. Possible explanations for this (negative) correlation are discussed, and the value of further study is suggested.

In the 100 years following the first description of alcoholic brain damage (Wernicke, 1881), many studies have been published on the subject. The more recent studies have approached the subject in two separate ways. The first assesses organic brain damage by radiological investigations and the second measures cognitive impairment using various psychometric tests.

Radiological studies have shown that a large percentage of alcoholics show evidence of significant cortical or ventricular atrophy. Brewer and Perrett (1971) reported that 70 per cent of their sample population had evidence of brain damage as determined by air-encephalography. Lee *et al* (1979) studied 37 male alcoholics using computerised axial tomography and found that 49 per cent had evidence of cortical atrophy.

Psychometric studies have used a variety of tests to assess impairment. Brewer and Perrett (1971) used the Benton visual retention test and the Wechsler adult intelligence scale (WAIS). Lee *et al* (1979) used the paired-association test, non-verbal learning and retention, sentence recapitulation, digit scan (forwards and backwards), cipher learning, serial 7's and various subtests of the WAIS. However, the work of Fitzhugh *et al* (1960 and 1965) and Jones and Parsons (1971) suggests that the Category test and the Trail-making test of the Halstead Reitan test battery are more sensitive indicators of alcohol-induced cognitive impairment: these tests measure abstracting ability, spatial scanning and problem-solving by reasoning. Fitzhugh *et al* found that alcoholics scored as badly on these two tests as known brain-damaged subjects, and significantly worse than normal controls. Jones and Parsons replicated these findings and also found that the degree of deficit was positively related to the number of years of drinking, independent of the age of the subject.

The relationship between alcohol and cirrhosis of the liver was first described in 1793 by Mathew Baille. Alcoholic cirrhosis is now considered to represent one end of a continuum of alcohol-related liver disease, with reversible fatty infiltration at the other end. Between these two is the condition known as alcoholic hepatitis, a reversible inflammatory process which can leave some residual fibrosis and may proceed to cirrhosis. The most accurate way of determining the degree of liver damage is to take a biopsy specimen which can be graded in terms of fibrosis and the degree of inflammation and necrosis. However, liver biopsy can have serious complications, especially in people with impaired clotting ability due to liver damage.

Biochemical investigations of the level of hepatic enzymes in the blood have been made to obtain an indication of the degree of liver cell damage. Wu *et al* (1976) found that the serum level of gamma-glutamyl transpeptidase (GGTP) showed some correlation with the degree of histological hepato-cellular necrosis, and Van Waes and Lieber (1977) found five liver enzymes for which there was a tendency for the mean serum level to rise with increasing degrees of liver-cell necrosis, as assessed by liver biopsy. The five enzymes were GGTP, glutamate dehydrogenase (GLDH), serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), and ornithine carbamoyl transferase (OCT). However, when the authors looked at the range of values of the five enzymes for each of the four degrees of liver cell necrosis—(1) absence of necrosis, no parenchymal inflammation (2) occasional cell drop-out with inflammation (3) scattered foci of necrotic cells (4) diffuse parenchymal necrosis— only GLDH showed minimal overlap.

Another study by Kyösola and Salorinne (1975),

showed no correlation between laboratory biochemical tests and the degree of fatty infiltration. However, the authors did not include GGTP and GLDH in their battery of biochemical tests. Lee *et al* (1979) looked at possible correlations between intellectual impairment, cerebral atrophy and liver damage in a group of 37 alcoholic males and found that 59 per cent were intellectually impaired, 49 per cent had cerebral atrophy on CAT scan, and only 19 per cent had cirrhosis as determined by liver biopsy. There was no significant correlation between the degree of liver damage and the degree of intellectual impairment ($P > 0.05$), nor between the degree intellectual impairment and the presence of cerebral atrophy. However, the tests used to determine intellectual impairment (these are listed above) did not include the two tests which are thought to be sensitive to the long-term effects of excessive alcohol ingestion, i.e. the Category test and the Trail-making test.

The present study was designed to investigate any possible relationship between cognitive impairment, as measured by the Category test and the Trail-making test, and impaired liver function as assessed by serum enzyme concentrations.

Method

The study was conducted at the Regional Alcohol Treatment Unit at Scalebor Park Hospital, Burley-in-Wharfedale, West Yorkshire. The population studied consisted of 30 consecutive admissions who satisfied the following criteria:

Age less than 60
Drinking until time of hospital admission
No history of drug abuse
No history of serious head injury
No history of serious medical illness
No previous psychiatric illness
No history of electroconvulsive therapy
No history of fits other than alcohol withdrawal fits

All the subjects gave their verbal consent to be included in the study. Information was collected at interview, from each of the subjects, about their social details and their drinking histories, including the number of years of heavy drinking and their average recent consumption.

