Autonomic dysfunction in Primary Biliary Cirrhosis (PBC) is associated with structural brain abnormalities, particularly in the globus pallidus

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Introduction: Primary Biliary Cirrhosis (PBC) is a chronic cholestatic liver disease that affects up to 20,000 UK patients [1]. The conventional view in PBC is that patient risk arises entirely from progression of the disease to end-stage liver failure. Our previous studies have demonstrated that this view is incorrect and that a complex collection of symptoms, including debilitating fatigue and cognitive impairment, is commonly found in PBC patients. Recent pilot studies have demonstrated poorer performance on cognitive testing in PBC patients compared to controls: this is associated with abnormalities of autonomic nervous system regulation of blood pressure, particularly hypotension [2]. The link between cognitive decline and white matter lesions has been established in dementia [3], but no systematic investigation of the prevalence of structural brain lesions and their relationship with autonomic nervous system function has been performed in PBC. White matter lesions appear bright on T2-weighted imaging owing to the replacement of healthy cells by increased tissue water (fig 1). As part of a larger MRC study of the mechanisms of fatigue in PBC, MR images were used to investigate the relationship between structural brain lesions (white matter lesions) and autonomic dysfunction (AD) in early-stage PBC patients.

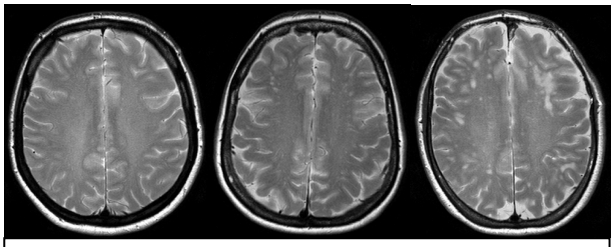

Figure 1 : Three typical T2 weighted images depicting: *left,* no discernable white matter lesions in a control subject, *middle* a moderate lesion load in a PBC patient, *right* a severe lesion load in a PBC patient.

Methods: 29 females with early stage (Stage 1 or 2) PBC attended the cardiovascular investigation unit for assessment. Subjects were excluded if they had a current or previous history of hypertension or encephalopathy or were taking any medications that could influence autonomic function. Subjects all attended the unit having refrained from caffeine and having eaten only a light breakfast. All measurements were performed at the same time of day in a room with constant ambient temperature. Autonomic function was assessed supine during a 10 minute rest. Baroreflex sensitivity (BRS) was performed using the sequence method and heart rate variability (HRV) using spectral analysis with the continuous beat-to-beat Taskforce system (CNSystems, Austria). *MRI protocol:* High-resolution T2w images (TR/TE = 2000/60ms, 0.49x0.49mm, 3mm thick) were acquired using a Philips 3T Intera Achieva (Best, NL) with a dedicated head coil. Two trained, independent observers used thresholding software to identify and measure the size and location of the white matter lesions. The Scheltens scale of lesion assessment [4] was used as a way of quantifying the severity of the white matter lesions (table 1) and a consensus score was calculated for each of thirteen defined anatomical regions (table 2). Due to the use of T2 weighted images assessments of ventricular caps and bands were not performed. Formal statistical testing was then performed on the autonomic test results of these patients to determine whether the lesion load correlated with autonomic dysfunction.

Table 1 : Scheltens rating scale used for grading the severity of white matter lesions

Score	Lesion diameter (largest)	Lesion number
0	No abnormalities	None
1	≤ 3 mm	≤ 5
2	≤ 3 mm	≥ 6
3	4-10 mm	≤ 5
4	4-10 mm	≥ 6
5	≥ 11 mm	≥ 1
6	Confluent lesions	-

Table 2 : Inter-observer kappa for two independent observers scoring the lesions according to the Scheltens scale.

Group	Region	Median lesion load	Interobserver κ
White matter	Frontal	3	0.86
	Parietal	2	0.77
	Occipital	1	0.64
	Temporal	2	0.69
Basal ganglia	Caudate Nucleus	1	0.58
	Putamen	0	0.53
	Globus Pallidus	1	0.77
	Thalamus	1	0.70
	Internal/External Capsule	1	0.69
Infra-tentorial	Mesencephalon	1	0.70
	Pons	0	0.56
	Medulla	0	0.73
	Cerebellum	0	0.63

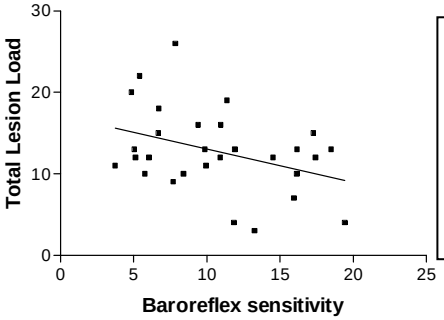

Figure 2: Negative correlation between total lesion load (as assessed on the Scheltens scale) and baroreflex sensitivity in study subjects (p = 0.03, r = -0.4)

Results: A large number of white matter lesions were found, the distribution of which was found to be similar to that observed in dementia [3] (table 2), with the most severe lesions being typically found in the frontal lobe, and more lesions identified in the white matter rather than the basal ganglia or infra-tentorial regions. As the images were analysed by two independent observers, interobserver values were calculated to evaluate consistency between them, see table 2. For larger regions, there was greater consistency in lesion identification and grading between observers. Certain areas of the brain stem (i.e. the pons) were difficult to assess owing to variations in normal appearance. BRS correlated with Total Lesion Load (TLL): reduced BRS was associated with greater TLL, see figure 2. When individual brain areas were considered the lesion load in the globus pallidus inversely correlated (using non-parametric testing) with impaired BRS (p=0.03, r=-0.4). It was found the total lesion load did not correlate with age or fatigue severity (FIS).

Conclusion: AD in PBC is associated with structural brain abnormalities when assessed using MR techniques. These abnormalities are found particularly in those brain areas that are associated with autonomic nervous system function. This suggests that the AD seen in PBC arises secondary to central effects. Further dynamic and longitudinal studies are needed to determine the nature of the association between AD and structural brain lesions in PBC.

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