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Evidence for a cerebral effect of the hepatitis C virus

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Patients with hepatitis C virus (HCV) infection frequently complain of symptoms akin to the chronic fatigue syndrome and score worse on health-related quality of life indices than matched controls. We address the hypothesis that HCV itself affects cerebral function. Using proton magnetic-resonance spectroscopy we have shown elevations in basal ganglia and white matter choline/creatine ratios in patients with histologically-mild hepatitis C, compared with healthy volunteers and patients with hepatitis B. This elevation is unrelated to hepatic encephalopathy or a history of intravenous drug abuse, and suggests that a biological process underlies the extrahepatic symptoms in chronic HCV infection.

Lancet 2001; **358**: 38–39

Several studies have shown that patients with chronic hepatitis C virus (HCV) infection score worse than matched controls on health-related quality of life indices and that their scores improve with successful antiviral treatment.¹ These findings agree with the clinical observation that such patients frequently complain of fatigue, lassitude, impaired memory (“brain fog”) and a perceived inability to function effectively, even in the absence of clinically significant liver disease. It is not known whether social, psychological, or biological factors cause these complaints.

We considered that HCV infection itself may affect cerebral function and looked at cerebral choline/creatine ratios with proton magnetic-resonance spectroscopy (¹H MRS) in patients and controls. 30 patients with histologically defined mild chronic HCV infection were randomly selected. Liver biopsies showed mild inflammation only, with no cirrhosis or significant fibrosis.

	Mean age (range)	Men (%)	Mean NI score	Mean fibrosis score
HCV (n=30)	44 (31–57)	14 (47)	2.4	1.0
Hepatitis B (n=12)	35 (21–59)	11 (92)	3.8	1.9
Healthy volunteers (n=29)	42 (30–54)	15 (52)

Liver biopsies were scored using the Ishak criteria. The necroinflammatory (NI) index is scored out of 18; the fibrosis index is scored out of 6.

Table 1: **Study group characteristics**

	Basal ganglia		White matter	
	Mean Cho/Cr	p	Mean Cho/Cr	p
HCV	1.17 (0.14)	0.01	1.35 (0.22)	0.001
Controls	1.06 (0.13)		1.18 (0.14)	
HCV	1.17 (0.14)	0.02	1.35 (0.22)	0.009
Hepatitis B	1.04 (0.14)		1.16 (0.12)	
Hepatitis B	1.04 (0.14)	1.00	1.16 (0.12)	1.00
Controls	1.06 (0.13)		1.18 (0.14)	
IVDU+	1.15 (0.16)	0.98	1.35 (0.23)	1.00
IVDU–	1.20 (0.10)		1.34 (0.21)	
IVDU–	1.20 (0.10)	0.02	1.34 (0.21)	0.04
Controls	1.06 (0.13)		1.18 (0.14)	
IVDU+	1.15 (0.16)	0.08	1.35 (0.23)	0.003
Controls	1.06 (0.13)		1.18 (0.14)	

Groups were compared with a one-way ANOVA and between group comparisons performed using post-hoc contrasts with a Bonferroni adjustment for multiple comparisons. p values greater than 1.00 are rounded down to 1.00.

Table 2: **Mean choline/creatine ratios (SD) from the basal ganglia and white matter**

¹H MRS was also performed in 29 age-matched and sex-matched healthy controls and in 12 patients with chronic hepatitis B. 20 (67%) patients with HCV infection, but no healthy controls or patients with hepatitis B infection, gave a history of intravenous drug use (IVDU).

All subjects underwent cerebral MRS, using a 1.5T Eclipse spectroscopy system (Marconi Medical Systems, Cleveland, OH, USA). We used T1-weighted magnetic-resonance (MR) images to exclude organic brain disease and to position the voxels of interest. We positioned three 8 cm³ voxels; in the basal ganglia, in the white matter at the level of the centrum semiovale, and in the occipital grey matter. We then performed single voxel ¹H MRS examinations with an automated PRESS sequence (TR/TE 1500/135 ms, 128 acquisitions). MR spectra were analysed by a single blinded observer. Peak areas were measured for choline (Cho), creatine (Cr) and N-acetylaspartate (NAA). Ratios for NAA/Cr and Cho/Cr were calculated and compared with a one-way analysis of variance (ANOVA) with post-hoc comparisons, using contrasts (SPSS version 9).

A neuroradiologist reviewed the MR images. One patient had an arachnoid cyst. There was no evidence of cerebral vasculitis or white-matter abnormalities in any of the patients or controls. The metabolite ratios were normally distributed. There were no differences in the grey matter metabolite ratios between the patients with HCV, healthy controls, and hepatitis B controls. However, the Cho/Cr ratios were significantly higher in the white matter and basal ganglia of the HCV group compared with both the hepatitis B group and healthy volunteers (table 2).

A second ANOVA was performed to compare the Cho/Cr ratios in HCV patients with and without a history of IVDU with the control groups. There were no statistically significant differences in the ratios between the HCV patients with a history of IVDU and those without. The mean alanine aminotransferase concentration was higher in the hepatitis B group than in the HCV group (93 vs 47 IU/L respectively, p<0.03), but no association was found between the concentration of alanine aminotransferase and the metabolite ratios in the HCV or hepatitis B group. There was also no association between viral genotype or liver biopsy score and the cerebral metabolite ratios.

