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High Alcohol Consumption, Liver Toxic Drugs and Brain Damage—a Population Study

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ABSTRACT

Computed tomography (CT) of the brain was performed in a random sample of 195 men to investigate the relationship between alcohol drinking 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. Three groups with different degrees of alcohol consumption were distinguished and the only differences in CT findings were a significantly higher frequency of frontal lobe atrophy with increasing alcohol consumption. The consumption of hepatotoxic drugs was also investigated and the following were the types of drug used: antiarrhythmics, antiepileptics, antibiotics. antiphlogistics, mixed analgetics, sulphonamides, benzodiazepines and derivatives of phenothiazines, all of which are metabolized by way of the liver. 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. The results indicate that drug use influences the incidence of cortical and subcortical aberrations. It is concluded that there is a typical frontal lobe atrophy associated with alcohol abuse; thus with increasing alcohol ingestion there is accelerated shrinkage of the brain, the frontal lobe being the first part affected. The groups with alcohol abuse who used hepatotoxic drugs show a picture of cortical changes and also of subcortical aberrations, expressed as an increased anterior horn index and widening of the third ventricle.

INTRODUCTION

In the last few years, a number of computed tomographic (CT) studies have been conducted in order to examine the nature of structural aberrations in the brains of

alcoholic patients. Fox and collaborators (12) used CT scan to study hospitalized alcoholic patients. They found a significantly increased ventricular size in alcoholic patients. The incidence of cortical atrophy in alcoholic patients as compared with controls has been reported by several workers (3, 16, 26). Carlen et al. (7) reported that all of the alcoholic patients they studied showed evidence of cortical atrophy on CT.

The purpose of the present interdisciplinary study was to investigate a random sample of men from the general population with regard to the incidence and location of morphological changes in the brain and also to examine these factors in relation to alcohol consumption.

MATERIAL

The present sample of 200 men was collected as a reference group for the KARTAD project which is being carried out at the Magnus Huss Clinic of the Karolinska Hospital in Stockholm. "KARTAD", stands for the KARolinska project for research and Treatment of Alcohol Dependence.

From the National Register covering all Swedish inhabitants, a random sample of 228 men was taken from the general male population resident in the urban districts of Solna and Sundbyberg, with altogether 80,000 inhabitants, in the catchment area of the Karolinska Hospital. Forty men in each of the age groups 20-29, 30-39, 40-49, 50-59 and 60-65 years were sampled in order to achieve the same degree of precision for all age groups in the estimation of different variables. The drop-outs (11%) did not differ from the examined persons in respect to social status, age, education, civil status, employment status, or entry in official registers (police, social register, local health insurance office, Temperance Board register)($p>0.05$).

Five men refused to undergo CT examination of the brain, and therefore CT scans for a total of 195 men were available.

The subjects were examined and interviewed at the Magnus Huss Clinic of the Karolinska Hospital in Stockholm. 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 the occurrence of three symptoms related to heavy drinking was recorded:

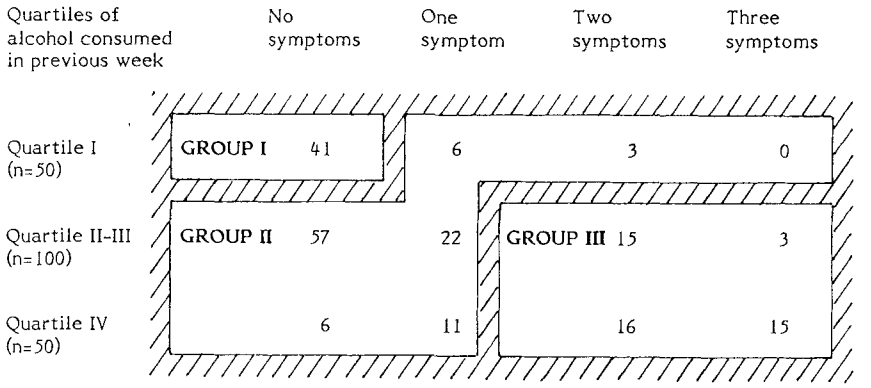
Inability to cut down or stop drinking, i.e. loss of control; morning shakes and malaise relieved by drinking, i.e. morning drinks; and alcohol amnesia or memory lapse after drinking of alcohol, i.e. blackouts. The participants were first divided into three groups:

(I) a group with low alcohol consumption without any of the above symptoms;

(II) an intermediate group with low, moderate or high alcohol consumption and different numbers of such symptoms; and

(III) a heavy-drinking group with high consumption and two or more such symptoms

Table 1. Prevalence of symptoms with different alcohol consumption quartiles. Groups I-III.



GROUP I Low alcohol consumption without alcohol symptoms (n=41)

GROUP II Intermediate group with low, moderate or high alcohol consumption with different numbers of alcohol symptoms (n=105)

GROUPP III Heavy-drinking alcohol group with moderate or high consumption and two or more symptoms (n=49)

The consumption of hepatotoxic drugs was also investigated and the following were the types of drug used: antiarrhythmics, antiepileptics, antibiotics, antiphlogistics, mixed analgetics, sulphonamides, benzodiazepines and derivatives of phenothiazines, all of which are metabolized by way of the liver. Four subgroups were then formed with respect to the use of 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)

Subjects taking antihypertensive drugs (beta-adrenoceptor blocking agents, hydrochlorothiazide, thiazides and hydralazines) were assigned to the groups without any use of drugs. Twelwe of the 125 men in group IA and one of the 39 in group IIA used antihypertensive drugs (23).

METHODS

An EMI Mark I head scanner was used. 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 five sulci exceeding 3 mm in diameter, 3=clear-cut changes, i.e. more than five sulci exceeding 3 mm in diameter and appearing in at least two cuts, and 4=high-grade changes, i.e. marked widening of a large number of sulci in all lobes. The interrater reliability of the four-step scale has been found to be 0.81 (11). For further information about the methods, see also (20-22).

RESULTS

Groups I-III

Actions on the part of the Temperance Board were recorded for 8% in group II and 33% in group III, compared with 2% in group I. Forty-six per cent of group I were smokers and 43% of group II, but 63% of group III. One person in group II and five in group III had alcohol in the blood on arrival at the hospital. The alcohol consumption during the week before examination at the hospital was 33 g of absolute alcohol per day in group III and 11 g in group II. The consumption in group III corresponds to almost a whole bottle of liquor a week.

CT findings in groups I-III

The frequency of cortical changes varied between 7% in group I and 20% in group III (Table 2). The frequency of frontal lobe atrophy was significantly higher in groups II and III (16% and 18% respectively) than in group I. Wide transport sulci were not observed in group I but were noted in 6% of group II and in 8% of group III. In group II 25% had one or more cortical changes and in group III 33%. Regarding the central subcortical parts of the brain, an anterior horn index of above 0.31 was found in 5% of group I and in 12% of both groups II and III. The frequency of an enlarged third ventricle according to the criterion value was 12% in group I, 11% in group II and 16% in group III; thus there was no significant difference between the three groups.

Table 2. CT findings in groups I-III.

CT Measures	GROUP I (n=41) %	GROUP II (n=105) %	GROUP III (n=49) %
Cortical			
Wide transport sulci	0	6	8
Cortical changes (subjective rating: clear-cut or high-grade)	7	17	20
Frontal lobe atrophy	2	16*	18*
One or more of the above	7	25*	33**
Subcortical			
Anterior horn index > 0.31	5	12	12
Width 3rd ventricle > 6 mm	12	11	16
Vermis atrophy	2	7	4

Degrees of significance tested in comparison with group I by Chi-square test.
* $p < 0.05$; ** $p < 0.01$.

Groups IA-IIB

Some characteristics of the four groups classified according to the use of hepatotoxic drugs are presented in Table 3. The ten heavy drinkers who used drugs had drunk 39 g of alcohol per day in the week before the hospital examination and the 39 heavy-drinking and no drug users had drunk 31 g per day. Actions were 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, two (5%) in group IIA and three (30%) in group IIB had alcohol in the blood on arrival at the hospital.

