Regional Cerebral Blood Flow-SPECT in Chronic Alcoholism: Relation to Neuropsychological Testing

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To determine the prevalence of central nervous system damage due to ethanol, we evaluated 40 asymptomatic chronic alcoholics and 20 age-matched controls. Studies included neuropsychological testing, brain ^{99m}Tc-HMPAO SPECT, and morphometric analysis by CT scan. In the qualitative analysis, 30 of the 40 alcoholics showed hypoperfused areas on SPECT scan. In the semiquantitative analysis, alcoholics exhibited significant reduction in regional cerebral blood flow (rCBF) ratio of all brain lobes compared to controls ($p < 0.001$). The rCBF ratio was mainly reduced in frontal lobes (65%). Only 11 alcoholics showed significant frontal lobe atrophy in the morphometric analysis; most also had abnormalities on SPECT scan. Alcoholics exhibited significant impairment of frontal tasks and visuospatial skills. Frontal test impairment was independently related to both frontal atrophy and hypoperfusion. In a group of ten alcoholics in whom another SPECT scan was performed after 2 mo of ethanol abstinence, rCBF ratio of the frontal lobes normalized in eight, without frontal atrophy. In patients without frontal atrophy, reduced rCBF ratio of the anterior portion of the frontal lobes correlated negatively with frontal test results ($r = -0.6535$, $p < 0.001$). A significant negative correlation between cerebral perfusion and the amount of ethanol consumed in the month prior to study was observed ($r = -0.6289$, $p < 0.001$). In conclusion, asymptomatic chronic alcoholics frequently show reversible frontal lobe hypoperfusion, which is related to recent ethanol intake, reflects brain function impairment and is independent of brain atrophy.

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Various studies have documented a wide range of effects of chronic ethanol intake on the central nervous system (*1–8*). Recently, impairment of the regional cerebral blood flow (rCBF) also has been observed (*9–11*). However, previous studies performed on human volunteers and chronic alcoholics yielded a variety of results, depending on the dose of ethanol administered and differences in type of subjects (*9–11*). Prevalence of such alterations in chronic alcoholics remains uncertain as does relation to factors such as nutritional status and the frequency and amount of ethanol consumed.

We studied a homogeneous population of asymptomatic patients with chronic alcoholism, who were submitted to determination of rCBF using technetium-99m-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) and single photon emission computed tomography (SPECT) (*12,13*) under controlled conditions. Frontal and memory tasks were evaluated by neuropsychological testing. Cerebral computerized tomography (CT) scan was used for atrophy correction of SPECT perfusion deficits.

MATERIALS AND METHODS

Patient and Control Selection

Patients. Over a one-year period, 381 patients with chronic alcoholism (DSM III-R) were seen in the Alcoholism Unit of the Hospital Clinic of Barcelona. The unit treats only ambulatory patients who seek assistance in terminating alcohol dependence and have no signs or symptoms of other diseases. Patients with overt alcohol-related diseases such as liver disease, cardiomyopathy or other disorders are referred to other clinics.

On Monday of each week, the first male patient to register who had a daily ethanol consumption >100 grams in 2 yr previous to admission, was selected for study. Initially, 49 chronic alcoholics were included. After percutaneous needle liver biopsy was performed on those who showed abnormal liver function tests or hepatic structural abnormalities on ultrasonography, nine of the 49 were excluded: five with withdrawal syndrome, two with liver cirrhosis, one who reported consumption of benzodiazepine drugs during the previous 6 mo, and one with HIV. Of the 40 patients with chronic alcoholism included in the study, none exhibited causes of brain damage other than alcoholism. No patients objected to the study and all gave informed consent for various procedures. Study protocols were approved by the Institutional Review Board.

Patients were Caucasian males of Spanish descent who lived with their families in or around Barcelona and had

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histories of stable employment. About 60% were skilled laborers or office workers and the rest were unskilled workers. None were indigent.

Control Group. This group was comprised of 20 (one control for two patients) asymptomatic males who did not drink. They were gathered from friends and relatives of the alcoholics. The group was matched with the group of alcoholics for age (± 2 yr), sex (male) and sociocultural status. Members of the control group were studied in the same manner as alcoholics.

