Arch Public Health
1998, 56, 93-107

Brain damage in alcoholics without neuropsychological impairment

by

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Abstract

Computed tomography (CT) of the brain and neuropsychological assessment were 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. Their consumption of hepatotoxic drugs was also investigated. The material was divided into four groups with regard to both alcohol consumption and use of hepatotoxic drugs: Group I, low or moderate alcohol consumption and no use of such drugs; II, low or moderate alcohol consumption with use of such drugs; III, high alcohol consumption with no use of such drugs; and IV, high alcohol consumption with use of such drugs. Group IV was found to have a higher incidence of cortical and subcortical changes than group I. Differences in CT variables were observed between the four groups I-IV, but there were no differences in the results of neuropsychological assessment. We found that a hidden alcoholic from the general population 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 correlation to cortical and subcortical CT changes.

Key-words

Computed tomography, neuropsychological impairment, liver toxic drugs, population study.

Introduction

A connection between alcoholism and cerebral damage as assessed by CT and/or magnetic resonance (MRT) analysis and neuropsychological tests has been observed in several studies on alcoholic patients (1-8). However, relationships between cerebral changes as assessed by CT and MRT and 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, as we can see from the following review.

Abe et al. (9) studied the usefulness of CT for evaluation of the brainstem in cerebellar atrophic processes. Twenty adult subjects without posterior fossa lesions were used for normal CT measurements of the brainstem. The remarkable thing is that they also reviewed 49 patients with cerebellar atrophy which included spinocerebellar degeneration and among them found only six chronic alcoholics. All but the chronic alcoholics showed atrophy of the brainstem at all locations of measurement when compared with normal controls ($p<0.05$). Carlen et al. (10) found that alcoholics showed greater cerebral atrophy than age-matched neurological controls, but again we have no controls from the general population. Supratentorial atrophy measurements correlated significantly with some neurobehavioural assessment measures. The cerebral atrophy reversed in some subjects with maintained abstinence. Computerised assessment of cerebrospinal fluid (CSF) volume (cerebral atrophy) and mean cerebral density showed decreased CSF volume and increased cerebral density with maintained abstinence over 4 weeks in a group of 20 alcoholics. Jernigan et al. (11) examined 28 chronic alcoholics and 36 age- and sex-matched non-alcoholic controls with MRT and brain morphometric analyses. The results confirmed large increases in subarachnoid CSF volume and mild ventricular enlargement in the alcoholics and associated volume reductions of localised cortical and subcortical cerebral structures. Significant correlations between some cognitive measures and subcortical and cortical fluid volumes were found but the sample was small and there were only 36 controls. Benzodiazepine users, as a group, have been found to have larger ventricle/brain ratios than controls but smaller than those of alcoholics (12).

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 them were currently abusing drugs (13). Rumbaugh et al. (14) 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 (15).

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 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 from the north of Greater Stockholm with about 240,000 inhabitants. The sample was drawn randomly from the National Register and was stratified with regard to age. A sample of 195 men was drawn, with 40 in each of the age groups 20-29, 30-39, 40-49, 50-59 and 60-69 years, in order to achieve the same degree of precision for all age groups in the estimation of different variables, and CT scans and neuropsychological tests were done in all of them. These 195 subjects were examined and interviewed. Laboratory tests were performed, including liver and pancreatic functions 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 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 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 phenothiazine derivatives, all of which are metabolised by the liver.

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

(I) low or moderate alcohol consumption and no use of such drugs (n=125);
(II) low or moderate alcohol consumption with use of such drugs (n=21);
(III) high alcohol consumption with no use of such drugs (n=39);
(IV) high alcohol consumption with use of such drugs (n=10).

Computed 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.

Neuropsychological examination

General intelligence was assessed by means of the Synonym Reasoning Block (SRB) test (16). In order to assess neuropsychological deficits, Halstead Category, Tactual Performance, Trail Making, Finger Tapping and the Rhythm Test of the Halstead-Reitan neuropsychological test battery were administered (17). In order to assess learning and memory functioning, Memory-for-Designs (18) and a Swedish version of the Schulze 10-word test called the Claeson-Dahl test were used (19). The incidence rates of neuropsychological deficits as assessed by the Halstead-Reitan battery were summarised 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 educational and occupational background; b) the differential score approach; c) qualitative deficiencies and pathognomonic signs during performance. The inter-rater reliability of the 3-step scale has been found to be 0.72 (20). 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 maximise the potential for diagnosing sensory or motor dysfunction, amnestic syndromes and cognitive impairment.

