

Fatigue in cholestatic liver disease—a perplexing symptom

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Fatigue is an important symptom and a quality of life determinant in patients with cholestatic liver disease. The pathogenesis of fatigue is obscure, although alterations in central neurotransmission and peripheral muscle dysfunction have been incriminated. No effective treatment is available at present. The available literature on fatigue in cholestatic liver disease is reviewed.

Cholestatic liver disease typically presents with pruritus, steatorrhoea, deficiency of fat soluble vitamins, and metabolic bone disease. In recent years, fatigue has been recognised as a significant symptom in this group of diseases.^{1,2} It remained neglected, until recently, because of its non-specific nature and lack of objective assessment techniques. Its pathogenesis and effective therapy, however, still remain elusive. Fatigue is a complex symptom, defined as a persistent sense of exhaustion, inability to perform usual routine work, and a decreased capacity for physical and mental work.³ Understanding the basis of this symptom has become more important now because many patients with primary biliary cirrhosis (PBC) are being diagnosed early in the natural course of this slowly progressive disease.⁴ Furthermore, ursodeoxycholic acid (UDCA) treatment has reduced the progression of the disease as suggested by many long term follow up studies,^{5–8} although one recent meta-analysis did not find any survival benefit with UDCA.⁹ In the absence of cholestatic symptoms and liver failure, fatigue is being considered as one of the most debilitating symptoms of cholestatic liver disease, adversely affecting the quality of life.^{1,2,10} In the present article, we review the available literature on fatigue in cholestatic liver disease.

PREVALENCE OF FATIGUE, ASSESSMENT, AND IMPACT ON QUALITY OF LIFE

Fatigue was present in 81% of patients and was the most prevalent symptom in the Canadian demography study of PBC.¹ Various clinical trials of PBC have shown that fatigue is present in 60%–76% of patients at entry into the trials.^{11–13} Recent reports, specifically addressing fatigue, have reported it to be present in 68%–85% of patients with PBC.^{2,10} It is almost equally prevalent among patients with primary sclerosing cholangitis and drug induced cholestasis.^{10,14,15} Half of the patients with fatigue consider it to be their worst or one of the worst symptoms, underscoring the importance of understanding this symptom.¹⁰

Most therapeutic trials of PBC have measured fatigue as a subjective symptom and reported it as either present or absent. Recognition of fatigue as an important symptom in PBC stimulated the search for an objective method to assess and measure it. Cauch-Dudek *et al*² measured fatigue as self rated fatigue severity score (FSS) using the fatigue assessment instrument.¹⁶ This measures both qualitative and quantitative aspects of fatigue. FSSs were significantly higher in patients having verbally reported fatigue as compared with those having no verbally reported fatigue.

The Fisk fatigue severity score (FFSS), originally developed to assess the impact of chronic fatigue syndrome on quality of life,¹⁷ has also been recently validated in patients with PBC to assess fatigue and its effect on quality of life.^{10,18} This tool consists of a questionnaire that scores the effect of fatigue on 40 aspects of day-to-day life. These aspects broadly pertain to psychosocial, cognitive, and physical activity. The FFSS was reproducible both at short and long intervals indicating its reliability in assessing fatigue. Median FFSS was found to be 2.3 times higher in patients with PBC than in chronic disease controls.¹⁸ A similar degree of fatigue was also found in patients with primary sclerosing cholangitis.¹⁰

The Canadian demography study of PBC concluded that fatigue interfered with physical activity, family life, and job performance in 73%, 57%, and 30% of patients, respectively.¹ The quality of sleep (subjective sleep quality, habitual sleep efficiency, sleep disturbance, daytime dysfunction) was poor in the fatigued patients, though the duration of sleep was similar in fatigued and non-fatigued patients and in normal subjects.² The poor quality of sleep could not be explained by pruritus, as 57% of patients with fatigue had no pruritus. Depression was present in 45% of patients with PBC.¹⁰ Further, 71% of fatigued patients had depressive symptoms as compared with 18% of non-fatigued patients.² More patients with fatigue had moderate or severe depression compared with those without. Fatigue, sleep disturbance, and depression often coexist in patients with PBC, but it remains to be determined whether fatigue induces sleep disturbance and/or depression or vice versa. Their inter-relationship is complex and needs further elucidation.

Abbreviations: FSS, fatigue severity score; FFSS, Fisk fatigue severity score; 5HT, 5-hydroxytryptamine; IL-1, interleukin-1; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid

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Box 1: Pathogenesis of fatigue

- Alteration in hypothalamo-pituitary-axis, diminished corticotrophin releasing hormone stores and release.
- Altered serotonergic neurotransmission.
- Abnormality of cytokine release particularly interleukin-1.
- Decreased hypothalamic nitric oxide formation.
- Peripheral muscle dysfunction.

