Alterations of globus pallidus magnetisation transfer ratio, T_1, T_2 in Primary Biliary Cirrhosis patients and controls: relationship with age and autonomic dysfunction

K. G. Hollingsworth[1], J. L. Newton[2], B. S. Aribisala[1], P. E. Thelwall[1], R. Taylor[1], A. M. Blamire[1], and D. E. Jones[2]

[1]Newcastle Magnetic Resonance Centre, Newcastle University, Newcastle Upon Tyne, Tyne and Wear, United Kingdom, [2]Liver Research Group, Newcastle University, Newcastle Upon Tyne, Tyne and Wear, United Kingdom

Introduction Primary Biliary Cirrhosis (PBC) is an autoimmune chronic cholestatic liver disease which affects up to 20,000 patients in the UK. At least 50% of the patients with the condition will develop severe, debilitating fatigue which is unrelated to underlying liver disease severity [1]. A clear link has been demonstrated between fatigue and abnormalities of the autonomic nervous system (e.g. blood pressure homeostasis) [2]. Recent work has shown imaging abnormalities in the globus pallidus (GP) which may be associated with accumulation of manganese not removed from the blood due to cholestasis or occupational over-exposure [3,4]. It is postulated from animal models that interruption of the HPA axis could be a mechanism for fatigue [5]. A previous imaging study in a small (n=14) group of early-stage (pre-cirrhotic) PBC patients suggested that magnetisation transfer ratios (MTRs) in GP are reduced in all PBC patients compared with controls, and that this reduction was correlated with fatigue [4]. However, this study did not control for the effect of age on GP MTR parameter, or have an age-matched control group. The literature on age-related changes of T_1, T_2 and MTR in the globus pallidus is scarce and equivocal [6,7], although significant age-related changes have been shown in other brain regions [6]. Given the potential importance of GP relaxometry to elucidating the mechanisms of fatigue in PBC, in this study we examined a larger age-matched cohort of PBC patients and controls using MTR and quantitative relaxometry (T_1 and T_2) to examine in detail (i) the relationship between GP MTR, T_1 and T_2 and subject age in PBC patients compared to matched controls and (ii) the relationship between GP MTR, T_1 and T_2 and autonomic dysfunction in the patients.

Methods 30 early-stage (Scheuer stage I-II) PBC patients were recruited from our specialist clinic together with 14 age-matched controls (patients - range 37-77y median 60.3y, controls - range 40-73y median 59.8y). A Fatigue Impact Score (FIS) was calculated for controls (median 5.5, range 0-39) and patients (median 48, range 0-160) by means of a previously-validated questionnaire (0 = no fatigue, 160 = severe fatigue) [4]. All examinations were performed on a 3T Philips Achieva (Best, NL) using an 8-channel SENSE head coil. A high-resolution anatomical scan and three quantitative scans were collected (a) a magnetisation transfer scan (matrix 256x192, TR/TE/NEX=2900ms/20ms/1, 1100Hz off-resonance, 700^o flip angle), (b) a fast T_1 measurement using a custom IR-EPI sequence (TR/TE/TI/NEX = 15s/24ms/0.25-2.5s(12 steps)/1), matrix 128x96 and, (c) a T_2 measurement (GraSe, TR/TE/NEX = 3000ms/22.5-180ms(8 echoes)/1, TSE factor 8, EPI factor 5, matrix 256x192). 26 axial sections (3mm thick/0.3mm gap, FOV 250m) with coverage from pons to corpus callosum were acquired. A low-resolution fieldmap was recorded using a dual echo 3D GRE (TR/TE=27ms/2.6,6.1ms) for distortion correction of the EPI data. Local ethics approval was granted for this study. Autonomic function was assessed by continuous beat-to-beat digital photophlethysmography (Taskforce;CNSystems) to obtain blood pressure (BP) and autonomic variables (heart rate variability, baroreflex sensitivity, BRS) during 10 mins supine rest, in response to standing and during a Valsalva manoeuvre: this was performed by blowing into a tube at 40 mmHg for 15 s. This is used in the assessment of adrenergic function and produces a blood pressure curve which divides into four phases attributable to mechanical, sympathetic and cardiomotor adrenergic function. The blood pressure changes between the phases are calculated, together with the total time that the systolic blood pressure is below baseline. Analysis was blinded to fatigue and liver disease status. *Analysis:* MTR values and quantitative T_1 and T_2 times were calculated on a pixel-by-pixel basis using standard algorithms: all images were registered to the anatomical scan. Using the anatomical scan, regions of interest were defined bilaterally in the globus pallidus. The bilateral ROI values were then averaged from the MTR, T_1 or T_2 maps. Statistical comparisons between the MR data and the autonomic function parameters used multivariate analysis to incorporate any age effect. All analysis was performed blinded to the clinical data.

