12. Mednick SA, Machon RA, Huttenen MO, Barr CE. Influenza and schizophrenia: Helsinki *vs* Edinburgh. *Arch Gen Psychiatry* 1990; **47**: 875–76.
13. Murray RM, Lewis SW, Owen MJ, Foerster A. The neurodevelopmental origins of dementia praecox. In: McGuffin P, Bebbington P, eds. Schizophrenia: the major issues. London: Heinemann, 1988: 90–106.
14. Guy JD, Majorski LV, Wallace CJ, Guy MP. The incidence of minor physical anomalies in adult male schizophrenics. *Schizophr Bull* 1983; **9**: 571–82.
15. Lewis SW, Murray RM. Obstetric complications, neurodevelopmental deviance, and schizophrenia. *J Psychiatr Res* 1987; **21**: 413–21.
16. Weinberger DR, Cannon-Spoor E, Potkin SG, Wyatt RJ. Poor premorbid adjustment and CT scan abnormalities in chronic schizophrenia. *Am J Psychiatry* 1980; **137**: 1410–13.
17. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet* 1976; **ii**: 924–26.
18. Bogerts B, Ashtari M, Degreef GM, Alvir JMAJ, Bilder RM, Lieberman JA. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. *Psychiatr Res Neuroimaging* 1990; **35**: 1–13.
19. Degreef G, Mukherjee S, Bilder R, et al. Season of birth and CT findings in schizophrenic patients. *Biol Psychiatry* 1988; **24**: 461–64.
20. Zipursky RB, Schulz SC. Seasonality of birth and CT findings in schizophrenia. *Biol Psychiatry* 1987; **22**: 1288–92.
21. Bogerts B, Meertz E, Schonfeldt-Bausch R. Basal ganglia and limbic system pathology in schizophrenia. *Arch Gen Psychiatry* 1985; **42**: 784–91.
22. Jakob H, Beckmann H. Gross and histological criteria for developmental disorders in brains of schizophrenics. *J R Soc Med* 1989; **82**: 466–69.

Regional cerebral blood flow and cognitive function in patients with chronic liver disease

R. E. O'CARROLL P. C. HAYES K. P. EBMEIER N. DOUGALL
C. MURRAY J. J. K. BEST I. A. D. BOUCHIER G. M. GOODWIN

Subtle impairments of cognitive function may be an important cause of occupational and psychosocial morbidity in patients with chronic liver disease. Correlation of structural brain abnormalities with cognitive deficits has yielded inconsistent results.

10 patients with cirrhotic liver disease were compared with 10 age, education, and intelligence matched control subjects. Neuropsychological assessment revealed significant overall cognitive impairments in cirrhotic patients compared with controls ($p = 0.02$). Regional cerebral blood flow was measured by single photon emission computed tomography (SPET or SPECT) and showed increased uptake of radiotracer in the right and left posterior parts of the basal ganglia and right occipital lobe, together with reduced uptake in the right anterior cingulate region. The degree of cognitive impairment was directly correlated with functional abnormalities in the basal ganglia and limbic cortex ($p < 0.05$).

Our results suggest that impaired cognitive status may be associated with abnormalities of regional brain function in patients with chronic liver disease. Since these deficits are clinically inapparent, our findings have important implications for identification and management of patients with chronic liver disease.

Lancet 1991; **337**: 1250–53.

Introduction

The encephalopathy that accompanies acute hepatic failure is well known and clinically obvious. The impairment of cognitive function that is found in chronic liver disease is more subtle and less well recognised, but may be an important cause of occupational and psychosocial morbidity.[1,2] Efforts to relate cognitive impairment in liver disease to structural brain abnormalities measured by either computed tomography or magnetic resonance imaging have given conflicting results.[3,4] However, single photon emission tomography (SPET or SPECT) with ^{99m}Tc-'Exametazime' offers an investigation of regional brain function as opposed to structure. Uptake of ^{99m}Tc-Exametazime is related to the regional cerebral blood flow that is normally dependent on local neuronal demand for glucose.[5] We predicted that there would be significant cognitive impairment in patients with chronic liver disease and that this impairment would be associated with changes in regional cerebral blood flow.