Statistics

Data were analysed by the Chi-square test in the statistical analyses. Means were compared by *t* tests for the samples, as appropriate, and we took $p<0.05$ to indicate statistical significance. In tables 2 and 4 we also present the relative risks or odds ratios for each group.

Results

Groups I-IV

Some characteristics of the 4 groups formed according to alcohol consumption and use of hepatotoxic drugs are presented in Table 1. There was a difference in mean age between the four groups and the drug-using groups were older, but not significantly so. The ten with high alcohol consumption and drug-use in group IV were significantly heavier. The recorded use of drugs was the dose prescribed by a doctor and no account was taken of possible overdosage. The ten with high alcohol consumption who used drugs had drunk 39 g in average of alcohol per day in the week before the hospital examination and the 39 with high alcohol consumption who had not used drugs had drunk 31 g per day. In groups I and II the alcohol consumption was 8 g and 6 g, respectively. One man in group I, none in group II, 2 (5%) in group III and 3 (30%) in

TABLE 1

Alcohol characteristics of the four groups of men with different drinking habits with and without the use of hepatotoxic drugs

	Low alcohol consumption		High alcohol consumption	
	Group I no drugs (n=125)	Group II + drugs (n=21)	Group III no drugs (n=39)	Group IV + drugs (n=10)
Alcohol characteristics				
Age (years)	45 ± 14	46 ± 15	41 ± 14	49 ± 5
Weight (kg)	76 ± 9	76 ± 12	76 ± 10	85 ± 5***
Alcohol intake previous week in g absolute alcohol/day	8 ± 9	6 ± 11	31 ± 29***	39 ± 29***
Alcohol in blood on arrival at hospital (%)	1	0	5	30***
Hypnotics/sedatives in blood or urine (%)	0	48***	0	100***
Registered by the Temperance Board (%)	6	10	33***	30**
Smokers (%)	42	52	62*	70

Level of significance 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.

group IV had alcohol in their blood on arrival at the hospital. Hypnotics and/or sedatives in blood or urine was present in 48% in group II and 100% in group IV, but was not found in groups I and III. Actions had been taken by the Temperance Board concerning 6% of group I, 10% of group II, 33% of group III and 30% of group IV. The proportion of smokers were 42% in group I, 52% in group II, 62% in group III and 70% in group IV. When consideration was paid to drug use, a number of alcohol markers were positive.

Liver tests

The results of tests for alcohol-related liver disturbances in the subgroups are presented in Table 2. In group II with low alcohol and drug consumption 48% had pathological values of S-GGT and in group IV with high alcohol consumption and drug consumption 60%. The corresponding values were 9% in group I, who only had low alcohol consumption and took no drugs, and 12% in group III, who only had high

TABLE 2

Pathological liver values of serum GGT, ASAT and ALAT in the four groups of men with different drinking habits with and without the use of hepatotoxic drugs.

	Low alcohol consumption		High alcohol consumption	
	Group I no drugs (n=125)	Group II + drugs (n=21)	Group III no drugs (n=39)	Group IV + drugs (n=10)
S-GGT	9	48	12	60
RR		5.45		5.16
95% CI		2.65-11.22		4.04-6.58
S-ASAT	3	19	16	60
RR		6.01		3.69
95% CI		1.63-22.20		1.33-10.20
S-ALAT	10	14	28	60
RR		1.50		2.15
95% CI		0.46-4.87		1.07-4.32

RR= relative risk; CI=confidence interval. Percentage for the four groups in comparison with low and high alcohol consumption, no drugs group

alcohol consumption. Significantly higher serum levels of GGT, ASAT, ALAT, CK and LD were found in the heavy-drinking group using drugs (IV) than in the other groups. In group III, with a high alcohol consumption and no drug use, only serum GGT, ASAT, ALAT and LD were elevated. GGT showed a correlation to alcohol consumption in combination with the use of drugs, but not to alcohol alone.

