Fatigue in primary biliary cirrhosis

K Cauch-Dudek, S Abbey, D E Stewart, E J Heathcote

Abstract

***Background*—Fatigue is a frequent and debilitating symptom in patients with primary biliary cirrhosis (PBC).**

***Aims*—To study fatigue in relation to sleep, depression, and liver disease severity.**

***Methods*—Patients with PBC completed validated self report questionnaires measuring fatigue, sleep quality, depression, and functional capacity. Verbally reported fatigue and observer rated measure of depression and ursodeoxycholic acid (UDCA) use were recorded. Liver biochemistry and tests to rule out metabolic causes of fatigue were performed.**

***Results*—Mean age of the 88 patients enrolled was 57 years; 86% were female and mean duration of disease was 6.6 years. Median bilirubin was 13 µmol/l (mean 18.6). Verbally reported fatigue (for more than six months) was present in 60 patients (68%). The self rated Fatigue Severity Score (FSS) correlated well with verbally reported fatigue (p=0.0001). The FSS did not correlate with age, duration of disease, serum bilirubin, Mayo Risk Score, or UDCA use, but correlation was seen with sleep quality. Fatigued patients had more sleep problems and higher depression scores than non-fatigued patients. Self rated depression was present in 28% (17/60) of fatigued compared with 4% (1/28) of non-fatigued patients.**

***Conclusions*—Long term fatigue affected 68% of the patients with PBC but it was not related to the severity of their liver disease. Poor sleep quality and depression were commonly associated with fatigue.**

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Keywords: primary biliary cirrhosis; fatigue; depression; sleep

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Fatigue, perceived as a persistent sense of exhaustion, inability to perform usual routines, and a decreased capacity for physical and mental work,[1] is often one of the most debilitating symptoms of primary biliary cirrhosis (PBC). The Canadian demographic study found that 81% of patients reported fatigue as their most prevalent symptom, with deleterious effects on quality of life.[2] These patients reported that their fatigue interfered with physical activity (73%), family life (57%), and job performance (30%). Recent clinical trials involving a total of 548 patients with PBC have shown that 64% report fatigue at entry to the studies.[3–5] Yet despite its prevalence, there have been no studies to date focusing directly on the issue of fatigue and its impact on the quality of life in patients with PBC.

The aetiology of fatigue in PBC is not known. In a previous study we have shown that fatigue did not correlate with liver histology in PBC patients; 76% of 222 patients with PBC reported fatigue and no correlation with histological stage of disease was observed.[6] In addition, treatments found to be effective in influencing the course of PBC do not necessarily improve the fatigue. Ursodeoxycholic acid (UDCA) may currently be considered the best treatment for PBC as its effect on survival has now been shown.[7 8] However, UDCA trials have failed to show that this therapy leads to any improvement in fatigue.[3–5]

A recent editorial focused on fatigue as an important determinant of the quality of life in patients with chronic liver disease and emphasised the importance of studying fatigue.[9] The aims of this study were to assess factors associated with fatigue in PBC, and simultaneously assess liver function and the physical and emotional aspects of quality of life. This paper reports on sleep, depression, and cognitive function in relation to fatigue.

Patients and methods

Between January and May 1995, of the 137 patients with liver biopsy proved antimitochondrial, antibody positive PBC actively followed at that time by The Toronto Hospital (Western Division) Liver Clinic, 125 were offered participation in the study. Participation was not offered to 12 patients either because of an inadequate understanding of the English language or an inability to travel to clinic due to the long distance or sickness. Of the 125 patients approached, 37 chose not to participate (26 were not interested in the study, nine were unable to travel, and a further two lacked an adequate understanding of English). The study was approved by the institutional review board (The Toronto Hospital Committee for Research on Human Subjects) and informed written consent was obtained from each patient.