PATHOGENESIS OF FATIGUE IN CHOLESTATIC LIVER DISEASE

The pathogenesis of fatigue is poorly understood. It is important to elucidate its pathogenesis to develop appropriate treatment. Fatigue constitutes a part of non-specific symptoms such as malaise, lethargy, anorexia, listlessness, loss of social interest and inability to concentrate, which are commonly associated with a number of disease states. These symptoms have been termed as sickness behaviours and are felt to be secondary to the disease process.^{19, 20} However, in cholestatic liver disease fatigue is a major symptom and is at times the presenting symptom. Patients with PBC have a higher FFSS compared with other hospital-attending patients with chronic disease, signifying that fatigue is a specific symptom related to PBC.¹⁸ The severity of fatigue, however, does not correlate with markers of liver disease severity like histological grades, age, serum albumin, bilirubin, prothrombin time, and aminopyrine breath test, indicating that the pathogenesis of fatigue is independent of the severity of liver disease.^{2, 10, 18} This has led to a suggestion that fatigue may be an extrahepatic association of cholestatic liver disease just like other associated autoimmune diseases.¹⁰

Sickness behaviours are a part of a specific, organised response to environmental insults (for example, infection or inflammation) and other stressful conditions.^{19, 20} Alterations in the hypothalamus-pituitary-adrenal axis are known to modulate behavioural changes occurring during stressful conditions.^{21, 22} Altered central neurotransmission appears to play a part in the generation of fatigue associated with many disease states,^{23, 24} and has also been implicated in the pathogenesis of pruritus in cholestatic liver disease.^{25, 26} Recently, cytokines have also been implicated in the pathogenesis of sickness behaviours.²⁷⁻²⁹ Working on these clues Swain and colleagues have performed a series of elegant experiments on bile duct resected rats, as a model of cholestasis, to elucidate the pathogenesis of fatigue in cholestatic liver disease.³⁰⁻³³ These experiments support the theory that fatigue in PBC is central in origin. The validity of these experiments in human disease states, however, has not been tested. There is evidence that peripheral muscle dysfunction may also contribute to the pathogenesis of fatigue in PBC.³⁴

(1) Alteration in the hypothalamus-pituitary-adrenal axis

In first of these experiments bile duct resected rats entered fewer inner squares of an open field apparatus and produced fewer faecal boluses than the control (sham resected) rats.³¹ Placing a rat in an open field is a stressful stimulus for the animal and exploration of inner versus outer squares in an open field can be affected by a number of factors, specifically a defective release of central corticotrophin releasing hormone.³⁵⁻³⁷ Diminished faecal bolus production during stress is also consistent with diminished central corticotrophin releasing hormone release.³⁸ The altered hypothalamus-pituitary-adrenal axis response was further confirmed by finding a low rise in plasma adrenocorticotrophic hormone on exposure to the stress of open space in bile duct resected rats.³¹ Thus, an abnormal pattern of behaviour and altered function of the hypothalamus-pituitary-adrenal axis coexist in rats with cholestasis, though a causal relationship between the two has not been established.

(2) Altered serotonergic neurotransmission

There is evidence to show that fatigue is associated with an altered serotonergic neurotransmission. Fatigued rats during prolonged exercise have raised levels of brain 5-hydroxytryptamine (5HT) and treatment with a 5HT₂ antagonist prolonged the exercise period, whereas treatment with a 5HT agonist shortened the exercise period.³⁹ Serotonin reuptake inhibitor (paroxetine), that acts as a serotonin agonist centrally, does indeed decrease exercise tolerance in male athletes.⁴⁰ Altered serotonergic neurotransmission has also been implicated in the pathogenesis of fatigue in diseased states like chronic fatigue syndrome and postviral fatigue.^{23, 24} Further, altered serotonergic neurotransmission is known to exist in cholestatic states—as has been suggested by the reversal of pruritus on administration of ondansetron, a 5HT₃ receptor antagonist.⁴¹

In a rat model of fatigue assessment, using a swim test, Swain and Maric demonstrated that bile duct resected rats (cholestatic rats) had significantly reduced activity scores compared with carbon tetrachloride treated rats (rat model for hepatitis) and sham resected rats (non-cholestatic controls).³² Administration of a serotonin (5HT_{1A}) receptor agonist reversed and improved activity scores in bile duct resected rats, implicating altered serotonergic neurotransmission in the pathogenesis of fatigue in cholestatic states.³²

