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Brain Damage in Alcoholics without Neuropsychological Impairment. A Population Study

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ABSTRACT

Computed tomography (CT) of the brain and neuropsychological assessment was performed in a random sample of 195 men to investigate the relationship between drinking of alcohol and brain damage. This sample from the general population was divided into subsamples on the basis of their self-reported loss of control over drinking, morning drinks and blackouts. The consumption of hepatotoxic drugs was also investigated. For this the material was divided into four groups with regard to both alcohol consumption and use of hepatotoxic drugs: Group IA, low or moderate alcohol consumption and no use of such drugs; IB, low or moderate alcohol consumption with use of such drugs; IIA, high alcohol consumption with no use of such drugs; and IIB, high alcohol consumption with use of such drugs. Group IIB was found to have a higher incidence of cortical and subcortical changes than group IA. Differences in CT variables were observed between the 4 groups IA-IIB, but there were no differences in the results of neuropsychological assessment. Thus, an alcoholic could have progressive cortical and subcortical changes without any neuropsychological impairment at all. Neither the duration of self-reported loss of control over drinking nor the amount of alcohol consumed per drinking occasion were found to be associated with cognitive impairment, but both showed a relationship to cortical and subcortical CT changes.

INTRODUCTION

A connection between alcoholism and cerebral damage as assessed by computed tomography (CT) and neuropsychological tests has been observed in several studies on alcoholic patients (3, 5, 6, 12, 13, 16-18). However, relationships between cerebral changes as assessed by CT, neuropsychological deficits, drinking habits and alcohol-related complications in the general population have seldom been reported.

Some authors have tried to assess the cerebral morphological status among persons without alcohol problems by comparison with various control groups. However, it is clear from the

selection criteria of the groups that they cannot be considered representative of a general population. Fox et al. (13) investigated CT scans from outpatients attending a department of internal medicine for symptoms such as headache, dizziness and nervousness. In a study by Hill (17), an unspecified group of 12 sex-matched subjects served as controls for 30 abusers of either alcohol or opiates. Gyldensted (15) reported results of CT scanning in 100 adults, 54 of whom, however, were inpatients at a neurological department. Elofsson et al. (11) chose a group of industrial workers as controls in their investigation of industrial painters.

Benzodiazepine users, as a group, have been found to have larger ventricle/brain ratios than controls but smaller than those of alcoholics (20). In a 4-6-year follow-up of 50 patients with primary dependence on sedative and hypnotic drugs, 26 patients (52%) were abusing drugs and/or alcohol at the time of follow-up. CT of the brain was performed in 33 of these 50 patients, and in 17 patients there were indications of cortical atrophy, 10 of whom were currently abusing drugs (1). Rumbaugh et al. (25) reported on 6 drug abusers with dilatation of the ventricles and subarachnoid spaces, suggesting that cerebral atrophy can be related to drug abuse. In addition, certain experimental findings in animal models parallel these observations (24).

The purpose of the present interdisciplinary study was to investigate a random sample of men from the general population with regard not only to the incidence and location of morphological cerebral changes but also to the neuropsychological performance in relation to drinking habits and to the use of hepatotoxic drugs in combination with high alcohol intake.

MATERIAL AND METHODS

The study comprised a sample from the general population consisting of men living in the catchment area of the Karolinska Hospital, a geographically limited area of the north of Stockholm (Solna and Sundbyberg) with about 80,000 inhabitants. The sample was drawn randomly from the National Register covering all Swedish inhabitants and was stratified with regard to age. It was intended that a sample of 200 men should be drawn, with 40 in each of the age groups 20-29, 30-39, 40-49, 50-59 and 60-65 years, in order to achieve the same degree of precision for all age groups in the estimation of different variables.