During a visit to the outpatient liver clinic, patients completed previously validated self report questionnaires measuring fatigue, sleep disturbance, depression, and cognitive and functional capacity.[10–15] Verbally reported fatigue was recorded and an observer rated measure of depression completed by a single observer (KC-D). Standard liver biochemistry was performed along with other standard tests (thyroid and renal function, haemoglobin, calcium) to rule out recognised metabolic causes of fatigue. Use of ursodeoxycholic acid (UDCA, Ursofalk, 14 mg/kg/day) at the time of study and the amount of weekly physical

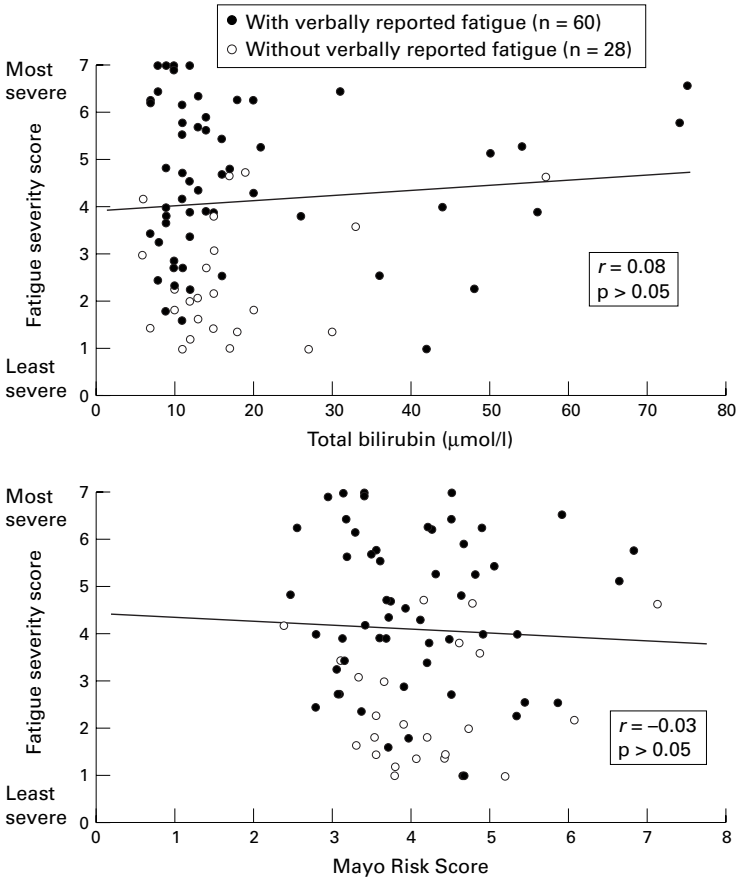

Figure 1 Fatigue Severity Scale score versus total serum bilirubin and Mayo Risk Score. There is some overlap of points within the figure.

exercise (in hours) were recorded. The Mayo Risk score, a validated prognostic index developed to predict survival in PBC,[16] was calculated for each patient as an indirect measure of disease severity.

Data were analysed with SAS using the Wilcoxon rank sum test, correlation, and linear regression. Non-parametric statistics were used as the data were not normally distributed. However, means (SD) are reported in order to compare results with work done in previously reported populations where large standard deviations were observed presumably due to skewness of data.

Table 1 Fatigue, sleep and depression in primary biliary cirrhosis

	Patients verbally reporting fatigue (n=60)	*Patients verbally reporting no fatigue (n=28)*	*Normal population controls*
Fatigue severity score (FSS)			
Mean (SD)	4.56 (1.6)*	2.4 (1.2)	2.53 (1.18)‡
Range	1–7	1–4.7	
Global sleep quality (PSQI)			
Mean (SD)	8.72 (4.9)†	5.07 (3.4)	2.67 (1.7)§
Range	1–21	1–16	
Depressive symptoms			
Observer rated HDRS			
Mean (SD)	9.56 (5.4)*	2.89 (3.9)	6¶
Range	0–28	0–15	
Self rated CES-D			
Mean (SD)	11.5 (9.3)†	5.12 (5.0)	9.25 (8.6)**
Range	0–42	0–18	

*p<0.0001, †p<0.0005 *v* patients with PBC verbally reporting no fatigue.
‡Schwartz *et al.*[10]
§Buysse *et al.*[11]
¶Hamilton *et al.*[12]
**Radloff, 15 maximum of three general population means, 7.94, 8.17, 9.25.[13]

INSTRUMENTS

Fatigue

Two measures of fatigue were used in this study. Verbally reported fatigue was assessed as being present if noted for more than six months by the patient. Fatigue was also measured by the self rated Fatigue Assessment Instrument (FAI),[10] developed to measure both the qualitative and quantitative aspects of respondents' fatigue during the previous two weeks. This 29 item questionnaire was designed for, and validated in, large groups of medical and psychiatric patients and includes subscales of fatigue severity (FSS), situation specificity, consequences of fatigue, and response to rest and sleep.