Table 3. Characteristics of the four groups of men with different drinking habits and 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.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

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 those who did not use drugs (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 vermis atrophy were not observed in group IIB, but were found in 6% of group IA, in 5% of group IB and again in 5% of group IIA (Table 4). The drugs used by the groups of heavier drinkers - group IIB - were antiarrhythmic agents, antiepileptics, antibiotics, mixed analgetics and benzodiazepines - and these drugs were combined with intake of alcohol.

Age groups

To find out whether the incidence of cortical and subcortical changes increased with age, the different age groups (20-29, 30-39, 40-49, 50-59 and 60-65) were investigated separately. The results show that the incidence of cortical and subcortical changes had an accelerated increase with advancing age and consequently also with the duration of heavy drinking. In the youngest age groups, 20-49 years, the excess of pathological cases compared with the age group 20-29 years was not statistically significant.

Table 4. CT scan variables used in the four groups with different drinking habits and 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*
Vermis atrophy	6	5	5	0

Degrees of significance tested in comparison with the Low alcohol - no drugs group by Student's t test and Chi-square test.
* $p < 0.05$

Table 5. Age-matched pairs from the group with high alcohol consumption and no drugs (IIA) vs the group with high alcohol consumption and drug use (IIB).

CT measures	GROUP IIA High alcohol - no drugs (n=20) %	GROUP IIB High alcohol - drugs (n=10) %
Cortical		
Wide transport sulci	0	20 *
Cortical changes (subjective rating: clear-cut or high-grade)	10	40
Frontal lobe atrophy	15	30
Subcortical		
Anterior horn index > 0.31	10	20
Width 3rd ventricle > 6 mm	5	40 *
Vermis atrohpy	5	0
Age (years)	49±10	49±5

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

Age-matched pairs

To find out whether age was a confounding variable with respect to the CT measures investigated, age-matched pairs from groups IIA and IIB were studied (see Table 5). Each subject from group IIB was matched with two from group IIA.

The matched groups had the same mean age, 49 years. Among the subjects who used hepatotoxic drugs, 20% had wide transport sulci, compared with none in the group that did not use drugs ($p<0.05$). The corresponding proportions with pathological cortical changes were 40% and 10%, and with frontal lobe atrophy 30% and 15%, respectively.

Concerning subcortical changes, 20% of the high alcohol consumption group with drug use had a pathological anterior horn index, as against 10% in the group with no drugs. For pathological ventricular enlargement the corresponding figures were 40% and 5% respectively ($p<0.05$).

DISCUSSION

In this random sample of 195 men, CT scanning of the brain was performed in order to investigate the relationship between social drinking and brain damage. A relationship was observed between cerebral changes and the quantity of alcohol consumed per day during the week before the examination, which was 33 g in group III and 0 g in group I. This finding corresponds to the results of Cala (6), who found a correlation between high daily alcohol intake and cerebral atrophy in Australian social drinkers. However, Cala's subjects were not representative of the general population. Our subsamples of excessive social drinkers were selected not only on the basis of their alcohol intake per day in the last week, but also on self-reported subjective relative loss of control over drinkning, morning drinks and blackouts.

Moreover, our material includes relatively more heavy social drinkers than some American studies (14, 19, 25). This is due to the fact that in our study no exclusion criteria were used, there was a much smaller drop-out in collecting the random sample, and we requested a 10-h period of abstinence prior to the investigation, in contrast to the 24-h period in the American studies mentioned above.