Clinical Examination

Using a structured questionnaire, one of two physicians obtained a detailed history of ethanol intake and dietary habits. The data were confirmed in consultation with family members. Average quantity per year and frequency of ethanol intake were recorded. Life events such as marriage, military service and work posts were used as "anchor points" to prompt recall ("time-line/follow-back method") (*14*). Total ethanol dose was estimated by multiplying the daily amount of ethanol by the number of years of each alcohol intake period times 365 and adding the amounts of each period. Withdrawal symptoms were evaluated according to the Clinical Institute for Withdrawal Assessment (CIWA) scale (*15,16*), and a score ≥15 was considered withdrawal syndrome. None of the patients or controls were on medication before or during the investigation.

Laboratory and Nutritional Studies

Within the first three days of admission, blood samples were obtained as baseline markers of alcohol intake and nutritional status. These included hemoglobin, lymphocyte count, total protein, albumin, prealbumin, retinol-binding protein, serum aspartate and alanine aminotransferases, gamma-glutamyl transpeptidase, amonia, red-cell and serum folate, vitamin B12 and erythrocyte transketolase activity, which were measured by standard semiautomated methods. Serologic assays for the Venereal Disease Research Laboratory test, Fluorescent Treponemal Antibody Absorption test, and human immunodeficiency virus antibodies (ELISA) were also done. Hepatic ultrasonography and percutaneous needle liver biopsy were performed in all patients with previous history of liver disease, hepatomegaly on physical examination and/or laboratory data of chronic hepatocellular failure or abnormally elevated serum aminotransferases for more than 2 mo during which the patient had maintained complete ethanol abstinence.

Overall nutrition was assessed in terms of the proportion of actual to ideal weight (*17*). The lean body mass and muscular area of the arm were calculated from the circumference of the upper nondominant arm and the thickness of the tricipital skin fold (*18*). The fatty area of the arm was calculated from the thickness of the tricipital skin fold and was considered indicative of total body fat (*18*). Patients were considered malnourished if body weight was less than 90% of ideal weight or if the calculated lean body mass was more than 10% below normal.

Neuropsychological Testing

A battery of neuropsychological tests was performed 10 days after hospital admission to assess Intelligent Quotient (IQ) (Wechsler Adult Intelligence Scale subtests of vocabulary, similarities and Kohs) (*19,20*), basic attention span (WAIS Digit Span) (*19*), logical and visual memory, delayed recall and associate learning (Wechsler Memory Scale Logical Memory and Visual Reproduction) (*21,22*) as well as various "frontal lobe" skills such as the ability to form categories (Weigl Color Sorting test) (*23,24*) and visual conceptual and visuomotor tracking (Trail Making tests) (*25*).

Brain SPECT

Regional cerebral blood flow images were obtained by SPECT using ^{99m}Tc-HMPAO (hexamethyl propylene amine oxime) (Ceretec, Amersham, Intl) on the tenth day after admission. In the last 10 patients of the series, a prior SPECT was performed on the day of admission, while maintaining positive alcoholemia (1.5 ± 0.78 g/liter, range 0.78–3.08), and another SPECT after two months of complete ethanol abstinence. Brain SPECT was performed using a rotating gamma camera (Elscint SP4-HR) equipped with a low-energy all-purpose parallel-hole collimator. Data acquisition started 15 min after intravenous injection of 740 MBq of ^{99m}Tc-HMPAO in a silent, dimly lit room. The radiochemical purity of lipophilic ^{99m}Tc-HMPAO determined by chloroform extraction (*26*) was 93.9% ± 2.4%. During a 360° rotation in a 64 × 64 matrix with a zoom of 1.5, 60 × 30-sec frames were collected and a 4.5-mm pixel size was obtained. Image data were processed on an Elscint SP1 computer (Apex SP-x Functions, software version 2.0). Reconstruction was performed by filtered backprojection using a Butterworth filter (cutoff frequency 0.35, power factor 5.8). No attenuation correction was performed. Spatial resolution was approximately 16 mm (FWHM) in the transaxial plane. Two-pixel thick slices were obtained in coronal, sagittal and oblique (parallel to the orbito-meatal line) planes. SPECT images were finally presented on a polychromatic scale (20 colors), and standardized by adjusting the upper discriminator threshold to render maximum pixel values within oblique slices within the most intense color table, and then applying the same factor to coronal and sagittal slices.

Qualitative Analysis. The SPECT scans were coded with random numbers and read independently by three nuclear medicine physicians who had no knowledge of the clinical data. Perfusion deficits were considered when at least two of the three observers agreed on the evaluation of the following cerebral regions: anterior (prefrontal) and posterior (superior) segments of the frontal lobes, anterior and posterior segments of the temporal, parietal and occipital lobes.