These data demonstrate cerebral ¹H MRS metabolite abnormalities in patients with histologically defined mild HCV infection. Patients with significant fibrosis or

cirrhosis were excluded from the study so we can conclude that the findings are not due to minimal hepatic encephalopathy. Indeed, spectroscopic studies of hepatic encephalopathy show globally reduced Cho/Cr ratios.² We found no statistically significant differences in ¹H MRS between HCV patients with or without a history of IVDU.

A number of cerebral MRS studies have investigated the effect of illicit drug use, but neither chronic use of cocaine or heroin has been found to increase cerebral choline-containing compounds.³ It is therefore unlikely that a history of IVDU underlies the MR abnormalities in the HCV group. In ¹H MRS the choline resonance mainly reflects intracerebral phospholipid cell membrane precursor and degradation products and is increased in conditions where there is cellular proliferation, most notably in inflammatory or infective conditions such as multiple sclerosis, or HIV infection.

Similar metabolite abnormalities in the same spatial distribution to those reported here have been extensively documented in cerebral HIV infection, in patients both with and without neurological symptoms.⁴ Infection of cerebral microglia by HIV, possibly via infected monocytes, and subsequent microglial activation are thought to underlie the MRS changes. There is good evidence to suggest that HCV infects cells of monocytic lineage,⁵ raising the possibility that HCV too may infect the brain. An alternative explanation for these findings is a centrally mediated effect of peripherally derived cytokines, either via their transfer across the blood-brain barrier or through an interaction with the cerebral vascular endothelium and the generation of secondary messengers. Our preliminary data suggest that there is altered cerebral metabolism in patients with chronic HCV infection which cannot be explained by hepatic encephalopathy or a history of drug use. These findings have implications for the direction of future research and ultimately for patient treatment.

We thank Mark Wright, Peter Karayiannis of the Hepatology section, ICSM and Glyn Coutts, Alison Fletcher, Serena Counsell, and Louise Goff of the Robert Steiner MR Unit, Hammersmith Hospital for their help with this study. We also thank Professor Graeme Bydder for neuroradiological advice. This work was partly supported by Marconi Medical Systems International (Cleveland, OH, USA) and the Medical Research Council, UK.

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Effects of fenofibrate and gemfibrozil on plasma homocysteine

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Fenofibrate increases plasma homocysteine. Because the concentration of plasma homocysteine depends on renal function, we postulate that increases in plasma homocysteine are a result of the known impairment of renal function caused by fenofibrate. Gemfibrozil, another fibrate, does not affect renal function. In a crossover study we tested whether gemfibrozil would raise homocysteine. 22 patients who had hypertriglyceridaemia were given 900 mg gemfibrozil or 200 mg fenofibrate daily for 6 weeks. Lipids were altered similarly, but homocysteine, creatinine, and cystatin C were raised by fenofibrate but not by gemfibrozil (p for differences between treatment effects: 0.007, 0.006, and 0.040, respectively). We propose gemfibrozil should be the fibrate of choice.

Lancet 2001; **358**: 39–40

Fenofibrate and bezafibrate raise plasma homocysteine,¹ which means that three to four million patients worldwide who are being treated with these drugs may develop iatrogenic hyperhomocysteinaemia. Because raised plasma homocysteine is regarded as an independent cardiovascular risk factor, this adverse effect can counteract the desired cardiovascular protection conferred by lipid lowering. Plasma homocysteine concentrations depend on renal function. We postulate that impairment of renal function by fenofibrate and bezafibrate is the underlying cause of raised plasma homocysteine. Gemfibrozil, another fibrate, has no effect on renal function.² We aimed to confirm that, unlike fenofibrate and bezafibrate, gemfibrozil does not raise plasma homocysteine concentrations.

22 men with hypertriglyceridaemia (2.7–57.5 mmol/L) who attended a lipid clinic at the University Hospital, Magdeburg, Germany were included consecutively in our randomised crossover trial. The age range was 36–66 years and the body-mass index was 25–37 kg/m². Patients with type III hyperlipoproteinaemia, thyroid dysfunction, and serum creatinine of more than 110 µmol/L were excluded. The Ethics Committee of the University Hospital Magdeburg approved the protocol and all patients gave their written informed consent. Before and between the two medication periods patients did not receive lipid-lowering drugs (wash-out periods). The duration of each wash-out and treatment period was 6 weeks. The patients and the investigator remained unaware of all laboratory results until the end of the study.

During the medication phases the patients received 900 mg gemfibrozil per day or 200 mg micronised fenofibrate once daily. At baseline and at the end of the treatment blood samples preceded by overnight fasting were taken for measurement of lipids, plasma homocysteine, cystatin C, creatinine, folate, vitamin B₆, vitamin B₁₂ (cobalamin), and creatine kinase. The blood samples were immediately cooled and serum was prepared within 2 h and stored at –20°C. To measure serum lipids and HDL-cholesterol the slightly modified Lipid Research Clinics methodology was used. Triglycerides, cholesterol, creatinine, and creatine-kinase activity were measured by commercial enzymatic methods (Roche Diagnostics, Mannheim, Germany). Plasma homocysteine was measured by high-performance liquid chromatography with fluorescence detection after derivatisation, in a single run to minimise day-to-day variation. Cobalamin and folate were measured with commercial test kits (Abbott,