During the first five days of their admission the subjects were given a short course of drug treatment to minimize withdrawal symptoms where this was thought to be clinically indicated. After three weeks in hospital the subjects had a fasting specimen of venous blood taken to determine the levels of the following liver enzymes:

alkaline phosphatase AP
gamma-glutamyl transpeptidase GGTP
glutamate dehydrogenase GLDH
aspartate transaminase AST (previously called serum glutamate oxalacetate transaminase—SGOT)
alanine transaminase ALT (previously called serum glutamate pyruvate transaminase—SGPT)

The cognitive function of the subjects was also assessed three weeks after admission. A composite IQ score was determined using Raven's progressive matrices and the Mill Hill vocabulary scale. The subjects were then administered the Trail-making test (TMT) and the Category test.

The TMT has two parts, A and B. Part A consists of a sheet of A4 paper with 25 numbered circles printed on it. The subject is required to join the numbers in ascending order, and the score for the test is the time taken to complete it correctly. Part B is similar to Part A, but has 13 numbers and 12 letters on it. The subject has to join these up in a predetermined way (1—A—2—B—3—C—4— etc.): the score is the time taken to complete it correctly.

The Category test consists of a box which projects a series of visual stimuli from a projector onto a screen in front of the subject. The person being tested is instructed to look at the screen and to press a numbered button which corresponds to the number that figure reminds him of. The subject receives instant auditory feedback on his answer—a bell for a correct answer and a buzzer for an incorrect answer. There are 208 slides arranged into seven sub-tests. Each sub-test has its own 'concept' which produces the correct answer. The present study used a shortened version of the Category test which has only 120 of the stimuli. This shortened version was described by Gregory *et al* (1979): it is as accurate as the longer form, but cuts administration time by 50 per cent.

Results

Fourteen variables were obtained for each of the 30 subjects:

1. Age
2. Number of years of heavy drinking
3. Daily consumption
4. GGTP level
5. GLDH level
6. AST level
7. ALT level
8. AP level
9. Category test score
10. TMT Part A score
11. TMT Part B score
12. Raven's progressive matrices score
13. Mill Hill vocabulary score
14. Composite IQ score

TABLE

The main significant correlations found in a comparison of 14 variables, for the whole group of 30 alcoholics and for various sub-groups

	Correlation *r*	Significance P
Whole group (n = 30)		
Age—Years drinking	0.415	<0.05
Age—Amount consumed	−0.440	<0.02
AST—ALT	0.704	<0.001
AST—AP	0.400	<0.05
TMT (A)—TMT (B)	0.569	<0.01
GGTP—Category score	−0.379	<0.05
Males (n = 20)		
Years drinking —Category score	0.452	<0.05
GGTP—Category score	−0.386	n.s.
Years drinking—GGTP	−0.283	n.s.
Less than ten year's drinking (n = 13)		
GGTP—Category score	−0.601	<0.05
Ten year's or more drinking (n = 17)		
GGTP—Category score	−0.280	n.s.

ALT Alanine transaminase
AP Alkaline phosphatase
AST Aspartate transaminase
GGTP Gamma-glutamyl transpeptidase
TMT (A) Trail-making test Part A
TMT (B) Trail-making test Part B

Each variable was compared with all of the other variables and the Pearson product moment correlation coefficient was determined.

The 30 subjects (20 males and 10 females) had a mean age of 38.3. The mean duration of heavy drinking was 13.3 years. The mean daily consumption prior to admission was 320 grams of alcohol per day—equivalent to just over a bottle of spirits per day. The mean IQ was 105.1

The Table shows the main significant correlation coefficients obtained. For the total group (N = 30) there was a significant negative correlation between age and average consumption (P <0.02). This suggests that the older an alcoholic is, the lower his estimated consumption: this may correspond to the clinical phenomenon of decreased tolerance in the latter stages of alcoholism.

There were also expected significant correlations between the different parts of the TMT (r = 0.569, P <0.01), between AST and ALT (r = 0.704, P <0.001) and between AP and AST (r = 0.400, P <0.05). There was, however, no significant correlations between GLDH and GGTP. The only significant correlation between a measure of liver function and a measure of cognitive function was between GGTP and the score on the Category test (r = −0.379, P <0.05). This negative correlation suggests a tendency for subjects who show *elevated* GGTP levels to have *normal* scores on the Category test, and for those subjects with evidence of cognitive deficit on the Category test to have normal GGTP levels.

The sub-group of 20 male subjects showed a significant correlation between the number of years of heavy drinking and the score on the Category test (r = 0.452, P <0.05), i.e. males who had been drinking heavily for a long time tended to show greater impairment on the test of abstracting ability. This finding replicates that of Jones and Parsons (1971). The correlation between GGTP and Category test was not significant in the male sub-group: thus the males who had a prolonged history of heavy drinking revealed some impairment of cognitive functioning, but not necessarily liver function deficit as assessed by GGTP.