Semiquantitative Analysis. Irregular regions of interest (ROIs) were drawn as previously described by Goldenberg et al. (*27*). Because some patients showed a diffuse supratentorial CBF impairment and because the most striking finding in the alcoholics' SPECT images by visual evaluation was the apparent absence of hypoperfusion in the cerebellum, regional indices of CBF in the ROIs were obtained, expressed as the ratio between average pixel counts in each ROI and average pixel counts of the cerebellum. Hypoperfusion was considered to be present when a regional index was 2 s.d. lower than the corresponding value of the age-matched control.

Neuroradiology

A brain CT scan was performed on a SOMATON DR3 (Siemens, Erlangen, Germany) matrix 512 × 512 with 12–14 slices of 8 mm thickness parallel to the orbitomeatal plane. Each section was transferred to floppy disks and photographed on 100-mm spotfilms. For each patient, maximal width of the frontal horns of the lateral ventricles (A), frontal brain width (B), maximal width of the brain (C), frontal intracranial area (D) and frontal lobe area (E) were measured by a KONTRON MOP-20 planimeter (Messgerate, Germany) using an enlarged picture of the CT slice at the

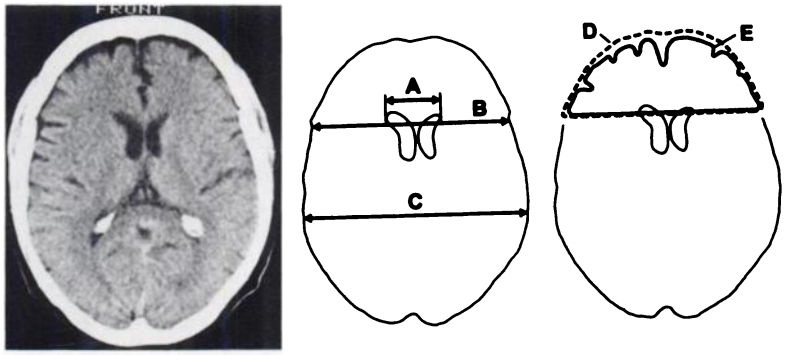

FIGURE 1. Brain computerized tomography (CT) scan of alcoholic patient with frontal atrophy (left). Tracing of CT scan shown with the parameters used to assess frontal atrophy: frontal lobe index (A/B), Evans ratio (A/C) and pericerebral frontal area considered as percentage of the difference between D minus E.

caudate nuclei, as reported elsewhere (*5,28*). The following combined indices, considered representative of frontal atrophy, were calculated from these measurements: frontal lobe index (A/B), Evans ratio (A/C) and pericerebral frontal area, considered the percentage difference between D minus E (Fig. 1). Measurements were obtained by one physician who had no knowledge of the clinical data. Frontal lobe atrophy was considered present when at least two of three indices were 2 s.d. greater than the value of their age-matched control.

Statistical Analysis

Standard statistical methods from SPSS Statistical Analysis System V4.0+ (SPSS, Chicago) were used. Differences between groups were analyzed using the two-tailed Student's t-test, Mann-Whitney, Wilcoxon, and chi-square tests. Correlation studies were obtained by Pearson's correlation coefficient and regression analysis. When two or more variables were significant in the univariate study, a stepwise multiple regression analysis was performed. All variables are expressed as mean ± s.d., and a significance level of $p < 0.05$ was used.

RESULTS

Clinical, Laboratory and Nutritional Data

The 40 alcoholic patients studied had an average age of 44 ± 10 yr (range, 26–63). The reported daily intake of ethanol ranged from 100 to 330 g (mean, 186 ± 69) over a period of 24 ± 9 yr. The mean total lifetime dose of ethanol was 26 ± 12 kg/kg (kilograms of ethanol per kilogram of body weight). The pattern of drinking was continuous excessive ethanol intake as part of everyday life. Only occasional binges were reported by the patients. Ethanol was consumed mainly in the form of wine, beer, brandy, and less frequently anisette, whiskey or gin. No relationship was observed between the type of beverage consumed and any of the measurements studied. More than 80% of alcoholics and controls had smoked one to two packets of cigarettes a day since the second decade of their lives. None of the subjects used any other drugs.

