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ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

A Predictive Model for Fatigue and Its Etiologic Associations in Primary Biliary Cirrhosis

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Background & Aims: **Excessive day-time somnolence and autonomic dysfunction are biological processes prevalent in Primary Biliary Cirrhosis (PBC) that associate with fatigue. Here we explore how these biological associates inter-relate, and their cumulative impact upon typical clinical cohorts.** ***Methods:*** **A predictive model for daytime hypersomnolence (Epworth Sleepiness Scale (ESS)) and autonomic dysfunction (Orthostatic Grading Scale (OGS)) was developed in a derivation cohort (n=124) and subsequently validated in a second cohort (n=114). Subjects also completed the disease specific quality of life tool, the PBC-40.** ***Results:*** **A composite predictive criterion (presence of either ESS ≥10 or OGS ≥4) for the presence of fatigue in PBC patients had a sensitivity of 0.71 (95% confidence intervals 0.59-0.81) and specificity 0.8 (0.67-0.9) (positive predictive value (PV); 0.84 (0.72-0.92), negative PV; 0.66 (0.53-0.78) for moderate or severe fatigue). Ninety-seven percent of severely fatigued patients (0% of non-fatigued) met the aetiology predictive criterion (χ^2 49.6, $P<.0001$). Expression of both significant daytime somnolence and autonomic dysfunction was not associated with more severe fatigue, suggesting that there is a threshold effect for fatigue in PBC. When applied to a second independent cohort, the composite criterion retained strongly significant predictive value for fatigue.** ***Conclusions:*** **A significant proportion of fatigue in PBC associates with one or both of autonomic dysfunction (OGS ≥4) and sleep disturbance (ESS ≥10). Those meeting both ESS and OGS criteria were not more severe fatigued than those meeting the diagnostic criterion for either OGS or ESS alone. A threshold effect for fatigue has implications for potential therapeutic interventions.**

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease that affects up to 1 in 700 women older than the age of 45 in the United Kingdom.[1] For many years the principle clinical goal in PBC has been to slow the progression to end-stage liver disease with its associated morbidity and mortality. Although this remains an important clinical goal (PBC is associated with significant mortality within its affected patient group including a significant component resulting directly from end-stage liver disease), it is becoming clear that PBC patients experience additional clinical problems, and that there are new clinical challenges to be faced by physicians who manage PBC patients.[2] PBC patients experience significant impairment of their quality of life for reasons that are largely independent of the severity of their underlying liver disease.[3–5] Although the impact of itch in the experience of PBC patients has been recognized for a long time, only more recently has it become appreciated that a significant proportion of PBC patients also experience a symptom complex consisting of fatigue, symptoms suggestive of cognitive dysfunction, and social and emotional dysfunction.[6] Given the apparent impact of this fatigue-based symptom complex in PBC patients, significant recent effort has gone into understanding the mechanisms that might underpin it.

Two significant biological processes have been identified recently that appear to be prevalent in PBC patients and to be associated with the fatigue symptom complex. The strongest association is with abnormality in sleep patterns with, in particular, excessive daytime somnolence.[3,7,8] Self-report of daytime somnolence in PBC patients is frequent and the degree of fatigue experienced by patients correlates with perception of degree of daytime sleep.[7] Moreover, objective sleep testing suggests a move from nighttime to daytime sleep, with a significant association between actual minutes of daytime sleep and fatigue severity. The presence of significant sleep abnormality in PBC patients has been postulated to reflect the presence of a chronic secondary central nervous system process occurring as a result of chronic inflammation and/or cholestasis. The second biological process seemingly associated with fatigue in PBC patients is autonomic dysfunction. Objective clinical features suggestive of autonomic dysfunction (including abnormality in heart rate variability, in blood pressure regulation in the context of the Valsalva maneuver, and after tilt testing) is frequent in PBC patients[9] and the degree of abnormality appears to be associated with severity of fatigue.[10–12] Population studies using validated symptom assessment tools suggest that symptoms

Abbreviations used in this paper: CI, confidence interval; ESS, Epworth Sleepiness Scale; OGS, Orthostatic Grading Scale.