(3) Cytokines

Cytokines have also been implicated in the pathogenesis of sickness behaviours.^{19, 27, 28} Interleukin-1 (IL-1) induces sickness behaviours in rats⁴²⁻⁴⁴ and central infusion of IL-1ra, a specific IL-1 receptor antagonist, reverses this.²⁹ In bile duct resected rats central infusion of IL-1 produced a marked reduction in locomotor activity, while in the control rats the same dose of IL-1 had an insignificant effect.⁴⁵ The anorectic response to the central IL-1 infusion was, however, similar in cholestatic and non-cholestatic rats. Thus, cholestasis is characterised by augmented central responsiveness to IL-1 with respect to a decrease in locomotor activity only. IL-1 expression is enhanced in brain in response to peripheral stimuli (endotoxin administration) and stress.⁴⁶⁻⁴⁸ Hence during inflammation or stressful conditions in cholestatic patients IL-1 may contribute to the fatigue. Mechanisms underlying the enhanced sensitivity of cholestatic rats to IL-1 induced decrease in locomotor activity are unknown. Decreased hypothalamic nitric oxide formation in cholestasis may contribute to an enhanced behavioural depression in response to IL-1 in bile duct resected rats.^{49, 50} The role of cytokines and nitric oxide in the generation of fatigue in cholestatic liver disease requires further investigation as both of these can be modulated for therapeutic advantage.

(4) Peripheral muscle dysfunction

A recent study suggests contribution of peripheral muscle dysfunction to the fatigue experienced by patients with cholestasis.³⁴ Fatigued patients with PBC had markedly accelerated reduction in muscle function on repeat activity compared with both control subjects and non-fatigued patients.³⁴ Further, the rate of reduction in muscle function correlated with the severity of fatigue experienced by the patient, suggesting a contribution of the peripheral muscle fatigability to the fatigue experienced by patients. The mechanism underlying peripheral muscle dysfunction is not known. Oxidative stress may play a part as muscle fatigue has been shown to be associated with oxidative stress to myocytes.⁵¹ Antioxidants prolong the time to development of fatigue in rabbits and humans.^{52, 53} Cholestatic liver diseases are associated with oxidative stress mainly due to the pro-oxidant action of retained hydrophobic bile acids,^{54, 55} while antioxidants protect against this pro-oxidant action.⁵⁶⁻⁵⁸ Three months of antioxidant therapy improved fatigue

Box 2: Treatment of fatigue

- Ursodeoxycholic acid: no relief.
- Antioxidants: more studies required.
- Serotonin antagonists: experimental.
- Interleukin-1ra: experimental.
- Liver transplant: last resort.

Box 3: Learning points

- Fatigue is a major symptom in cholestatic liver diseases, present in 60%–85% of patients with primary biliary cirrhosis.
- It is worst or one of the worst symptoms in 50% of patients.
- It has an adverse effect on quality of life.
- Fatigue severity does not correlate with severity of underlying liver disease.
- Pathogenesis of fatigue is still obscure.
- At present there is no treatment for fatigue.

considerably in patients with PBC, suggesting a role of oxidative stress in the development of fatigue.⁵⁹

TREATMENT OF FATIGUE IN CHOLESTATIC LIVER DISEASE

Currently no therapy is effective in relieving the symptoms of fatigue in patients with cholestatic liver disease. UDCA is considered the treatment of choice for PBC at present. It reduces the pace of disease progression and delays time to transplantation.⁶⁰ It, however, has no effect on the accompanying fatigue.^{11–13} Liver transplant also does not help much in relief of fatigue. Fatigue remains the most distressing symptom even one year after liver transplantation, though its intensity is reduced.¹⁴

Other known causes of fatigue such as anaemia, electrolyte imbalance, renal failure, hypothyroidism, or side effects of drugs should be looked for and treated. Avoidance of stress and promotion of healthy lifestyle including adequate sleep, regular exercise, and alcohol and caffeine restriction may help.^{61,62} Antidepressants may relieve fatigue partially in depressed patients.⁶¹

It is important to understand the pathogenesis of fatigue in cholestatic liver disease before any therapeutic breakthrough can be achieved. The role of serotonergic neurotransmission, IL-1 and nitric oxide in the pathogenesis of fatigue, as suggested in rat experiments, may provide a rationale for treatment in future as these can be modulated using specific antagonists. In this respect, the reports of reversal of fatigue in cholestatic rats using 5-HT_{1A} receptor antagonist³³ and similarly, reversal of sickness behaviour using IL-1ra²⁹ are encouraging.

Antioxidants were found to reduce fatigue in a pilot study.⁵⁹ However, the role of antioxidants in amelioration of fatigue needs further evaluation by larger controlled trials.

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