The relative risk (RR) of having pathological liver test values was 5.45 in group II and 5.16 in group IV. The RR for pathological S-ASAT was 6.01 in group II and 3.69 in group IV.

CT findings in groups I-IV

Cortical changes were found in 40% of group IV ($p<0.05$ compared with group I), frontal lobe atrophy in 30% (n.s.) and wide transport sulci in 20% ($p<0.05$); users of hepatotoxic drugs had a higher prevalence of cortical changes than non-users (Table 3). In the groups that used drugs, 19-20% had a pathological anterior horn index. The prevalence of an enlarged third ventricle varied from 24 to 40% in the drug-using groups. Wide cerebellar sulci indicating vermian atrophy were not observed in

TABLE 3

CT variables used in the four groups with different drinking habits with and without the use of hepatotoxic drugs. Percentages.

CT measures	Low alcohol consumption		High alcohol consumption	
	Group I no drugs (n=125)	**Group II** + drugs (n=21)	**Group III** no drugs (n=39)	**Group IV** + 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 > 6mm	9	24*	10	40*
Vermian atrophy	6	5	5	0

Level of significance tested in comparison with low alcohol, no drugs group by Chi-square test. *p<0.05; ** p<0.01; ***p<0.001.

group IV, but were found in 6% of group I and in 5% each of groups II and III. The prevalence of cortical changes varied between 5% in the two youngest groups who were judged to show clear-cut or high-grade changes and 31% in the 60-65 year olds. Looking at the central, subcortical parts of the brain, the prevalence of an anterior horn index above 0.31 varied from 3% in the age group 20-29 to 23% in the age group 60-65 years. The prevalence of an enlarged third ventricle according to the criterion value varied from 9% among those 20-29 years old to 23% of those 60-65 years old. Wide cerebellar sulci indicating vermian atrophy were not diagnosed in the 20-29 year old group but were present in 10% of those 60-65 years old. Cerebellar changes were also assessed by the presence of wide cisterns. The prevalence was 2% in the whole group.

Pairwise correlations between age, ventricular, cortical and cerebellar changes

Pairwise correlations between age, ventricular, cortical and cerebellar changes are shown in Table 4. All correlations were significant (p<0.001) except those between vermian atrophy and ventricular

TABLE 4

Product-moment correlations between chronological age and CT measures (upper triangle). Values when effects of age are partialled out within parentheses (lower triangle).

	2	3	4	5
1. Age	38***	26***	44***	12
2. Anterior horn index		33***	26***	03
3. Width third ventricle	(25***)	39***	-01	
4. Cortical atrophy	(11)	(32***)		31***
5. Vermian atrophy	(-02)	(-01)	(28***)	

Level of significance *p<0.05; **p<0.01; ***p<0.001.

changes. All morphological changes were significantly correlated to age except vermian atrophy. The correlation between cortical changes and the anterior horn index was no longer significant when age was partialled out.

Neuropsychological findings in groups I-IV

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 years group. There were no significant differences in intellectual impairment between the four groups I-IV. Only 10-22% of this random sample of men from the general population had "definite signs of intellectual impairment" (Table 5).

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 although 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

TABLE 5

Neuropsychological impairment in the four groups with different drinking habits with and without the use of hepatotoxic drugs. Percentages.

Neuropsychological impairment	Low alcohol consumption, Group I no drugs (n=125)	Group II + drugs (n=21)	High alcohol consumption Group III no drugs (n=39)	Group IV + 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

Level of significance in comparison with low alcohol, no drugs group by Chi-square test. *p<0.05; **p<0.01; ***p<0.001.

(Mützell). None of the subjects were drunk at the time of the tests or had cerebral oedema according to the CT findings. They were thoroughly assessed concerning the amount of alcohol consumed, indications of alcohol dependence and alcohol-related complications by means of a standardised 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 (7,8,16-20). At the 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. 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 (20).

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 I (low alcohol consumption, no drugs). In the heavy-drinking subjects who used drugs (group IV), the drugs taken included antiarrhythmic agents (quinidine, verapamil), antiepileptics (phenytoin), antibiotics (doxycycline), dextropropoxyphene, and benzodiazepine

derivatives, all of which can alone cause an increase in the serum GGT values. The most important of these drugs in this respect are anticoagulants, antiepileptic agents and barbiturates (7,8).