Patients and methods

10 patients (7 female, 3 male; mean [SD] age, 57 [8] years) with histologically proven cirrhosis were studied. 5 patients had alcoholic cirrhosis (Child severity scores, A [n = 2] and C [n = 3][6]) and 5 had non-alcoholic-related liver disease (primary biliary cirrhosis, 3 [1 Child B, 2 Child C]; primary sclerosing cholangitis, 1 [Child B]; haemochromatosis, 1 [Child C]). These patients were compared with 10 age (mean 64 [3] years), education (mean 10·6 [1·7] *vs* 10·9 [2·6] years), and premorbid intelligence quotient[7] (110 [9] *vs* 115 [6] points) matched control subjects (8 female, 2 male). These differences were not significant. Cognitive status was assessed by the trail making test (parts A and B), the digit symbol substitution test, and the auditory verbal learning test. Subjects were also assessed by the CAMCOG subsection of the Cambridge mental disorders of the elderly examination.[8] For SPECT scanning, ^{99m}technetium-labelled Exametazime (hexamethyl-propylene-amine oxime) was given as a lipophilic flow marker that is taken up rapidly into brain and trapped by conjugation with glutathione.[9] Subjects were injected with 250 MBq of ^{99m}Tc-Exametazime at rest (eyes patched and ears unplugged). The head was aligned with reference to the orbito-meatal line, and scanned by a tomographic camera with twelve focused photon detectors mounted on a gantry that controlled the radial and tangential excursions of each detector (SME Multi-X 810). Acquisition time per slice was 300 s. The pattern of tracer uptake was reconstructed as 10 mm slices, with a transverse resolution of about 10 mm. Quantitative estimates of tracer uptake (as mean counts per pixel) were measured bilaterally in eighteen regions of interest drawn from two slices 5–6 cm and 7–8 cm above the orbito-meatal line. Regions of interest were identified

ADDRESSES: **Medical Research Council, Brain Metabolism Unit** (R. E. O'Carroll, PhD, K. P. Ebmeier, MRCPsych, N. Dougall, BSc, C. Murray, RMN, G. M. Goodwin, MRCPsych), **Royal Edinburgh Hospital, Edinburgh, UK; Department of Medicine** (P. C. Hayes, MRCP, I. A. D. Bouchier, FRCP), **Royal Infirmary, Edinburgh; Department of Medical Radiology** (J. J. K. Best, FRCP), **Royal Infirmary, Edinburgh.** Correspondence to Dr R. E. O'Carroll, MRC Brain Metabolism Unit, Royal Edinburgh Hospital, Edinburgh EH10 5HF, UK.

TABLE I—COGNITIVE IMPAIRMENT IN STUDY GROUPS

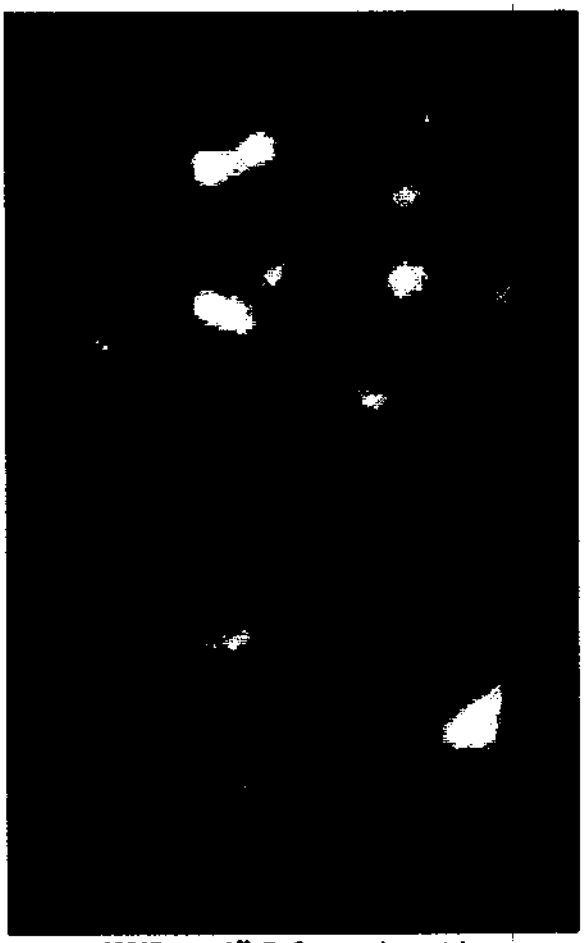
Test	Cirrhotic patients (n = 10)	Controls (n = 10)	F	p
CAMCOG total	92·3 (88·9–95·6)	99·13 (95·9–102·3)	11·07	0·004
AVLT total	36·2 (29·9–42·5)	47·25 (42·2–52·3)	9·13	0·008
AVLT delayed	7·20 (5·4–9·0)	10·00 (7·9–12·1)	5·38	0·034
AVLT recognition	7·20 (2·5–11·9)	12·62 (10·6–14·7)	4·81	0·043
Trail A	52·5 (38·5–66·5)	43·5 (29·7–57·3)	1·07	0·316
Trail B	168·4 (113·0–223·8)	80·13 (62·7–97·6)	9·73	0·007
Digit symbol	7·00 (5·9–8·1)	11·38 (9·6–13·2)	25·26	0·000