Sleep

The Pittsburgh Sleep Quality Index (PSQI)[11] was used to assess sleep quality and disturbances in sleep patterns during the previous month. Designed and validated to discriminate between "good" and "poor" sleepers in clinical populations, this 19 item self rated questionnaire generates seven component scores of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, daytime dysfunction, and use of sleeping medication. Each component score is weighted equally on a 0–3 scale. The frequency with which pruritus interfered with sleep was also recorded as part of the PSQI. A global PSQI sleep quality score with a range of 0–21 is generated by summing the component scores, with a higher score indicating worse overall sleep quality.

Depression

Two well validated scales were used to assess depression. Observer rated depression was measured by the 17 item Hamilton Depression Rating Scale (HDRS).[12] Although originally developed to assess the severity of depression in psychiatric populations, use of this scale is no longer restricted to this group. There are standard "cut point" scores which have been used to identify differing levels of depressive symptomatology in research studies.[17] The HDRS has a possible range of scores from 0 to 55. Scores of 7–17 are described as indicating mild depression, 18–24 as moderate depression, and scores of greater than 24 as severe depression. A score of 18 or more is typically required for entry into clinical trials of antidepressant therapy.

The self rated 20 item Centre for Epidemiologic Studies Depression Rating Scale (CES-D)[13] was designed to assess depressive symptomatology within the previous week in general population groups. Each of the items is scored from 0 to 3 on a scale of frequency of occurrence of the symptom. Scores on the CES-D range from 0 to 60. In studies which have used the CES-D, means for three general population samples of Caucasian respondents were 7.94, 8.17, and 9.25,[13] while the mean for psychiatric patients was 24.42.[18] A "cut point" score of 16 is commonly used to indicate the likely presence of depression.[15]

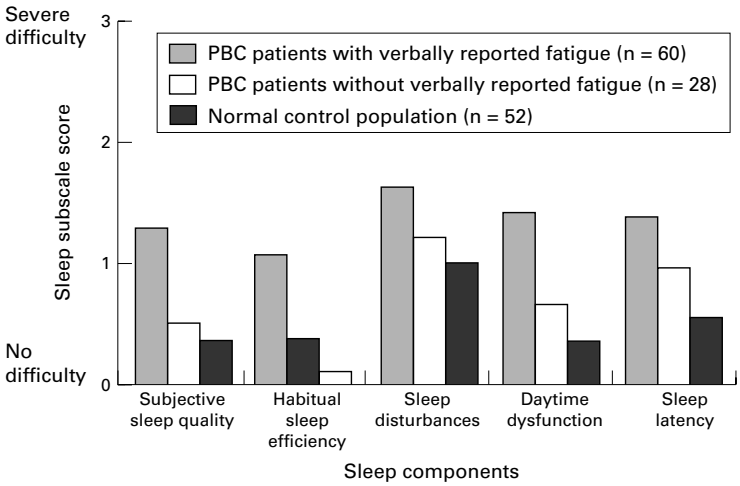

Figure 2 Comparison of sleep in patients with and without verbally reported fatigue and a normal control population.

Cognitive function

During patient interviews, the Folstein Mini Mental State was used to assess cognitive function.[14] This 11 item test focuses on patient orientation to time and place, registration, attention and calculation, recall and language. Function was also determined by timed performance on the Trails A and B tests, where patients were asked to connect sequential letters and numbers.[15]

Results

A total of 88 patients with PBC was enrolled in the study. The mean age was 57 (11) years (range 36–80); 86% were female and the mean duration of disease, from date of diagnosis, was 7 (5) years (range 1–23). Fifty per cent of the patients were receiving UDCA treatment for their PBC at the time of study entry. Median bilirubin was 13.0 µmol/l (mean 18.6 (15.0), range 6–75) and the mean Mayo Risk Score was 4 (1) (range 2–7). Only two of the 88 patients had decompensated liver disease and they were the only subjects taking diuretics for ascites. Haemoglobin, thyroid stimulating hormone, creatinine, or calcium levels did not indicate a metabolic basis for fatigue in any study patient.