The drugs are known to be metabolised by the liver and phenytoin, for instance, may cause viral hepatitis-like reactions. 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 (7,8,21,22). 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 synergistic effects by an additive action on the central nervous system and by the inhibition of drug metabolism (7,8,22). Lader et al. (12) 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 correlation between the CT findings and the duration of benzodiazepine therapy. Allgulander et al. (13) studied 50 of 55 patients originally hospitalised 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 investigation. CT indicated cerebral cortical atrophy in 17 of 33 patients, 10 of whom were abusing drugs. Enlarged lateral ventricles were found in six patients, and an enlarged third ventricle in two patients. Di-Sclafani et al. (23) used MRT and neuropsychological tests to measure atrophy and cognitive function in 14 older abstinent alcoholic men and 11 older controls in the expectation that these subject groups would show the greatest and most persistent cerebral effects consequent to chronic alcoholism. The abstinent alcoholics exhibited cognitive impairments (primarily in memory and visual-spatial-motor skills) compared with the controls. In contrast, they found no difference in global cerebral atrophy between the groups, although two alcoholics had extensive atrophy compared with all other subjects.

However, there was a stronger association between age and ventricular dilatation in the alcoholic sample compared with controls.

We found in our material that all morphological changes were significantly correlated to age except vermian atrophy and that the correlation between cortical changes and the anterior horn index was no longer significant when age was partialled out.

Di-Sclafani et al. (23) conclude that a substrate other than MRT-detectable atrophy must underlie the persistent cognitive impairments evident in the sampled alcoholics. If there are global atrophic changes in the brain associated with chronic alcoholism, these effects are not ubiquitous and/or may be reversible in most patients with sufficient abstinence.

Most sedative-hypnotic abusers also show high rates of primary alcohol problems. Many of the patients in this study (13) developed secondary alcohol abuse, implying that sedative-hypnotic dependence is one factor conducive to abuse of alcohol. Bergman (24) found that among alcoholic patients, cognitive impairment was associated with ventricular dilatation on CT, but not with cortical changes. Conversely, there was no association 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 (7,8). Bergman (24) found that alcoholic patients had poorer results in 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. Purely from the CT aspect, they resembled the social outcasts in Bergman«s study, the difference being that they drank smaller quantities of alcohol but used drugs at the same time.

The groups III and IV (49 men) with high alcohol consumption reported an average consumption between 31-39 g of absolute alcohol per day previous week. This is equivalent to 3-4 drinks per day, which is commonly considered as the upper limit of a safe consumption in men, but of course not together with drugs. To see if there were any alcohol-dependent persons in the cohort, we divided the group of 49 high alco-

hol consumers into 23 alcohol-dependent heavy drinkers with > 4 drinks per day and alcohol dependence according to DSM IV criteria (25), and a group of 26 not alcohol-dependent heavy drinkers with < 4 drinks per day. Differences in CT variables were observed between the two groups, but there were no differences in the results of neuropsychological assessment.

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

From a purely scientific viewpoint, this means that even though there may be major CT changes in some patients, the neuropsychological test results show no differences between different alcohol consumption groups and give no indication as to whether the subject 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. A person may thus show considerable cerebral damage on CT but perform fairly well in the tests.

The group of randomly sampled persons who used alcohol and at the same time took drugs of the type metabolised by 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 summarising 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 CT images should be assessed with caution.

Conclusion

CT scan of the brain and neuropsychological assessment were 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 I, low or moderate alcohol consumption and no use of such drugs; II, low or moderate alcohol consumption with use of such drugs; III, high alcohol consumption with no use of such drugs; and IV, high alcohol consumption with use of such drugs. Group IV was found to have a higher incidence of cortical and subcortical changes than group I. Differences in CT variables were observed between the four groups I-IV, but there were no differences in the results of neuropsychological assessment.

Thus, a hidden alcoholic from the general population 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 occassion were found to be associated with cognitive impairment, but both showed a correlation to cortical and subcortical CT changes.

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