Results given as mean (95% CI). Overall MANOVA F = 4·12, p = 0·02. AVLT, auditory verbal learning test.

with a predetermined standard template derived from a neuroanatomical atlas.[10] The uptake of radiotracer was expressed per region of interest as a density function (counts per pixel). SPECT data were normalised by calculation of each regional value relative to the whole slice uptake for each individual. Multivariate analysis of variance was applied to compare regions of interest. Attempts to identify a simple group effect are meaningless because of the normalisation of tracer uptake. The appropriate omnibus test to define an overall effect must be able to measure an interaction between groups both by right/left hemisphere and by region of interest. Between-group comparisons of individual regions of interest were made with univariate ANOVA. Neuropsychological indices were also subjected to multivariate analysis of variance followed by univariate ANOVA. The relation between SPECT scan data and cognitive measures was tested by Pearson's correlation coefficient.

Results

Cirrhotic patients were significantly impaired in all cognitive measures with the exception of the trail making test part A (table I). An overall MANOVA (patients *vs* controls) revealed that significant differences in regional cerebral blood flow existed between the groups (p = 0·002). A characteristic pattern of ^{99m}Tc-Exametazime uptake was identified (table II); chronic liver disease patients showed increased uptake in the right and left posterior parts of the basal ganglia (putamen and pallidum), and in the right inferior occipital lobe. A statistically significant decrease in tracer uptake was observed in the right anterior cingulate. Other areas showed no differences between patients and controls. For example, the uptake to a reference sensory area (calcarine cortex) was equal, as was uptake in high frontal and posterior temporal areas, which are abnormal in organic conditions such as Alzheimer's disease and Korsakoff's psychosis.[11] Representative SPECT scans of a patient and a control subject are shown in the figure to illustrate the pattern of differential uptake in the region of the putamen/pallidum. Slight intersubject variation is a common feature of SPECT scans.



SPECT scan of ^{99m}Tc-Exametazime uptake.

Upper, patient with haemochromatosis; lower, control subject. Exametazime uptake is indicated by bright areas. In the patient, these bilateral brighter regions either side of the lateral ventricles represent the putamen.

To support the pathophysiological significance of abnormal uptake of tracer in individual regions of interest, a limited correlational analysis was completed between each statistically abnormal area of tracer uptake and neuropsychological measures of impairment. Within the patient group, the degree of cognitive impairment was correlated with uptake of radiotracer to the left putamen/pallidum. Statistical significance was reached for digit symbol ($r = -0·76$, $p < 0·05$) and trail making test part B ($r = 0·74$, $p < 0·05$). Trail making test part A correlated positively with uptake to the right putamen/pallidum