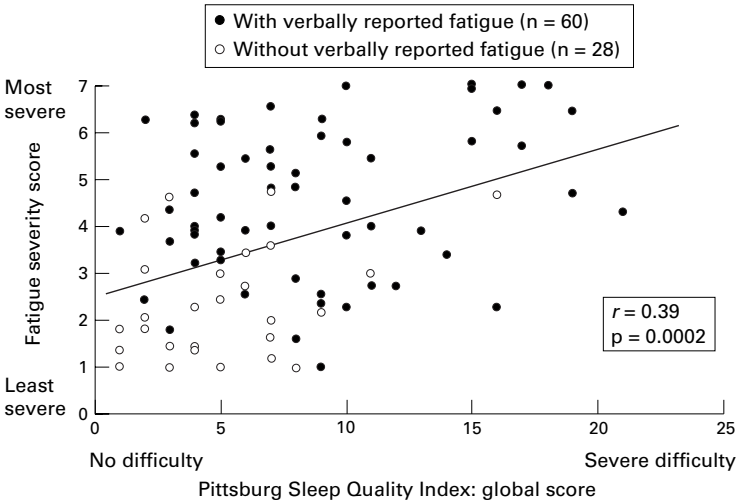

Figure 3 Fatigue Severity Scale score versus global sleep quality. The PSQI global score range for normal controls is 0–2.67.[11] There is some overlap of points within the figure.

FATIGUE

On clinical interview, verbally reported fatigue lasting longer than six months was present in 60 patients (68%). The 50% of patients receiving UDCA treatment had identical rates of verbally reported fatigue to those in non-treated patients. Using the self rated fatigue severity score (FSS) from the Fatigue Assessment Instrument (FAI), patients who had verbally reported fatigue also had significantly higher FSS scores than those with no verbally reported fatigue ($p<0.0001$) (table 1). UDCA treated and non-treated patients had similar FSS scores (means of 4.0 and 3.8 respectively). There was no correlation of FSS with patient age, duration of disease, or hours of weekly physical exercise. PBC severity as indicated by total serum bilirubin and Mayo Risk Score did not correlate with FSS (fig 1).

SLEEP

Patients who verbally reported fatigue had significantly more difficulty with global sleep quality as measured by the PSQI than those not reporting fatigue ($p<0.0005$) (table 1). Those with fatigue reported greater impairment than non-fatigued patients in subjective sleep quality, habitual sleep efficiency, sleep disturbances, and daytime dysfunction (fig 2). PSQI sleep quality score was found to be highly correlated with the FSS (fig 3). Total sleep duration (in hours) was similar for patients reporting and those not reporting fatigue: 43% (26/60) of fatigued and 29% (8/28) of non-fatigued patients reported less than six hours of sleep (this 14% difference is not significant; 95% confidence interval −6 to 36). Global sleep quality was similar for UDCA treated and non-treated patients. Pruritus reported by the patients was not found to correlate with PSQI sleep quality or the specific aspects of sleep noted above; 57% (34/60) of patients with fatigue had no pruritus. Medications to assist sleep were used more than twice per week by 15 (25%) of the patients with fatigue versus three (15%) of those without fatigue.

DEPRESSION

Patients reporting fatigue had significantly more depressive symptomatology than those not reporting fatigue, both on the observer rated HDRS and self rated CES-D (table 1). On the HDRS, which is generally considered to be the gold standard rating scale for measuring clinical depression, 71% (42/59) of fatigued patients had at least some evidence of depressive symptomatology (HDRS score of seven or more) whereas these symptoms were only present in 18% (5/28) of patients without fatigue (this 53% difference is significant; 95% confidence interval 35 to 72). Using classic cut points for this scale,[17] 63% of fatigued patients were mildly depressed (score of 7–17), 7% were moderately depressed (score of 18–24), and 2% were severely depressed (score greater than 24). In the non-fatigued patients, the