None of the alcoholic patients had clinical or laboratory evidence of gross malnutrition, although they tended to show thinner tricipital skin folds compared to the controls

TABLE 1
Laboratory and Nutritional Data

	Alcoholics n = 40	Controls n = 20	p
Percentage ideal body weight	99.5 ± 16	105.4 ± 11	NS
Lean body mass (kg)	51 ± 5	53 ± 5	NS
Arm circumference (cm)	25 ± 3.7	28 ± 3.4	0.003
Triceps skin fold thickness (cm)	0.85 ± 0.42	1.18 ± 0.44	0.006
Hemoglobin (g/liter)	147 ± 11	147 ± 26	NS
Lymphocytes (10^6/liter)	1787 ± 586	2100 ± 612	NS
Albumin (g/liter)	47 ± 4	46 ± 5	NS
Prealbumin (mg/dliter)	33 ± 15	34 ± 12	NS
Retinol-binding protein (mg/liter)	51.1 ± 17.4	65.6 ± 19.6	0.005
Erythrocyte transketolase*	18.2 ± 5.7	15.8 ± 6.5	NS
Aspartate aminotransferase (UI/liter)	56 ± 34	29 ± 6	0.001
Alanine aminotransferase (UI/liter)	49 ± 35	30 ± 4	0.017
G-glutamyl transpeptidase (UI/liter)	179 ± 189	32 ± 5	0.001

*Percent difference between the enzymatic activity with and without the addition of thiamin pyrophosphate (TPP effect).

TABLE 2
Qualitative and Semiquantitative Results of Brain SPECT Scans

	Controls (n = 20)		Alcoholics (10th day, n = 40)		Alcoholics (1st day, n = 10)	Alcoholics (2 month, n = 10)
	QH*	rCBF ratio†	QH†	rCBF ratio†	rCBF ratio†	rCBF ratio†
Anterior frontal	0	83.8 ± 6.7	20	71.6 ± 9.5§	70.5 ± 6.5	84.3 ± 10.1§
Posterior frontal	1	80.9 ± 6.6	30	67.1 ± 9.2§	68.5 ± 7.6	79.9 ± 7.3§
Parietal	0	81.1 ± 5.9	12	70.1 ± 8.9§	69.5 ± 6.1	79.6 ± 4.2§
Anterior temporal	0	83.1 ± 7.1	12	73.6 ± 8.2§	72.5 ± 8.8	84.7 ± 8.7§
Posterior temporal	0	83.9 ± 6.2	20	73.6 ± 8.6§	73.5 ± 5.6	83.5 ± 4.1§
Occipital	0	86.4 ± 6.7	10	77.2 ± 7.8§	78.5 ± 6.7	88.0 ± 8.2§

*Hypoperfusion evaluated in the qualitative analysis of SPECT scans.
†Regional cerebral blood flow, expressed as percentage of activity compared to that of the cerebellum (mean ± s.d.).
‡Significantly different from controls, $p < 0.001$.
§Significantly different from alcoholics (day 10), $p < 0.05$.

(Table 1). Mild elevations of hepatic enzymes after 2 mos of ethanol abstinence were found in six alcoholic patients and structural abnormalities of hepatic ultrasonography in two additional cases. Fasting serum amonia was normal in all patients (<50 μM/liter). Liver biopsy was performed in these eight patients and the following diagnoses were made: normal liver in four cases, fatty liver in three cases, and alcoholic hepatitis in the remaining patient. No differences were found between the groups with and without abnormalities in the SPECT, CT scan or neuropsychological testing.

HMPAO-SPECT Data: Relationship With Ethanol Intake

Significant differences between the SPECT scans of alcoholics and controls were found. In the qualitative analysis, 30 chronic alcoholics (75%) showed abnormal SPECT scans. Table 2 details results of the qualitative SPECT analysis. All alcoholics with abnormal SPECT had hypoperfusion of the frontal lobes. In the semiquantitative analysis, alcoholics exhibited a significant reduction in the rCBF ratio of all brain lobes compared to controls (Table 2). Twenty-six of 40 patients showed significant reduction in rCBF ratio of the different ROIs compared to only one control, who showed mild hypoperfusion of one frontal lobe ($p < 0.001$). Frontal lobes were usually found to be hypoperfused (65%) measured by rCBF ratio. Less frequently, patients exhibited hypoperfusion in the temporal (40%), parietal (30%) and occipital (20%) lobes, always concurrently with involvement of the frontal lobes (Fig. 2). No differences occurred in the mean value or the frequency of altered rCBF ratio with respect to either cerebral hemisphere. Association between qualitative SPECT abnormalities and a significant decrease of the rCBF ratio were found to be highly statistically significant ($p < 0.001$).