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Table 1. Clinical Features of the Independent Development (NE1-25 Geographically Based Cohort) and Validation PBC Cohorts (Clinic-Based Cohort)

	Development cohort	Validation cohort
n	124	114
Age, *y*	62 ± 13	64 ± 11
Bilirubin level, *μmol/L*	21 ± 12	13 ± 15
Albumin level, *g/L*	40 ± 3.4	41 ± 4.0
Alkaline phosphatase level, *IU/L*	171 ± 208	170 ± 190
Disease stage at last biopsy (%) No biopsy/cirrhotic/precirrhotic	29 (23)/29 (23)/66 (54)	60 (53)/32 (28)/22 (19)

NOTE. Values shown are mean ± SD unless stated otherwise.

typical of autonomic dysfunction are frequent in the PBC population, and are themselves associated with fatigue.[10] The cause of autonomic dysfunction in PBC is likely to be complex with at least some contribution coming from the hemodynamic change associated with progressive liver disease. The presence, however, of significant autonomic dysfunction in patients with very early stage disease is suggestive of an additional mechanism postulated, again, to result from brain stem changes secondary to inflammatory cholestasis.

The identification of sleep regulation abnormality and autonomic dysfunction as strong biological associates of fatigue in PBC is potentially of real clinical importance because both processes may be amenable to therapeutic intervention. If these processes are related causally to fatigue in PBC such interventions might be expected to be of benefit in terms of fatigue reduction. Early observations already have suggested that the anti-daytime somnolence drug modafinil has some merit in the treatment of fatigue in PBC,[8,13] whereas simple interventions aimed at ameliorating the effects of autonomic dysfunction, such as withdrawal of inappropriate antihypertensive agents, have shown similar early promise.[10] However, the logical exploration of such interventions requires a clearer understanding of how the identified biological associates of fatigue interact, and how they impact on typical clinical cohorts. In this study we set out to develop a clinical decision making model for the identification of significant sleep abnormality and autonomic dysfunction in PBC patients to establish a clinical predictive framework to allow the rational application of future therapeutic interventions.

Patients and Methods

Study Design

This was a 2-phase study. A predictive model for sleep and autonomic dysfunction associated with fatigue in PBC was developed initially in a derivation cohort and subsequently was validated in an independent second cohort. The study was approved by our local research ethics committee. All subjects provided written permission for the use of clinical data and the local research ethics committee considered the return of questionnaires as implied consent.

Study Cohorts

The derivation cohort consisted of prevalent patients within the geographic postal code area NE1-25 at the study point. The derivation and validation of the NE1-25 cohort have been described extensively elsewhere.[14] The benefit of this clinical cohort is that it is representative of the whole PBC population and is not subject to clinic attendance bias (eg, as might result from particularly symptomatic patients attending a clinic more frequently). The validation cohort consisted of a group of patients attending a specialist PBC clinic but who were otherwise unselected with regard to symptomatology. Cohorts 1 and 2 were fully independent. The clinical details of patients in these clinical cohorts are outlined in Table 1.

Symptom Assessment Tools

PBC-40. Health-related quality of life and the symptoms that contribute to its impairment in PBC were assessed in the PBC study cohorts using the PBC-40, a fully validated PBC-specific, multidomain, quality-of-life measure.[15] The PBC-40 contains 40 questions in 5 domains (Fatigue, Itch, Cognitive, Social and Emotional, and Other Symptoms—a domain relating to a number of PBC-related symptoms that did not map to the other domains). A recent study defined ranges of severity for the symptom domains contained in the PBC-40.[10] By using these clinically meaningful cut-off values applied to the scores from the PBC-40 Fatigue domain, no fatigue was a score of 11 or less, mild was a score of 12 to 28, moderate was a score of 29 to 39, and severe was a score of 40 or greater.

Orthostatic Grading Scale. To determine the degree of orthostatic intolerance as an indicator of autonomic dysfunction the subjects completed the Orthostatic Grading Scale (OGS). This is a fully validated, self-report, assessment tool for the symptoms of orthostatic intolerance caused by orthostatic hypotension (eg, severity, frequency, and interference with daily activities) that consists of 5 items, each graded on a scale of 0 to 4.[16] Adding the scores for the individual items creates a total score. Studies have shown that scores from the OGS correlate with conventional tests of the integrity of the autonomic nervous system. A score greater than 9 is considered to be consistent with a formal diagnosis of orthostatic hypotension. A score of 4 or greater and less than 9 was regarded as being indicative of moderate orthostatic hypotension.[16]

Epworth Sleepiness Scale. In view of the recently identified associations between excessive daytime sleep and fatigue in PBC all subjects completed the Epworth Sleepiness Scale (ESS; possible score range, 0–24). This fully validated tool assesses daytime hypersomnolence, a score of 10 or more being indicative of significant daytime hypersomnolence.[17]

Statistical Analysis

Analysis was performed using Graphpad Prism Software (Graphpad Prism Software Inc, San Diego, CA). All vari-