TABLE II—REGIONAL CEREBRAL BLOOD FLOW IN STUDY GROUPS

Region of interest	Left			Right		
	Cirrhotic patients	Controls	p	Cirrhotic patients	Controls	p
Frontal (inferior)	0·99 (0·95–1·04)	0·99 (0·93–1·05)	0·98	1·00 (0·95–1·05)	0·99 (0·96–1·03)	0·83
Frontal (superior)	1·07 (1·03–1·12)	1·09 (1·06–1·11)	0·65	1·06 (1·01–1·10)	1·07 (1·04–1·09)	0·68
Anterior cingulate (inferior)	1·07 (1·00–1·14)	1·09 (1·03–1·15)	0·71	1·01 (0·95–1·06)	1·12 (1·08–1·15)	0·002
Anterior cingulate (superior)	1·04 (0·95–1·12)	1·07 (1·02–1·13)	0·43	1·04 (0·99–1·09)	1·10 (1·03–1·17)	0·11
Posterior temporal	1·07 (1·05–1·10)	1·08 (1·05–1·10)	0·76	1·09 (1·05–1·13)	1·08 (1·05–1·11)	0·73
Putamen/pallidum	1·26 (1·20–1·31)	1·19 (1·15–1·23)	0·05	1·26 (1·20–1·31)	1·20 (1·18–1·22)	0·04
Calcarine (inferior)	1·21 (1·21–1·31)	1·23 (1·17–1·30)	0·68	1·25 (1·15–1·35)	1·24 (1·19–1·30)	0·78
Calcarine (superior)	1·31 (1·25–1·36)	1·32 (1·27–1·37)	0·73	1·28 (1·24–1·33)	1·27 (1·21–1·33)	0·71
Occipital (inferior)	1·08 (1·01–1·15)	1·04 (0·98–1·10)	0·35	1·15 (1·10–1·20)	1·07 (1·01–1·13)	0·03
Occipital (superior)	1·06 (1·03–1·10)	1·06 (1·03–1·09)	0·96	1·08 (1·04–1·13)	1·08 (1·04–1·12)	0·93

Results given as mean (95% CI). Overall MANOVA (grouped by right/left hemisphere and by region of interest), F = 453·36, p = 0·002.

($r = 0.71$, $p < 0.05$) and negatively with the right anterior cingulate ($r = -0.70$, $p < 0.05$). Although the trail making test part A does not discriminate patients from controls (table I), within the patient group its score was highly correlated with that of the other timed visuospatial tests that did differentiate the two groups (trail making test part B, $r = 0.79$; digit symbol, $r = -0.75$; both $p < 0.05$). There was no association between tracer uptake to the right inferior occipital lobe and neuropsychological measures.

Discussion

The patients studied in this investigation did not have hepatic encephalopathy that was apparent by bedside clinical assessment. However, detailed neuropsychological examination revealed significant cognitive impairment. The only cognitive measure that failed to differentiate the groups was the trail making test part A, which is essentially the same as the number-connection test.[12] The number-connection test is widely applied as a screening instrument in hepatology clinics, and in a recent review of hepatic encephalopathy, the number-connection test was recommended for routine clinical use.[13] Our results show that patients with liver disease can present with a normal performance on this test but have gross impairment in other cognitive areas, which is in agreement with other reports.[4] The characteristic cognitive deficits appear to be in memory and time-dependent visuospatial tasks. The relation between visuospatial tasks and everyday activities such as driving are obvious. Schomerus et al[14] have estimated that 60% of their patients with "latent" hepatic encephalopathy were unfit to drive, and a further 25% were of dubious driving ability. We agree with Dunk and Moore[1] who suggest that patients with "latent" hepatic encephalopathy who drive or operate heavy machinery may put themselves and others at risk. Such patients are unlikely to be identified by routine clinical application of the number-connection test.

We have identified a relative increase in basal ganglia blood flow, and a decrease in limbic cortex flow, in patients with both alcoholic and non-alcoholic chronic liver disease. Abnormalities of basal ganglia function in patients with liver disease might have been anticipated given the prominent and persistent motor sequelae that can occur in hepatic encephalopathy, such as tremor, rigidity, slurred speech, orofacial dyskinesia, choreoathetosis, and ataxia. Positron emission tomography has revealed increased blood flow in the basal ganglia of patients with liver disease and "minimal encephalopathy".[15] Some evidence of structural change in the caudate nucleus of patients with chronic liver disease has also been provided by both computed tomography and magnetic resonance imaging in alcoholic and non-alcoholic cirrhotics;[3,4] in one study, reduced caudate scan dimensions correlated significantly with neuropsychological measures.[3] Increased GABAergic output from the pallidum, equivalent here to an increase in the uptake of ^{99m}Tc-Exametazime in the posterior portion of the basal ganglia, may feed forward to reduce function in anterior cingulate areas. Involvement of the anterior cingulate cortex in the pattern of dysfunction seen in the brains of patients with liver disease is especially interesting given the current hypothesis that the loop between basal ganglia and anterior cingulate areas subserves attentional mechanisms.[16,17] The neuropsychological impairment in our patients was correlated directly with the abnormality of function in both of these areas.