In the 10 patients in whom a SPECT scan was performed on the day of admission, SPECT data were similar to scans performed 10 days later. The mean rCBF ratio of frontal lobes was initially 68.1% ± 5.9%, whereas the mean value increased to 70.4% ± 6.8%, 10 days later, a difference that was not statistically significant. The SPECT scans taken after 2 mo of complete ethanol abstinence were normal in the eight alcoholics without frontal atrophy, and their mean rCBF values were comparable to those of controls (Table 2). By contrast, the SPECT scans of two patients with frontal atrophy showed mild hypoperfusion of the frontal lobes, although their mean frontal rCBF ratio was not as low as previously observed (63.2% versus 72.1%). Figure 3 shows SPECT scans of a representative alcoholic, in which the SPECT normalized with ethanol abstinence.

Analysis of alcoholics with or without cerebral lobe hypoperfusion demonstrated no differences in the mean age, duration of alcoholism or nutritional parameters evaluated. Likewise, no differences were observed in the total dose of ethanol consumed over the previous year or the total lifetime consumption of ethanol. However, alcoholics with reduced rCBF ratio reported a significantly greater ethanol intake during the month previous to admission ($p < 0.001$, all ROIs), and the rCBF ratio of each ROI correlated significantly with the total dose of ethanol (kg ethanol/kg body weight) consumed during the previous month ($r = -0.6356$, $p < 0.001$, for anterior portion of frontal lobes). In addition, the number of hypoperfused brain lobes also correlated significantly with the amount of ethanol consumed during the previous month ($r = 0.6167$, $p < 0.001$).

CT Scan Data: Relationship With rCBF Ratio and Ethanol Intake

Significant differences were observed between alcoholics and controls in the mean values of the three planimetric brain indices calculated (Table 3). Compared with controls, four alcoholics showed a significantly greater pericerebral frontal area alone, six had a significantly greater pericerebral frontal area and higher frontal lobe index, and five presented significant increases in all three indices. In accordance with criteria mentioned above, the diagnosis of frontal lobe atrophy was made in 11 cases.

Eight of these 11 patients with frontal lobe atrophy also showed hypoperfusion of the frontal lobes in the SPECT scans and a significant reduction of rCBF ratio of these lobes. However, 18 additional alcoholics without frontal lobe atrophy also exhibited a marked reduction in their frontal rCBF ratio.

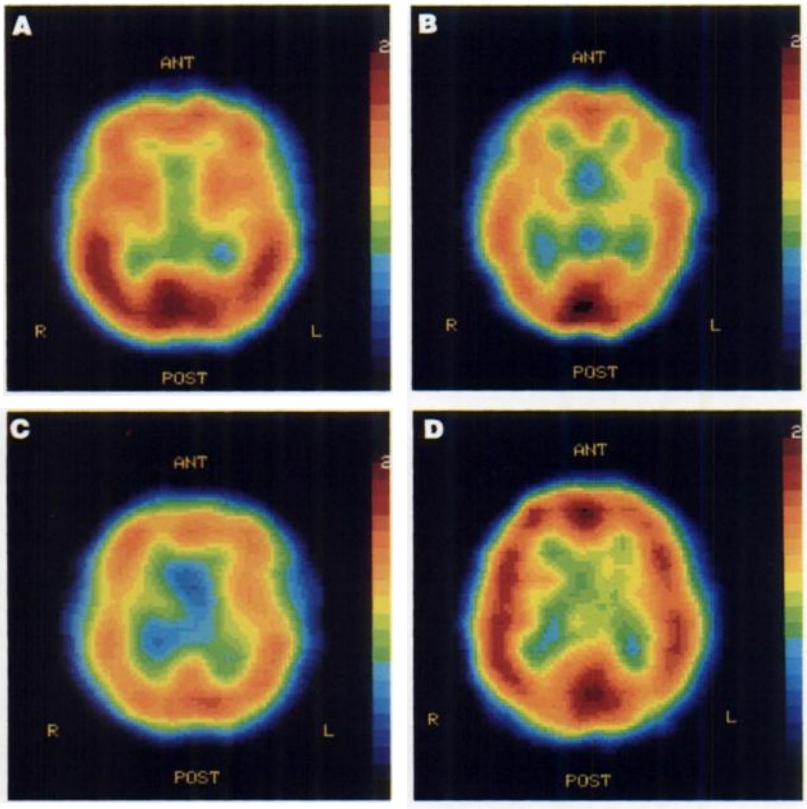

FIGURE 2. SPECT scan images of chronic alcoholics without brain atrophy that exhibit bilateral hypoperfusion of frontal lobes (A), frontal and temporal lobes (B) and diffuse hypoperfusion of all brain lobes (C) compared to control (D). All images correspond to a slice 45 mm above the orbitomeatal (O-M) line, except for figure B (O-M + 36 mm).