CT findings in alcoholics have been reported from several studies in which no control subjects were included (1, 3, 7, 12, 13, 17, 18, 24). The incidence of atrophy varied between 33-100%. In our study we have used a representative material of the general population to compare with alcoholics. We have all come to speak of "alcoholics" as if they were a garden variety, as if they were similar across countries and within countries. Clinically, this is certainly not the case. For example in New York, one is dealing primarily with people who are totally unemployed, have virtually never been employed, and who remain without a household for an indeterminate period of time. Obviously, this is not the case in all other parts of the USA, nor in other parts of the world (2). It is therefore very important that we try to describe the patient sample in as detailed a fashion as possible. It is essential to obtain a good drinking history, but a good medical history is also necessary. In our material we did not have the criteria for exclusion as applied by Cala et al. (4) - a history of migraine, head injury, heart disease, asthma, hypertension, epilepsy, neurological disorder, regular drinking, or medical or addictive drugs.

We drew a random sample from the general population and paid consideration to the use of drugs for illnesses. The drugs used are known to be metabolized by the liver and for instance phenytoin can cause viral hepatitis-like reactions, phenothiazines can cause inflammatory cholestatis, methyldopa can cause chronic hepatitis and sulphonamides can cause granulomas in the liver (9).

Regarding the four subgroups IA-IIB, it was found that in group IIB there was a higher incidence of wide transport sulci, cortical changes, a pathological anterior horn index and a pathologically wide third ventricle. The incidence of frontal lobe atrophy, which was strongly correlated to alcohol intake, was 30% in group IIB and 15% in group IIA (Table 4). Thus we have found that the use of hepatotoxic drugs influences the incidence of pathological cortical and subcortical changes and the most typical finding associated with such drugs was a pathologically wide third ventricle and wide transport sulci.

The typical change related to alcohol abuse was frontal lobe atrophy, and the incidence of this aberration was almost twice as high in alcohol abusers who used hepatotoxic drugs than in those who did not (Tables 2 and 4).

Courville (10) reported 1955 that frontal lobe atrophy can result from a relatively long period of exposure to alcohol, and Hunter and Walker (15) demonstrated in a more recent excellent study that changes occur in hippocampal cells as a result of chronic alcohol exposure or abuse. Interestingly enough, in animals at least, it looks as though there are many areas of the limbic system, including the hippocampus, that are very susceptible to the effects of alcohol. Have we been careful enough to look in our scans to see whether there are changes in subcortical areas?

Most of us look at ventricular changes, or changes in the cortex or cerebellum. In some instances, when the films are good enough, we should make every effort to look in other areas, and not just concentrate on the most obvious and easiest areas to be seen. Is a positive scan indicative of brain damage caused by alcohol, or is it a premorbid condition? It seems that we ought to make an effort to look at the offspring of alcoholics. What is the CT scan like in children with the foetal alcohol syndrome?

The relation between CT findings in alcohol abusers and the use of drugs has not received attention earlier, but it is important to make a distinction between those who use drugs and those who do not. In what way drugs increase the incidence of cortical and subcortical changes we do not know, but the use of liver-metabolized drugs has an additive effect on that of alcohol and as we can see, it leads to a remarkably high incidence of pathological values.

Other studies in which normal subjects served as controls are worth mentioning: Cala et al. (5) did not use "blind" radiological ratings as we did, and made no statistical comparisons between patients and controls. Furthermore, a period of abstinence before scanning was not observed by all patients. Another problem is the question as to whether total abstinence from alcohol improves the morphology of the brain in chronic alcoholics as assessed by computed tomography. Carlen et al. have found that alcoholics show a

measurable decrease in the degree of cerebral atrophy on repeated CT scans after alcohol abstinence (8). Of eight alcoholics, aged 35-67 years, four displayed such a decrease on abstinence, and the authors propose that this reversal of atrophy represents a form of morphological plasticity in the central nervous system. We have not made any serial CT studies on subjects from our group who have abstained from alcohol for six months or more, and therefore have not been able to examine the question of the reversibility of the changes of atrophy.

To sum up: there is a typical frontal atrophy in persons who abuse alcohol, and increasing alcohol ingestion is associated with accelerated shrinkage of the brain, the frontal lobes being the first part affected. The groups with both alcohol abuse and use of liver metabolized drugs showed a picture of increased cortical and subcortical changes, the latter expressed as an increased anterior horn index and a widened third ventricle.

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