The initial random sample drawn consisted of 209 men aged 20-65 years. Of this sample, two persons had died, five had moved more than 120 miles away from Stockholm, and ten were living permanently abroad at the time of investigation and were thus excluded from the study. Nine persons refused to be examined and two refused to take part in the CT and psychological investigations. Thus, of the initial sample of 209 men, 181 were available for investigation. To increase the sample to 200, a supplementary sample of 19 men was drawn in exactly the same way as before, and all these men were available for investigation. The non-participant group was small and the drop-outs (11%) did not differ from the examined persons with respect to social status,

age, education, civil status, employment status or data from official registers ($p>0.05$). Five men refused to undergo CT examination of the brain, and CT scans and neuropsychological tests for a total of 195 men were therefore available. These 195 subjects were examined and interviewed at the Magnus Huss Clinic of the Karolinska Hospital in Stockholm. Laboratory tests were performed, including liver and pancreatic function tests. In studies of alcohol consumption, the consumption in the last week was recorded, as it was considered that the subjects' recall would be poorer for the period further back in time. In the present study occurrence of 3 symptoms related to heavy drinking was recorded: Inability to cut down or stop drinking, i.e. loss of control ; morning shakes and malaise relieved by drinking, i.e. morning drinks; and alcohol amnesia or memory lapse after drinking of alcohol, i.e. blackouts.

The consumption of hepatotoxic drugs was also investigated and the following were the types of drugs used: antiarrhythmic agents, antiepileptic agents, antibiotics, antiphlogistics, mixed analgesics, sulphonamides, benzodiazepines and derivatives of phenothiazines, all of which are metabolized by way of the liver.

Four subgroups were formed with respect to the use of alcohol consumption and hepatotoxic drugs:

- (IA) low or moderate alcohol consumption and no use of such drugs (n=125);
- (IB) low or moderate alcohol consumption with use of such drugs (n=21);
- (IIA) high alcohol consumption with no use of such drugs (n=39);
- (IIB) high alcohol consumption with use of such drugs (n=10).

Computer tomography

The tomographic images were evaluated with regard to ventricular, cortical and cerebellar changes. An anterior horn index, i.e. Evan´ s ratio, was obtained by dividing the width of the anterior horns by the largest inner skull diameter. Values exceeding 0.31 were considered pathological.
A transverse diameter of the third ventricle exceeding 6 mm was also considered pathological. A four-step scale of degenerative cortical changes was used, based on a general assessment of the tomographs by the radiologist with regard to observations of widened sulci. In this scale, 1 = normal, i.e. no sulci visible or sulci less than 3 mm in natural size, 2 = suspected degenerative changes, i.e. up to 5 sulci exceeding 3 mm in diameter, 3 = clear-cut changes, i.e. more than 5 sulci exceeding 3 mm in diameter and appearing in at least 2 cuts, and 4 = high-grade changes, i.e. marked widening of a large number of sulci in all lobes. The inter-rater reliability of the scale has been found to be 0.81 (11).

Neuropsychological examination

General intelligence was assessed by the SRB battery (10). In order to assess neuropsychological deficits, Halstead Category, Tactual Performance, Trail Making (part A+B), Finger Tapping and Rhythm Test of the Halstead-Reitan neuropsychological test battery were administered (23). In order to assess learning and memory functioning, Memory-for-Designs (14) and a Swedish version of the Schulze 10-word test called the Claeson-Dahl test were given (8). The incidence rates of neuropsychological deficits as assessed by the Halstead-Reitan battery were summarized to form the Halstead Impairment index according to the prorating schedule.

An overall assessment of intellectual impairment was also carried out by the psychologists, using a 3-step rating scale: 1 = no signs of impairment, 2 = slight signs of impairment and 3 = definite signs of impairment. The ratings were not made blindly. The methods used in the impairment rating were: a) evaluation of the level of performance in relation to normative data and to educational and occupational background; b) the differential score approach; c) qualitative deficiences and pathognomonic signs during performance. The inter-rater reliability of the 3-step scale has been found to be 0.72 (2). The premorbid intellectual competence and the age of the subject are taken into consideration in the rating. Both neuropsychological deficits and personality traits were assessed. The neuropsychological test battery satisfied the criteria of well documented validity for diagnosing brain damage and a broad sample of behaviours on different levels of complexity, chosen in order to maximize the potential for diagnosing sensory or motor dysfunction, amnestic syndromes and cognitive impairment.

RESULTS

Groups IA-IIB

Some characteristics of the 4 groups formed according to the alcohol consumption and use of hepatotoxic drugs are presented in Table 1. The 10 heavy drinkers who used drugs had drunk 39 g of alcohol per day in the week before the hospital examination and the 39 heavy drinkers who had not used drugs had drunk 31 g per day. Actions had been taken by the Temperance Board concerning 33% of group IIA and 30% of group IIB. In group IIA 62% were smokers and in group IIB 70%. One man in group IA, 2 (5%) in group IIA and 3 (30%) in group IIB had alcohol in the blood on arrival at the hospital (Table 1).