Patients with frontal atrophy were older and reported a significantly greater lifetime intake of ethanol ($p < 0.001$, both). Highly significant correlations were observed between the frontal atrophy indices (age-corrected) and the total lifetime intake of ethanol ($r = 0.6363$, $p < 0.001$, for pericerebral frontal area).

Neuropsychological Test Results: Relationship With rCBF Ratio, Frontal Atrophy and Ethanol Intake

Although none of the patients exhibited a significantly diminished intelligence quotient in the WAIS test, significant differences were observed between alcoholics and controls in frontal tasks and visuospatial skills (Table 3). Moreover, the 20 alcoholics with significantly reduced rCBF ratio of the anterior portion of the frontal lobes (prefrontal) showed significantly greater impairment in the frontal tests than those with normal rCBF ratio (Table 4). In the univariate analysis, patients with frontal lobe atrophy also showed a significant impairment of frontal tests ($p < 0.05$, all tests). However, in the stepwise regression analysis, frontal task impairment related independently to both hypoperfusion of the anterior portion of the frontal lobes ($p < 0.01$, all tests), and frontal atrophy ($p < 0.05$, all tests). Consistent with these findings, rCBF ratio of the anterior frontal lobes correlated significantly with the fron-

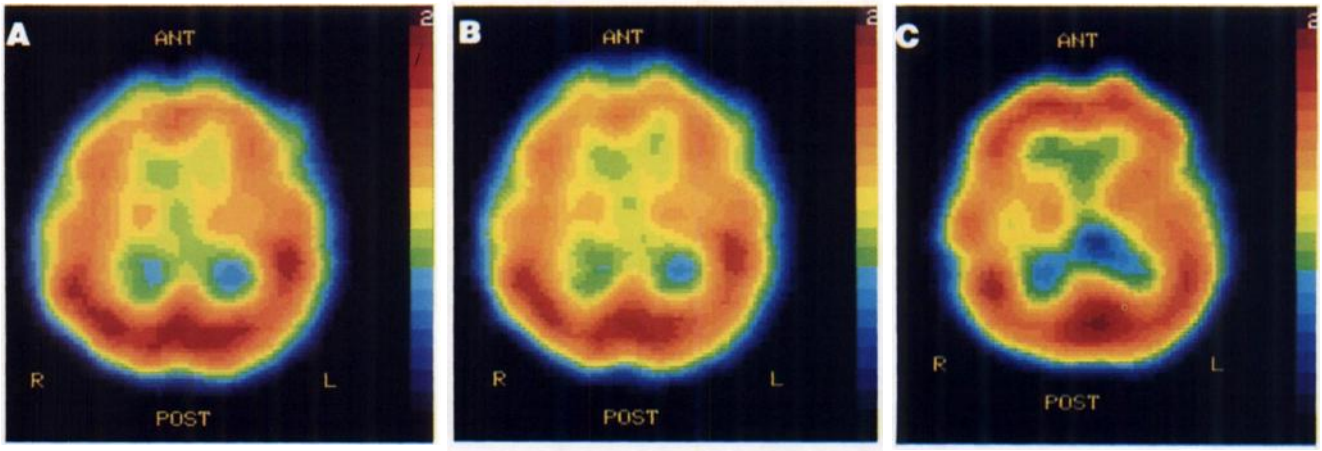

FIGURE 3. SPECT scans of a representative alcoholic. The first scan performed the first day shows hypoperfusion of frontal lobes (A) similar to that carried out 10 days later (B). SPECT scan performed after 2 mo of complete ethanol abstinence was normal (C) (slices at O-M line + 45 mm).

