Magnetisation transfer ratio (MTR) of basal ganglia in primary biliary cirrhosis (PBC) patients: correlation with fatigue impact score and age

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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 fatigue which is unrelated to underlying liver disease severity [1,2], but which is a significant impairment to quality of life. Little is known about pathogenic mechanisms although a clear link has been demonstrated between fatigue and abnormalities of the autonomic nervous system (e.g. blood pressure homeostasis). It has previously been observed in a small group of PBC patients that magnetisation transfer ratios (MTRs) in the globus pallidus are reduced compared with normal individuals, and that this reduction may be correlated with fatigue and/or liver disease severity [3]. This MTR change is thought to reflect manganese accumulation, causing reduction in local T_1 (and to a lesser extent T_2), since blood magnanese levels are elevated in this disease. In this study we examined a large cohort of PBC patients using MTR and quatitative relaxometry to examine in detail the correlation between brain abnormalities and fatigue in PBC.

Methods

Subjects: 22 patients with previously diagnosed PBC (confirmed by AMA test and/or compatible liver histology) were recruited along with 6 age-matched controls (patients - range 38-77y median 60.3y, controls - range 39-73y median 59.8y, p=0.91, Mann-Whitney test). A Fatigue Impact Score (FIS) was calculated for patients and controls by means of a previously-validated questionnaire [4].

MR protocol: All examinations were performed on a 3T Philips Achieva (Best, NL) using an 8-channel SENSE head coil. A high-resolution anatomical scan was collected for definition of regions of interest (matrix 400x300, TR/TE/NSA = 2000ms/15ms/1, TSE factor 10). Three quantitative scans were acquired for each individual (a) a magnetisation transfer scan (matrix 256x192, TR/TE/NEX=2900ms/20ms/1, 1100Hz off-resonance, 700° flip angle), (b) a fast T1 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 T2 measurement (GraSe, TSE factor 8, EPI factor 5, matrix 256x192). In all cases, 26 axial sections (3mm thick/0.3mm gap, FOV 250m) with coverage from pons to corpus callosum were acquired. Finally, 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.

Analysis: MTR values and quantitative T1 and T2 times were calculated on a pixel-by-pixel basis using standard algorithms. Using the anatomical scan, regions of interest were defined bilaterally in the globus pallidus, putamen, frontal white matter and head of the caudate nucleus and applied to the quantitative scans. The bilateral ROI values were then averaged. Statistical comparisons were performed between subject groups using non-parametric statistics. All analysis was performed blinded to the clinical data.

Results

(i) The FIS results for patients and controls are shown in figure 1. A range of 0-120 was measured within the group and a cut-off value of 60 was used to divide the patients into two groups representing low fatigue and high fatigue. Figure 2b shows the MTR measured in the globus pallidus for the 3 groups. There was a significant difference between the globus pallidus MTR measured in control subjects and those patients with high fatigue ($p < 0.039$) though the high fatigue group is heterogeneous. The difference between the globus pallidus MTR for the control and low fatigue groups did not reach significance with these patient numbers.

(ii) It was found that the MTR values measured in the globus pallidus correlated with those observed in the white matter, putamen and head of caudate, although the % change in MTR was smaller than in the globus pallidus (table 1). Group differences however did not achieve significance.

(iii) For the cohort of patients and controls, a significant correlation was found between 1/T1 and 1/T2 in the globus pallidus (Spearman rho 0.43, p = 0.008). The ratio of the changes of $1/T_1$ to the change in $1/T_2$ for this correlation was 0.46, which is in agreement with the literature on the effect of chelated manganese and a previously measured ratio in cirrhotic hepatitis C patients, (also thought to be manganese deposition) was 0.52 [5]. This alteration ratio is too large to be due to iron (0.07) *in vivo* [6].

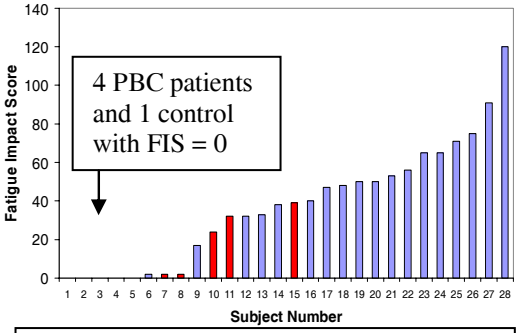

Fig 1 : Fatigue impact scores for PBC patients (blue) and controls (red).

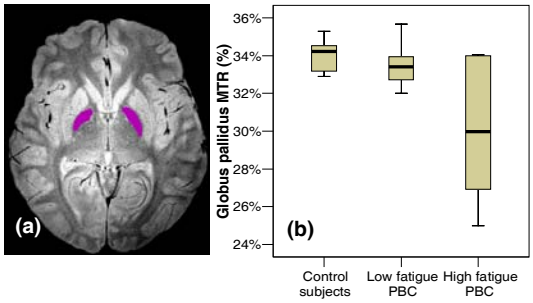

Fig 2 : (a) Anatomical image with globus pallidus ROIs. (b) Magnetisation transfer ratios (MTR) for globus pallidus, illustrating the difference between the control subjects, PBC patients with low fatigue (FIS < 60) and high fatigue (FIS>60).

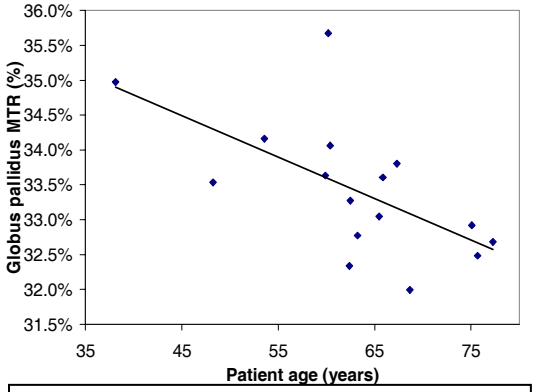

Fig 3 : Correlation between globus pallidus MTR and age within the low fatigue group $\kappa = -0.51$, $p = 0.02$ (n=16)

(iv)A correlation was also found between globus pallidus MTR and patient age (Spearman rho -0.51, p=0.021) amongst the low fatigue group (fig 3), suggesting that Mn accumulation may be a progressive feature of PBC, though fatigue is not a progressive feature of the disease.

Conclusions

This study has shown that for high fatigue PBC patients globus pallidus MTR is reduced compared to controls. There is the suggestion that there may be a link between age and globus pallidus MTR, which may dilute the association with fatigue for FIS < 60. The T_1 and T_2 data, recorded directly for the first time for this disease, are consistent with Mn as the causative agent of MTR change. Further studies, with a larger number of patients with high FIS (>60) may allow us to stratify the disease within the currently heterogeneous high fatigue group.

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Table 1 : Median MTR scores for control subjects, low and high fatigue PBC groups. % reduction from control shown in parentheses

	Control	Low fatigue PBC	High fatigue PBC	Correlation with globus pallidus MTR (Spearman rho,p value)
Globus Pallidus	34.2	33.4	30.0 (12.3%)	-
White Matter	34.6	35.4	33.4 (3.5%)	0.52, 0.003
Head of caudate	30.3	29.7	28.8 (2.0%)	0.64, 0.0005
Putamen	31.6	30.7	29.7 (2.9%)	0.70, 0.0005

References

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