The differences observed in basal ganglia blood flow are unlikely to represent an "alcohol effect" independent of liver disease. In alcoholic Korsakoff's syndrome we found no differences in basal ganglia or limbic uptake of radiotracer compared with controls.[11] However, one magnetic resonance imaging study suggested changes in cerebral structure, which were largely confined to alcoholic cirrhotics.[4] Alcoholic cirrhotics are likely to have the combined cerebral sequelae of chronic liver disease and direct neurotoxic effects of alcohol,[18] but even in non-alcoholic cirrhotics there is cognitive impairment of the degree found here with computed tomographic evidence of reduced bicaudate diameter.[3]

Our results suggest an abnormality of regional brain function in patients with hepatic cirrhosis, which is both striking and neuropsychologically meaningful. None of the patients studied were recovering from an acute illness or from coma, and it is unlikely that changes in cerebral blood flow represent resolving localised cerebral oedema. The existence of neuropsychological deficits in patients who were not frankly encephalopathic by the usual clinical criteria has important implications for their identification and management. SPECT imaging offers a new method for investigating the underlying mechanisms of hepatic encephalopathy.

We thank the Wellcome Trust for financial support, and Norma Brearley for her careful preparation on the manuscript.

REFERENCES

1. Dunk AA, Moore JW. Cognitive dysfunction in latent portasystemic encephalopathy. In: Crawford JR, Parker DM, eds. Developments in clinical and experimental neuropsychology. London: Plenum, 1989: 39–46.
2. Tarter RE, Edwards KL, Van Thiel DH. Neuropsychological dysfunction due to liver disease. In: Tarter R, Van Thiel D, Edwards K, eds. Medical neuropsychology: the impact of disease on behavior. New York: Plenum, 1988: 75–97.
3. Bernthal P, Hays A, Tarter RE, Van Thiel D, Lecky J, Hegedus A. Cerebral CT scan abnormalities in cholestatic and hepatocellular disease and their relationship to neuropsychologic test performance. *Hepatology* 1987; 7: 107–14.
4. Moore JW, Dunk AA, Crawford JR, et al. Neuropsychological deficits and morphological MRI brain scan abnormalities in apparently healthy non-encephalopathic patients with cirrhosis: a controlled study. *J Hepatol* 1989; 9: 319–25.
5. Sokoloff L. Localisation of functional activity in the central nervous system by measurement of glucose utilisation with radioactive deoxyglucose. *J Cereb Blood Flow Metab* 1981; 1: 7–36.
6. Pugh RNH, Murray-Lyon IM, Dawson JL, Pretroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60: 646–49.
7. Nelson H. The National Adult Reading Test (NART): test manual. Windsor: NFER-Nelson, 1982.
8. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br J Psychiatry* 1986; 149: 698–709.
9. Neirinckx RD, Burke JF, Harrison RC, Foster AM, Anderson AR, Lassen NA. The retention mechanism of Technetium-99m HMPAO: intracellular reaction with glutathione. *J Cereb Blood Flow Metab* 1988; 8: S4–12.
10. Matsui T, Hirano A. An atlas of the human brain for computerized tomography. New York: Gustav Fischer, 1978.
11. Hunter R, McLuskie R, Wyper D, et al. The pattern of function-related regional cerebral blood flow investigated by single photon emission tomography with ^{99m}Tc-HMPAO in patients with presenile Alzheimer's disease and Korsakoff's psychosis. *Psychol Med* 1989; 19: 847–55.
12. Conn HO. Trailmaking and number connection tests in the assessment of mental state in portal systemic encephalopathy. *Am J Dig Dis* 1977; 22: 541–50.
13. Gammal SH, Jones EA. Hepatic encephalopathy. *Med Clin North Am* 1989; 73: 793–813.