TABLE 3
CT Scan and Neuropsychological Test Data

	Alcoholics n = 40	Controls n = 20	p
Age (yr)	44 ± 10	43 ± 12	NS
Education (yr)	8.3 ± 5.1	8.8 ± 4.5	NS
Intelligence quotient	97.5 ± 17.2	102.4 ± 12.4	NS
Weigl sorting test*	4.4 ± 1.3	5.3 ± 1.0	0.012
Trail making test A†	60.8 ± 30.5	45.6 ± 20.0	0.024
Trail making test B†	240 ± 203	124 ± 53	0.001
Digit span (age corrected)‡	8.1 ± 3.2	8.2 ± 1.9	NS
Logical memory§	79.8 ± 26.4	87.2 ± 19.9	NS
Visual memory§	75.0 ± 32.1	90.1 ± 11.2	0.041
Associated learning‡	13.5 ± 4.4	14.4 ± 3.0	NS
Frontal lobe index	0.33 ± 0.04	0.29 ± 0.03	0.005
Evans ratio	0.28 ± 0.03	0.27 ± 0.04	0.031
Perifrontal area (%)	6.9 ± 3.2	3.3 ± 1.9	0.001

*Number of categories correctly identified.
†Seconds to complete the task.
‡Direct score.
§Percentage of retention.

tal test results in the nonatrophic chronic alcoholics (r = −0.6535, −0.4983, and 0.4293, for Trail Making A and B, and Weigl tests, respectively; $p < 0.001$ all). In fact, of the 18 patients without frontal atrophy who showed a reduced rCBF ratio of anterior portion of the frontal lobes, 17 presented a significant cognitive dysfunction compared to only one of the eleven nonatrophic alcoholics with normal perfusion of these lobes ($p < 0.001$, for all neuropsychological frontal tests). There was no significant relationship between neuropsychological test impairment and the rCBF ratio of other ROIs.

Finally, the relationship between ethanol consumption and cognitive performance in chronic alcoholics also was evaluated. Those patients with significant impairment of frontal tests reported higher ethanol intake during both the previous month and throughout their lives. Thus, alcoholics with significant impairment in part B of the Trail Making test reported higher ethanol intake during the previous month (104 ± 52 versus 75 ± 43 g ethanol/kg body weight, $p < 0.05$) and throughout their lives (31.0 ± 12.4 versus 22.6 ± 9.2 kg ethanol/kg body weight, $p < 0.005$).

TABLE 4
Neuropsychological Test and CT Scan Data of Alcoholics With and Without Hypoperfusion of the Anterior Portion of Frontal Lobes

	Normal n = 20	Hypoperfused* n = 20	p
TEPM (g/kg)	61.8 ± 16.7	99.5 ± 47.4	0.001
TLDE (kg/kg)	26 ± 12	28 ± 12	NS
Intelligence quotient	101.6 ± 17.0	93.1 ± 17.1	NS
Weigl Sorting test†	4.9 ± 1.0	4.0 ± 1.4	0.045
Trail Making test A‡	44.7 ± 19.2	77.8 ± 32.1	0.001
Trail Making test B‡	172 ± 163	317 ± 224	0.028
Digit span (age corrected)§	8.6 ± 3.3	7.6 ± 3.2	NS
Logical memory¶	78.3 ± 21	78.8 ± 30	NS
Visual memory¶	83.6 ± 19	65.2 ± 40	NS
Associate learning§	14.6 ± 3.4	12.2 ± 5.0	NS
Frontal lobe index	0.32 ± 0.04	0.33 ± 0.04	NS
Evans ratio	0.27 ± 0.03	0.28 ± 0.04	NS
Perifrontal area (%)	6.2 ± 2.6	7.7 ± 3.7	NS

*Patients exhibited hypoperfusion in the qualitative analysis and also showed significant reduction in rCBF ratio of the anterior portion of frontal lobes.
†Number of categories correctly identified.
‡Seconds to complete the task. Direct score.
§Percentage of retention.
¶TEPM, ethanol intake the previous month and TLDE, total lifetime dose of ethanol intake.

DISCUSSION

In the current study, two-thirds of asymptomatic chronic alcoholics with active ethanol consumption showed significantly hypoperfused cerebral areas mainly in the frontal and temporal lobes. However, only 25% of patients exhibited morphometric evidence of frontal lobe atrophy. Studies in chronic alcoholism have yielded a variety of results, depending on the type of subjects included, ethanol intake history and alcohol-related diseases (*11,29–31*). Thus, Rogers et al. (*29*)—using the xenon-133 inhalation method to study the relationship between social drinking and CBF in 218 normal volunteers divided into four groups according to their average alcohol intake during a 5-yr period—found progressive reduction in CBF that inversely correlated to the amount of alcohol consumed. Melgaard et al. (*11*) found that reduced CBF correlated to structural abnormalities seen on CT scan, but patients without brain atrophy also had a higher incidence of brain low-flow areas. On the other hand, Berglund reported that the average 30- to 40-yr-old alcoholic is likely to have normal CBF values and that alcoholics with delirium tremens and hepatic cirrhosis were more prone to reductions in CBF (*31*). Nonetheless, the prevalence of these alterations in asymptomatic chronic alcoholics has remained uncertain, as has their relation to factors such as nutritional status, the frequency and the amount of ethanol consumed and brain function. For these reasons, we studied a homogeneous population of asymptomatic chronic alcoholics, well nourished and without withdrawal symptoms, and determined rCBF using ^{99m}Tc-HMPAO-SPECT. We took the cerebellum as reference for quantitation analysis, because in the alcoholics studied all brain lobes exhibited variable perfusion rates, the distribution of which may affect the validity of the uptake ratios (*32*). Although cerebellum hypometabolism has been observed in alcoholics with cerebellar degeneration (*33*), the absence of symptoms and the seemingly normal appearance of cerebellar perfusion in all the alcoholics studied, led us to consider it the best choice to evaluate rCBF.