The sub-group of subjects with a history of heavy drinking of less than ten years (n = 13) again showed negative correlations between GGTP and Category test score (r = −0.601, P <0.05). The sub-group with a history of heavy drinking of *greater* than ten years (n = 17) showed no significant relationships between parameters of liver function and cognitive function.

Of the 30 subjects, 14 had abnormal GGTP scores (10 men, 4 women) and 19 (11 men, 8 women) had abnormal Category test scores.

Discussion

The literature suggests that the two liver enzymes, γ-glutamyl transpeptidase (GGTP) and glutamate dehydrogenase (GLDH), are the most sensitive determinants of alcoholic liver damage available from the investigation of a patient's blood. The present study failed to show any significant correlation between these two enzymes, either for the total group or for any of the sub-groups.

There are also many references in the literature to the use of the Category test and the Trail-making test in measuring cognitive deficits in the alcoholic. These two tests measure different aspects of cerebral function: one is a test of abstracting ability and concept formation and the other tests the speed of spatial scanning. This difference helps to explain the lack of any significant correlation between the results of the two tests in the present study.

The *only* significant relationship found between a measure of liver function and a measure of cognitive function was the negative correlation between GGTP and the Category test. This inverse relationship

suggests that people with evidence of cognitive deficits (high Category score) tend to have normal liver function (low GGTP) and *vice versa*. One explanation for this negative correlation may be that the tests used for liver function are reflecting enzyme induction in the liver-cells in the early stages of alcoholism. This enzyme induction increases the liver's ability to metabolise alcohol and may therefore protect the individual from its neurotoxic effects. In the later stages of the drinker's history, the liver may undergo permanent damage and lose its ability to metabolise large amounts of alcohol (loss of tolerance). At this stage, alcoholic brain damage may begin to develop and the permanently damaged liver may then fail to show evidence of enzyme induction.

Another interpretation of the results is that they support a theory of organ specificity which postulates that one type of organ tissue is more susceptible to the toxic effects of alcohol than other types of tissue: thus, a particular type of alcoholic beverage, or a particular pattern of drinking, may affect a particular individual in one way rather than the other. Some form of genetic predisposition may operate in the individual to make him or her prone to the neurotoxic effects of alcohol rather than the hepatotoxic effects, or *vice versa*.

Lee *et al* (1979) found no relationship between the degree of liver damage and brain damage in their group of 37 male alcoholics. The present study found a negative relationship between just two parameters for the 30 subjects tested, and also for the sub-groups of 13 with a history of less than ten years' heavy drinking. However, this relationship did not hold for the other sub-groups of 'males', 'females' and 'those with a history of heavy drinking of more than 10 years'.

The possibility of there being an inverse relationship between liver function and cognitive function warrants further investigation, possibly using the Category test and liver biopsy. Such an inverstigation could be used to help identify the factors which put an individual at risk of acquiring these serious and irreversible complications of heavy drinking. A profile of the 'at-risk' drinker could prove useful in the future management of alcoholism, which is likely to concentrate on prophylaxis by education of the public, rather than on the treatment of established problem drinkers.

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References

BREWER, C. & PERRETT, L. (1971) Brain damage due to alcohol consumption: an air-encephalographic, psychometric and electro-encephalographic study. *British Journal of Addiction*, **66**, 170–82.

FITZHUGH, K. B., FITZHUGH, L. C. & REITAN, R. M. (1960) Adaptive abilities and intellectual functioning in hospitalised alcoholics. *Quarterly Journal of Studies on Alcoholism*, **21**, 414–23.

—— —— —— (1965) Adaptive abilities and intellectual functioning of hospitalised alcoholics—further considerations. *Quarterly Journal of Studies on Alcoholism*, **26**, 402–11.

GREGORY, R. J., PAUL, J. & MORRISON, M. W. (1979) A short form of the Category Test for adults. *Journal of Clinical Psychology*, **35 (4)**, 795–8.

JONES, B. & PARSONS, O. A. (1971) Impaired abstracting ability in chronic alcoholics. *Archives of General Psychiatry*, **24**, 71–5.

KYÖSOLA, K. & SALORINNE, Y. (1975) Liver biopsy and liver function tests in 28 consecutive long-term alcoholics. *Annals of Clinical Research*, **7**, 80–4.

LEE, K., MØLLER, L., HARDT, F., HAUBEK, A. & JENSEN, E. (1979) Alcohol-induced brain damage and liver damage in young males. *Lancet*, **12**, 759–61.

VAN WAES, L. & LIEBER, C. S. (1977) Glutamate dehydrogenase: a reliable marker of liver cell necrosis in the alcoholic. *British Medical Journal*, **ii**, 1508–10.

WERNICKE, C. (1881) *Lehrbuch Gehirnkrankh*, **2**, 229–42.

WU, A., SLAVIN, G. & LEVI, A. J. (1976) Elevated serum gamma glutamyl transferase (tranpeptidase) and histological liver damage in alcoholism. *American Journal of Gastroenterology*, **65**, 318–23.

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