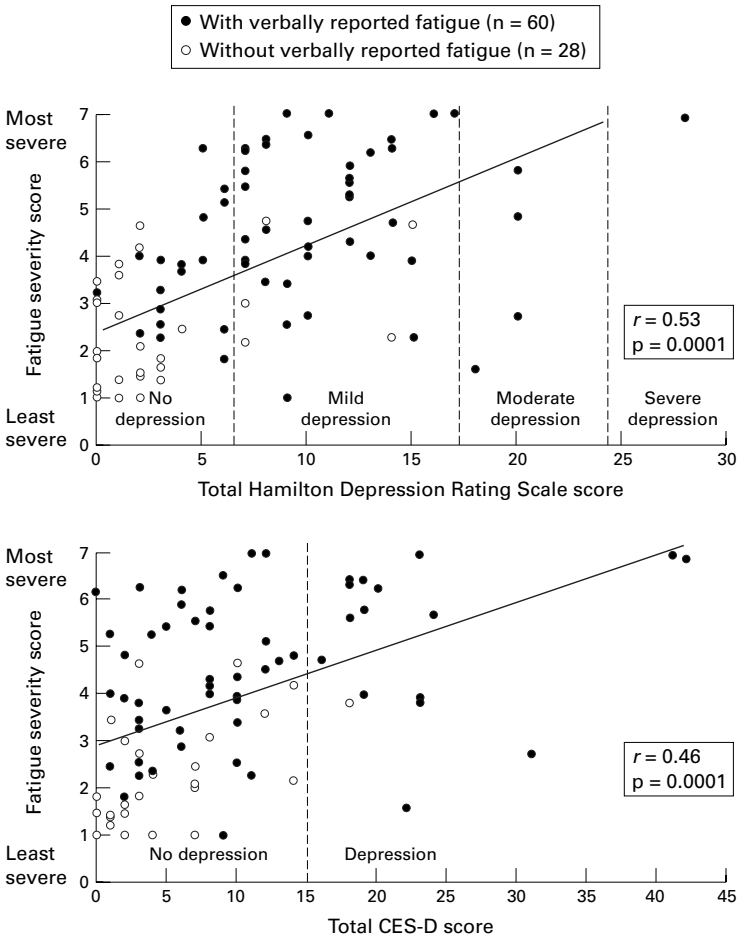

Figure 4 Fatigue Severity Scale score versus depression. There is some overlap of points within the figure.

figures for these same indexes were 18%, 0%, and 0% respectively.

The CES-D, which recorded self rated depressive symptomatology, found 28% (17/60) of fatigued patients had depressive symptoms comparable in severity (CES-D score of 16 or more) to that reported in depressed patients undergoing psychiatric consultation,[18] whereas only 4% (1/28) of the patients reporting no fatigue had depressive symptoms of similar severity (this 24% difference is significant; 95% confidence interval 11 to 38). Both depression measurements were highly correlated with fatigue severity as measured by the FSS subscale of the FAI (fig 4).

Both the observer rated and self rated depression scores were similar for the fatigued patients being treated with UDCA and those receiving no treatment (observer rated mean scores of 9.1 and 10.0 and self rated mean scores of 10.7 and 12.4 respectively). Both depression scores remained within the normal range for patients without fatigue, regardless of UDCA use. The correlation of fatigue severity with both measures of depression was similar for both UDCA treated and non-treated groups.

COGNITIVE FUNCTION

The fatigued and non-fatigued groups did not differ significantly on screening tests for cognitive dysfunction, total score on the Folstein Mini Mental State Examination, and time on Trail Making A and B tests. The scores for both groups were well within the normal range and no patients scored in the abnormal range.

Discussion

Fatigue lasting for more than six months was reported on interview by 68% of our PBC patients; there was no correlation with UDCA use. The fatigue severity scores of our PBC patients reporting fatigue (4.6 (1.6)) were comparable to scores published for patients with multiple sclerosis (4.8 (1.3)) and systemic lupus erythematosus (4.7 (1.5)).[19] Patients with PBC reporting no fatigue on interview had fatigue severity scores comparable to those of normal healthy adults (2.4 (1.2) versus 2.3 (0.7)).[19]

Both our fatigued and non-fatigued patients had global PSQI sleep quality scores that indicated worse sleep than normal population controls[11]; only 5% (3/60) of our patients with fatigue reported sleep quality comparable to normal controls, whereas 25% (7/28) of those without fatigue had normal sleep quality (fig 2). The pruritus reported by our patients was not associated with global sleep quality score; thus it seems that poor sleep quality could not be simply attributed to itching. Our patients did not compensate for their fatigue by sleeping longer nor was rest found to be restorative to those with fatigue. Sleep duration of at least six hours reported by 57% of our fatigued and 71% of our non-fatigued patients is comparable to the duration of sleep reported by normal population controls.