Cognitive impairment also was observed in a large proportion of asymptomatic chronic alcoholics. Other neuropsychological studies have demonstrated that chronic alcoholics manifest deficits in abstraction, problem solving

and tasks involving speed and complex perceptual-motor response (*1,2*). Although subdivision of the cerebrum into different lobes has only limited functional validity (*34*), difficulties in categorizing and inflexibility of thinking, assessed by different instruments such as the Weigl color-form and Trail Making tests, are consistent with selective frontal-lobe dysfunction, especially in the absence of severe global impairment (*35–37*). Our sample reflected this situation. In addition, previous studies have demonstrated a loss of neurons, primarily from the frontal cortex (*3,5,38*), which apparently correlates with other CT scan (*6,8,39*), SPECT (*11*) and neuropsychological findings, suggesting that the frontal lobes are more susceptible to ethanol damage than other brain regions (*3,40*).

Brain function is closely related to metabolism (*9*). In our study, neuropsychological deficits were related to both frontal hypoperfusion and frontal atrophy. It is possible that hypoperfusion in frontal areas may be secondary to frontal lobe atrophy, because reduced blood flow is observed when part of the tissue block is missing (atrophy) (*41*). In fact, in the current study most of the patients with frontal atrophy showed hypoperfused areas in the SPECT scans and frontal dysfunction. However, 17 of the 29 nonatrophic alcoholics showed significant hypoperfusion of the frontal lobes and neuropsychological impairment. In patients without frontal atrophy, SPECT abnormalities could be attributed to structural lesions not detected by CT scan-morphometric analysis. These patients may mimic those subjects affected by frontal lobe degeneration who show impairment of frontal neuropsychological tests and cerebral blood flow changes, in the absence of apparent brain atrophy (*42*). However, the fact that brain perfusion normalized after 2 mo of ethanol abstinence suggests that other nonatrophic mediated effects of ethanol cause this situation. Another possibility which deserves consideration is that ethanol may also affect some of the subcortical structures intimately related to the frontal lobes and disrupt one or more of the frontal systems that currently are postulated (*43*).

SPECT changes may be due to cerebral vessel spasms. Previous studies performed on alcoholics during withdrawal syndrome found a significant reduction in the cerebral blood flow, probably due to increases in the concentration of circulating catecholamines (*44,45*). In our study, since none of the patients exhibited alcohol withdrawal symptoms as assessed by the CIWA scale and patients with positive alcoholemia also showed changes in the rCBF ratios of the different ROIs, hypoperfusion of these alcoholics can not be explained by withdrawal syndrome. On the other hand, experimental studies have shown that high concentrations of ethanol cause spasms of brain vessels (*46,47*), either related to changes in the intracellular calcium concentration due to the effect of ethanol on voltage-dependent calcium channels in the muscle fibers of cerebral blood vessels, or by inhibiting the endothelium-dependent relaxation of the blood vessels (*48,49*).

Finally, it is possible that two types of ethanol effects may have a role in brain damage exhibited by chronic alcoholics: a subacute effect on cerebral microcirculation and a more chronic effect on cortical or subcortical structures. The former effect may be explained by the hypoperfusion of the frontal lobes and its correlation with recent ethanol intake. The latter effect may play a part in the origin of the cerebral atrophy exhibited by chronic alcoholics, which correlates with the total lifetime consumption of ethanol.

In summary, two-thirds of patients with active chronic alcoholism exhibited frontal lobe impairment demonstrated by neuropsychological testing and SPECT, independently of brain atrophy. The severity of the hypoperfusion in SPECT scans correlated with recent ethanol intake, suggesting an early effect of ethanol on the central nervous system.

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