Table 1. Characteristics of the 4 groups of men with different drinking habits with and without the use of hepatotoxic drugs

	GROUP IA Low alcohol - no drugs (n=125)	GROUP IB Low alcohol - drugs (n=21)	GROUP IIA High alcohol - no drugs (n=39)	GROUP IIB High alcohol - drugs (n=10)
Age (years)	45 ± 14	46 ± 15	41 ± 14	49 ± 5
Alcohol intake previous week in g absolute alcohol/day	8 ± 9	6 ± 11	31 ± 29****	39 ± 29****
Actions on part of the Temperance Board (%)	6	10	33****	30**
Smokers (%)	42	52	62 *	70
Alcohol in blood on arrival at hospital (%)	1	0	5	30****

Degrees of significance tested in comparison with low alcohol - no drugs group by Student's t test and Chi-square test. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

Liver and pancreatic tests

The results of tests of alcohol-related liver and pancreatic disturbances in the subgroups are presented in Table 2. Significantly higher serum levels of GGT, ASAT, ALAT, CK and LD were found in the heavy-drinking group using drugs (IIB) than in the other groups. In group IIA, with a high alcohol consumption and no drug use, only serum ASAT, ALAT and LD were elevated, but these values lay within the reference ranges of the Karolinska Hospital. GGT showed a relationship to alcohol consumption in combination with the use of drugs, but not to alcohol alone.

A study was made of the question as to whether and to what extent drugs combined with alcohol influenced the laboratory findings, by comparison with group IA (low alcohol, no drugs). In the heavy-drinking subjects who used drugs (group IIB), the drugs taken included antiarrhythmic agents (quinidine, verapamil), antiepileptics (phenytoin), antibiotics (doxycycline), dextropropoxyphene, and derivatives of benzodiazepines, all of which can alone cause an increase in the serum levels of GGT, ASAT, ALAT and LD. Seventy per cent of the heavy-drinking group had pathological serum GGT values and 60 per cent pathological serum values of ALAT. The most important of these drugs in this respect are anticoagulants, antiepileptic agents and barbiturates (9,19) (Table 2).

Table 2. Alcohol-related liver and pancreatic disturbances in the four groups as reflected by mean values of serum bilirubin, ALP, GGT, ASAT, ALAT, CK, LD and amylase.

		GROUP IA Low alcohol - no drugs (n=126)	GROUP IB Low alcohol - drugs (n=21)	GROUP IIA High alcohol - no drugs (n=43)	GROUP IIB High alcohol - drugs (n=10)
S-bilirubin	(umol/l)	11 ± 7	9 ± 5	13 ± 6	8 ± 3
S-ALP	(ukat/l)	2.9 ± 0.8	3.3 ± 1.2 *	3.1 ± 1.0	3.2 ± 0.5
GGT	(ukat/l)	0.50 ± 0.43	1.15 ± 1.24 ****	0.57 ± 0.37	1.34 ± 0.93 ****
S-ASAT	(ukat/l)	0.38 ± 0.12	0.37 ± 0.13	0.53 ± 0.61 **	0.60 ± 0.28 ****
S-ALAT	(ukat/l)	0.38 ± 0.27	0.38 ± 0.22	0.54 ± 0.70 *	0.64 ± 0.28 **
S-CK	(ukat/l)	2.2 ± 1.2	1.9 ± 1.1	2.8 ± 2.7	5.2 ± 7.1 *
S-LD	(ukat/l)	5.5 ± 0.9	5.7 ± 0.6	5.9 ± 1.1 **	7.1 ± 3.5 ***
S-amylase	(uktat/l)	3.3 ± 1.8	2.7 ± 0.8	3.3 ± 0.9	2.9 ± 0.9

Significance levels tested in comparison with group IA by Student's t test and Chi-square test.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

Head injury, serious body injury and cerebrovascular disease

Regarding degenerative changes of the brain, one man in this population had cerebrovascular disease. There was no increase in the frequency of head injury with increased alcohol consumption and no differences between the groups concerning serious body injury, see Table 3.