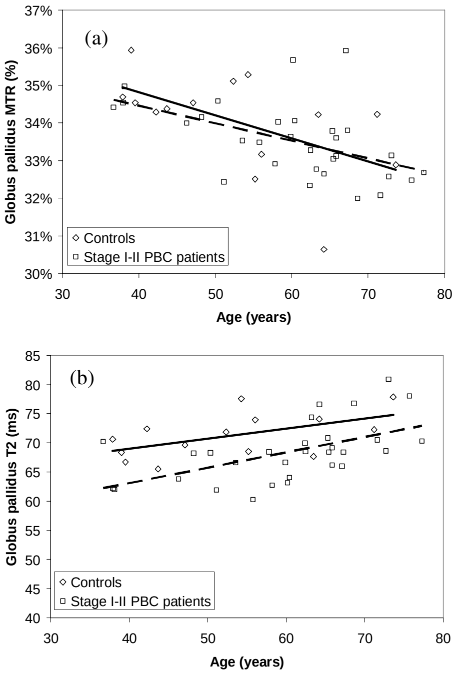

Fig 1: Relationship between globus pallidus (a) MTR and (b) T_2 with subject age comparing early stage PBC patients (dashed line) and matched controls (solid line).

Results ***(i)*** No significant difference was found between the control group and PBC patients for GP T_1 or MTR, though the patients had significantly reduced GP T_2 (table 1).

(ii) For both PBC patients and controls, patient age and GP MTR were negatively correlated (patients, r=-0.51,p=0.002, controls, r=-0.55,p=0.022: fig 1a), and GP T_2 was positively correlated with age (patients: r=0.57, p=0.001, controls: r=0.55, p=0.022: fig 1b). These results contrast with the healthy controls studied in [7] where ROI-based analysis detected no change in MTR with age. There was no correlation of T_1 with age in either group.

(iii) In the early stage patients, two of the blood pressure parameters measured during the Valsalva manoeuvre were found to correlate with GP T_2, allowing for age. Of these two measures, (i) a reduction in the blood pressure change between phase III and phase IV, and (ii) an increase the total time below baseline blood pressure are considered indicators of sympathetic failure. The correlations were significant for the patients, allowing for age (figs 2a and 2b) but were absent in the control subjects. For each variable the worsening of the sympathetic function correlated with increased GP T_2.

(iv) No relationship was found between patient fatigue (as indicated by FIS) and any of the MRI parameters studied. It was noted that in an additional 4 PBC patients studied with cirrhosis, the MTR and T_1 of the globus pallidus was reduced by up to 27%, mirroring measurements made in cirrhotic patients of other etiologies. A substantial reduction in globus pallidus MTR and T_1 appears to be a marker of end-stage disease.

Conclusions Measurements of globus pallidus T_2 and MTR have been found to be similarly correlated with age in PBC patients and controls. This means that age must be controlled for when comparing these MR parameters against fatigue or autonomic dysfunction. In this study, after controlling for the age effect, increases in globus pallidus T_2 occurred in association with autonomic dysfunction in PBC, as represented by two measures of sympathetic failure. An increase in T_2 concomitant with a decrease in MTR may indicate an increase in intra- and extra-cellular tissue water due to cell loss, representing an ageing process. The group change in T_2 between controls and PBC patients may be due to iron deposition in the patients. Our study found no relationship between fatigue status and GP MTR, T_1 or T_2 in PBC.

Acknowledgements MRC Grant G0500020 for funding, Carol Smith, Louise Morris, Jessie Pairman and Katherine Wilton.

References [1] Jones DEJ, *J. Hepatol.* 2003;39:639-648 [2] Newton JL, *Hepatol.* 2007;45:1496 [3] Dietz MC *Environ. Res.* 2001;85: 37 [4] Forton D, *Gut* 2004;53:587-592 [5] Swain MG *Hepatol.* 1997 ;25 :291 [6] Ge Y *AJNR* 2002;23:1334 [7] Mehta RC *AJNR* 1995;16:2085.

Table 1: Globus pallidus properties in controls and patients: ($^\$$ $p < 0.05$)

	MTR (%)	T_1 (ms)	T_2 (ms)
Controls	34.0 ± 1.3	901 ± 61	71.2 ± 3.8
PBC patients	33.5 ± 1.0	901 ± 52	68.4 ± 5.1$^\$$

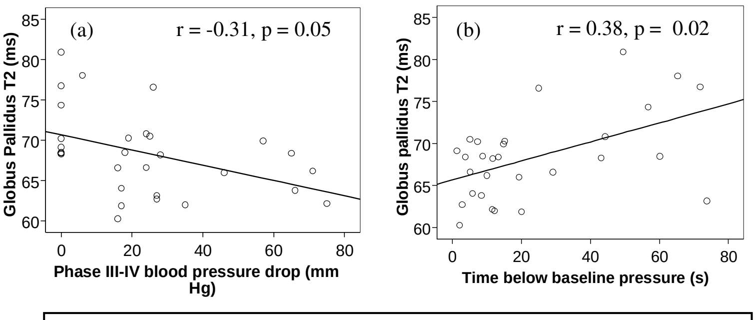

Fig 2 : Correlation between globus pallidus T_2 and (a) Phase III-IV blood pressure drop and (b) time below baseline blood pressure, both assessed during a Valsalva manoeuvre.