Gross cognitive dysfunction was not found in our screening tests or on interview with our patients, and as only two patients had clinical evidence of hepatic decompensation, we conclude that none had hepatic encephalopathy to account for their poor sleep quality. However, despite the absence of hepatic encephalopathy, daytime dysfunction was a significant problem for many of the patients; 92% of fatigued patients had higher daytime dysfunction scores on the PSQI than normal controls, compared with 63% of those patients without fatigue. Many factors may cause daytime dysfunction, aside from poor sleep quality.

Depression was common in our fatigued patients, regardless of UDCA use. The minimum score on the observer rated HDRS required for the study of antidepressant medications in outpatients is 18.[17] Thus using this scale, 9% (5/59) of our fatigued PBC patients had depression scores sufficient to warrant therapy with antidepressants, whereas none of the patients without fatigue had scores in this range (fig 4). The rate of depression in our PBC patients is higher than that observed in a recent Ontario study which reported that 4.2% of middle aged women (aged 45 to 64 years) suffered from depression.[20] The combination of depression and fatigue is not unusual and has been found in the general population,[21 22] in primary care samples,[23] in medically unexplained syndromes such as the chronic fatigue syndrome (CFS),[24 25] as well as in well defined

disease groups such as survivors of Hodgkin's disease[26] and end stage renal disease.[27]

Fatigue has been studied in few patients with liver disease,[28–31] but there have been studies reporting fatigue in association with other chronic autoimmune diseases such as rheumatoid arthritis[32] and systemic lupus erythematosus.[33 34] A multivariate model of fatigue was proposed in an attempt to sort out the contributions of disease activity, depression, sleep patterns, and fatigue in systemic lupus erythematosus.[35] It was postulated that, through reciprocal effects on each other, both depression and sleep act as mechanisms through which fatigue is increased by disease activity. However, as in this study of PBC patients no correlation was observed between severity of disease (serum bilirubin and Mayo Risk Score) and fatigue, it would seem that it is not the liver disease directly that is causative. This study has raised some interesting questions about the relations between sleep, depression, and fatigue. It remains to be determined whether fatigue induces sleep disturbance and/or depression or vise versa in PBC patients.

Based on the assumption that fatigue and other behavioural changes are part of a "natural homoeostatic reaction" used by the body in response to stressful conditions, Swain and Maric have recently studied the role of corticotropin releasing hormone (CRH) in bile duct resected cholestatic rats and sham resected controls.[36] Defective CRH mediated responses were found in the cholestatic rats, and they conclude that the altered CRH mediated behaviours resulting from the cholestasis may contribute to fatigue and other non-specific symptoms of PBC. These same authors have reported evidence of an altered pituitary-adrenal axis in PBC patients who were found to have elevated serum cortisol levels.[37]

Long term fatigue can have a debilitating effect on the quality of life in PBC patients.[2] We found that the fatigue is similar in UDCA treated and non-treated patients, and a previous study by our group failed to show that UDCA aleviates fatigue.[4] Sleep disturbance, which is often a symptom of depression,[38] can compound this effect. Studies of sleep architecture in patients with PBC are required to determine whether sleep disturbances induce fatigue, as sleep disturbances are treatable. Similarly, this study has shown that depression is a major factor associated with fatigue, but it is not clear whether fatigue leads to depression or vice versa. As PBC is primarily a disease of women and in epidemiological studies, depression is twice as common in women as in men,[39 40] depression may explain in part why fatigue is a predominant symptom of PBC. Given that depression is eminently treatable and may result in alleviation of fatigue and general improvement in quality of life, studies of antidepressant therapy may be indicated to assess the effect on the depression and fatigue associated with PBC.

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