Table 3. Head injury with unconsciousness, serious body injury and cerebrovascular disease in the 4 groups of men with different drinking habits with and without use of hepatotoxic drugs.

	GROUP IA Low alcohol - no drugs (n=125) %	GROUP IB Low alcohol - drugs (n=21) %	GROUP IIA High alcohol - no drugs (n=39) %	GROUP IIB High alcohol - drugs (n=10) %
Head injury with unconsciousness	11	24	23	0
Serious body injury (accident necessitating hospital treatment)	10	24	16	20
Cerebrovascular disease	1	0	0	0

Degrees of significance tested in comparison with low alcohol - no drugs group by Chi-square test.
* $p < 0.05$

CT findings in groups IA-IIB

Cortical changes were found in 40% of group IIB ($p<0.05$ compared with group IA), frontal lobe atrophy in 30% (n.s.) and wide transport sulci in 20% ($p<0.05$); users of hepatotoxic drugs had a higher frequency of cortical changes than non-users (Table 4). In the groups that used drugs, 19-20% had a pathological anterior horn index. The frequency of an enlarged third ventricle varied from 24-40% in the drug-using groups. Wide cerebellar sulci indicating vermian atrophy were not observed in group IIB, but were found in 6% of group IA, and in 5% of each of groups IB and IIA (Table 4).

Table 4. CT variables used in the 4 groups with different drinking habits with and without drug use.

CT Measures	GROUP IA Low alcohol - no drugs (n=125) %	GROUP IB Low alcohol - drugs (n=21) %	GROUP IIA High alcohol - no drugs (n=39) %	GROUP IIB High alcohol - drugs (n=10) %
Cortical				
Wide transport sulci	4	5	5	20*
Cortical changes (subjective rating: clear-cut or high-grade)	14	19	15	40*
Frontal lobe atrophy	13	10	15	30
Subcortical				
Anterior horn index > 0.31	9	19	10	20
Width 3rd ventricle > 6 mm	9	24*	10	40*
Vermian atrophy	6	5	5	0

Degrees of significance tested in comparison with low alcohol - no drugs group by Chi-square test.
* $p < 0.05$

Neuropsychological findings in groups IA-IIB

According to the psychologist´s overall assessment of the test results, there were no definite signs of intellectual impairment in any of the subjects of the age groups 20-39 years. Such signs were observed in 18% of the 60-65-year group. There were no significant differences in intellectual impairment between the 4 groups IA-IIB (Table 5). Only 10-22% of this random sample of men from the general population had "definite signs of intellectual impairment" (Table 5).

Table 5. Neuropsychological impairment in the 4 groups with different drinking habits with and without drug use.

Neuropsychological impairment	GROUP IA Low alcohol - no drugs (n=125) %	GROUP IB Low alcohol - drugs (n=21) %	GROUP IIA High alcohol - no drugs (n=39) %	GROUP IIB High alcohol - drugs (n=10) %
1 = no signs of intellectual impairment	71	60	74	78
2 = slight signs of intellectual impairment	19	20	14	0
3 = definite signs of intellectual impairment	10	20	12	22

Degrees of significance tested in comparison with low alcohol - no drugs group by Chi-square test.
* $p < 0.05$

DISCUSSION

Regarding potential bias, the CT images were assessed by two radiologists independently and the assessments were made blindly, i.e. without the radiologists having any knowledge of the alcohol consumption of the patient in question. The study was performed on a representative sample of the population of Greater Stockholm, and the sample was completely unselected, randomly chosen and age-stratified, and drawn by the National Statistics Office of Sweden.

The subjects knew that they were to undergo a health examination, and even if they may have consumed some alcohol the day before, they had not taken any on the day they came to the hospital. Several of the patients were brought to the hospital by the examining physician (Mützell). None of the subjects were drunk at the time of the tests or had cerebral oedema according to the CT findings. They were throughly assessed concerning the amount of alcohol consumed, indications of alcohol dependence and alcohol-related complications by means of a standardized procedure combining a self-administered questionnaire and a structured interview.

The methods used in assessment of the CT images of the brain and in the neuropsychological examinations are well known and have been well documented for several years (2, 8, 10, 11, 14, 23). At the Magnus Huss Clinic of the Karolinska Hospital, the same methods have been used for these purposes since 1976, both in alcoholics and in healthy control persons, with each subject assessed blindly by two examiners. The reliability has been ≥ 0.81 (11). In consideration of the above, there should be no important sources of bias regarding the population sample, the CT examinations of the brain or the neuropsychological tests. In the latter tests the inter-rater reliability is 0.72 (2).

