Understanding and Treating Fatigue in Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

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KEYWORDS

• Fatigue • Primary biliary cirrhosis • Primary sclerosing cholangitis • Cholestasis
• Quality of life

KEY POINTS

- In primary biliary cirrhosis fatigue is unrelated to the severity of the underlying liver disease and unresponsive to ursodeoxycholic acid therapy.
- Further work is warranted to understand the pathogenesis of fatigue in primary sclerosing cholangitis and the development of disease-specific quality of life measures to assess fatigue is needed.
- Despite the lack of specific therapies for fatigue there are several management strategies that can be implemented to improve fatigue severity and quality of life in patients with cholestatic liver disease.

INTRODUCTION

The most common cholestatic liver diseases are primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Fatigue in cholestatic liver disease represents a real challenge for patients and clinicians. It is the commonest problem reported by patients with PBC, is not related to the severity of the underlying liver disease, does not improve with conventional disease treatments, and has no recognized specific treatment.[1,2] Fatigue in PSC has been much less studied but seems to be a significant problem in a minority of patients.[3] The normal disease management paradigm for patients with cholestatic liver diseases is the prevention and treatment of

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progressive liver injury and cirrhosis. Clinicians treating these patients often find the management of severely fatigued patients with complex problems challenging. This article summarizes current thinking regarding the epidemiology, pathogenesis, and treatment of this important clinical problem.

THE CLINICAL SCENARIO

The classic clinical scenario is of a young patient with PBC who has mild disease that has responded well to ursodeoxycholic acid (UDCA) therapy in terms of liver biochemistry, but who is still experiencing profound fatigue. This classic fatigue has two elements. The first is a sense of "brain fog," clouded thinking and poor concentration that may have been bad enough to cause problems at work. Patients may feel the need to sleep during the day but fight against it. The second is a sense of profound peripheral weakness, like the "batteries have run down" in their muscles. Patients have good days and bad days but sense that they "pay the price" the following day if they exert themselves. Typically, patients feel less fatigued in the morning and get progressively worse during the day. This makes evenings difficult and shift work challenging. Fatigued patients often decrease their activity, particularly nonessential activities, such as paid employment or caring for children, with a knock-on effect on social life and relationships that can lead to increasing social isolation. A sense that this will never end can lead to frustration and depression. Being told by clinicians how well they are doing because their biochemical tests are good, and by friends and families how well they are looking, can add to the frustration.

THE SCALE OF THE PROBLEM

Current studies suggest that up to 50% of patients with PBC experience clinically significant fatigue[4] and it is more common in younger patients presenting with the disease.[5] The problem seems to be less frequent in PSC (although severe fatigue is still reported) and the phenomenon has been little studied in other cholestatic conditions.[3] Fatigue was not reported as a problem in PBC before 1980 (when the first mention was made of "lethargy" in patients with PBC).[6] Since that time the reported prevalence of fatigue has risen. There are two factors that are likely to underpin this apparent change in disease phenotype. The first is the changing spectrum of disease. In the 1950s, when the first case series of PBC was reported and the phenotype of the condition established, PBC was a rare disease of patients typically in the end stages of disease.[7] The problems a patient experienced, therefore, were likely to be dominated by those of end-stage disease. With the advent of serologic testing and its widespread use in the assessment of cholestatic liver function tests, patients are now typically diagnosed in the early stages of disease. Furthermore, effective treatment approaches are now available for pruritus, which can result in an "unmasking" of fatigue (when present, pruritus tends to predominate in a patient's experience).[8,9] In simple terms, the typical patient with PBC diagnosed in the modern era is well enough in relation to the other aspects of the disease for their fatigue to be their predominant problem.

The second factor is the advent of effective tools to measure fatigue (covered in detail in the next section), and the awareness among clinicians and patients that fatigue is part of the patient experience. These tools are increasingly used in normal clinical practice. The definitive study is the UK-PBC Study, which uses the PBC-40, a patient-derived, disease-specific quality of life (QoL) tool in a very large sample of patients who are representative of the PBC patient population in the United Kingdom as a whole.[10] Using defined PBC-40 fatigue domain cut-offs, severe fatigue was found to affect approximately 20% of patients with PBC and moderate or severe fatigue more