The drugs used are known to be metabolized by the liver and phenytoin, for instance, may cause viral hepatitis-like reactions (7). The findings in the subjects with combined drug abuse and alcoholism show the clinical importance of alcohol and drug interactions. Many of the central nervous effects of various drugs are potentiated by simultaneous use of alcohol, and the elimination rates of various drugs are influenced both by chronic alcohol consumption and by possible liver damage (21). The adaptive hypertrophy of the hepatic smooth endoplasmic reticulum as a result of chronic alcohol intake is accompanied by an increased content of microsomal cytochrome P450 and of NADPH-cytochrome P450 reductase and these play a key role in the microsomal hydroxylation of various drugs and explain enhanced clearance of drugs. This metabolic adaptation evidently contributes to the tolerance of alcoholics to drugs, including sedatives. The adaptive response is seen only when the alcoholic is sober. Simultaneous alcohol and drug intake (e.g. alcoholic drinks and tranquillizers) results in additive or even in synergistic effects by an additive action on the central nervous system and by the inhibition of drug metabolism (21).

Lader et ál. (20) performed CT scanning in 20 patients who had taken benzodiazepines for a long period. The mean ventricular/brain area as measured by planimetry was larger than the mean value in an age-and-sex-matched group of control subjects, but was smaller than that in a group of alcoholics. There was no significant relationship between the CT findings and the duration of benzodiazepine therapy.

Allgulander et al. (1) studied 50 of 55 patients originally hospitalized for primary sedative-hypnotic dependence 4-6 years after hospital discharge. Twenty-six patients (52%) were abusing drugs and/or alcohol at the time of the follow-up investigaion. CT indicated cerebral cortical atrophy in 17 of 33 patients, 10 of whom were currently abusing drugs. Enlarged lateral ventricles were found in six patients, and an enlarged third ventricle in two patients.

Most sedative-hypnotic abusers also show high rates of primary alcohol problems. Many of the patients in this study (1) developed secondary alcohol abuse, implying that sedative-hypnotic dependence is one factor conducive to abuse of alcohol. Bergman (4) found that among alcoholic patients, cognitive impairment was associated with ventricular dilatation on CT, but not with cortical changes. Conversely, there was no relationship between the morphological and functional cerebral state among the random controls.

The present findings are in accordance with reports in the literature concerning cerebral changes on CT and the effects of a combination of alcohol and drugs, namely that simultaneous alcohol and drug intake has an additive action on the central nervous system. Bergman found that alcoholic patients had poorer results at neuropsychological tests and that these were related to CT changes. In Bergman's study the subjects in the alcoholic group were severely alcoholic, whereas our heavy drinkers from the random sample of the male population of Greater Stockholm were not social outcasts but had a very high alcohol consumption. From the purely CT aspect they

resembled the social outcasts in Bergman's study, and the difference was that they drank smaller quantities of alcohol but used drugs at the same time.

In the present study the greatest cortical and subcortical changes were found in the men of the small group IIB, who both had a relatively high alcohol consumption and used drugs daily, but regarding the neuropsychological findings no differences were noted between the four groups IA-IIB.

From a purely scientific viewpoint this means that even though there may be major changes on CT in some patients, the neuropsychological test results show no differences between different alcohol-consumption groups, and give no indication as to whether the examinee has used alcohol in large amounts for a long time or does not drink at all. Consequently, in practice one cannot rely completely on the present neuropsychological tests, and what we see on the CT image is not reflected in the test result of the person in question. Thus a person may show considerable cerebral damage on CT, but function fairly well in the tests.

The group of randomly sampled persons who used alcohol and at the same time took drugs of the type metabolized in the liver, had poorer cortical and subcortical CT images than those who did not use drugs and were only moderate drinkers. No difference was found in the test results when a summarizing evaluation was made of the subjects to see whether there was any deterioration in neuropsychological function in the former group - those who used alcohol and at the same time used drugs did not differ from those who never consumed alcohol and never used drugs. It is concluded that the results of psychological tests should be interpreted with much reservation and the CT images should be assessed with caution.

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