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EDITORIAL

Tired of Hepatitis B?

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Fatigue is a symptom complex encompassing that is often reported as malaise, exhaustion, and lethargy, with a reported prevalence of 25 % in the overall population [1]. While some fatigue is to be expected as a consequence of daily activities (i.e., exercise, work, activities of daily living), it is also an important patient-reported outcome in chronic diseases. Fatigue can be either central or peripheral (or both) in etiology [2]. Peripheral fatigue is a result of neuromuscular dysfunction, which often manifests clinically as weakness in patients with advanced liver disease, whereas central fatigue is often associated with neuropsychiatric problems (i.e., depression and anxiety) and sleep issues. Central fatigue often manifests as difficulty in performing physical and mental activities that require self-motivation and internal signals.

Fatigue scales and scores are used to define its presence, severity, and response to therapy in several chronic illnesses; however, its exact prevalence is less well defined in chronic liver diseases such as primary biliary cirrhosis, chronic hepatitis C infection, and nonalcoholic liver disease [3]. Fatigue as a primary outcome even less studied in chronic hepatitis B. Thus far, the studies that have evaluated fatigue in chronic hepatitis B have had limited sample size and lack of focus on fatigue as an independent symptom complex. Fatigue has been associated with depression, cognitive impairment, poor work performance, and reduced quality of life in chronic hepatitis C and in primary biliary cirrhosis [4, 5]. Yet, fatigue is not specifically associated with hepatitis C viral load and genotype [6]. Given the increasingly recognized hepatitis B prevalence in North America, and the relatively long duration of inflammation in chronic hepatitis B, patient-reported outcomes such as fatigue gain added relevance. Therefore, fundamental questions need to be answered moving forward—is fatigue associated with chronic hepatitis B and does ongoing viremia and disease severity have any relationship to this symptom?

In this issue of *Digestive Diseases and Sciences,* Evon et al. [7] addressed this question. Using the Hepatitis B Research Network (HBRN), the authors enrolled 948 participants, of whom the majority were inactive carriers (40.7 %), were Asian (74 %), and had limited comorbid illnesses (27.8 %). Only 2 % of participants had advanced fibrosis that was estimated by the aspartate transaminase (AST) to platelet index (APRI). Each participant enrolled was analyzed by the National Institutes of Health (NIH) Patient-Reported Outcomes System (PROMIS) tools that are a highly valid and reliable set of instruments that measures physical, mental, and social functioning. The authors in the case, however, used the PROMIS Fatigue Short Form, which only included a subset of items from the larger PROMIS item bank in an effort to accurately capture the patient's emotional responses toward fatigue and its frequency. Importantly, scoring from the PROMIS instruments, compared to norms from the US population, has been used to assess fatigue states in several chronic illnesses [8] as well as patient-reported outcomes in cirrhotic patients [9]. Furthermore, in order to evaluate the impact of mental health on fatigue, each participant also was evaluated by the Medical Outcomes Study 36-item Short Form Mental Health Functioning subscale. In order to further focus on fatigue, the group had excluded those being

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treated for chronic hepatitis B and those with decompensated cirrhosis.

Interestingly, the authors reported that fatigue scores in the majority of the participants were much lower than the US norm (a lower score indicates less fatigue), presumably because of the random US sample used to generate norms that could have skewed them. There was also no association between fatigue scores and hepatitis B virological disease activity. They did demonstrate, however, that those who had advanced fibrosis (APRI score > 1.5), women, those with other comorbid illnesses (especially diabetes), and inferior mental health functioning had higher fatigue scores. Of these factors, the strongest predictor for fatigue was low mental health functioning, which has also been recently associated with increased risks of liver disease mortality [10].

Strengths of the Evon et al. study include the large number of chronic hepatitis B participants studied by a unifying research network group (HBRN) who used a previously validated instrument to assess fatigue and its relationship to disease phenotype. To further strengthen their study, the authors also controlled for factors such as other comorbid illness, sex, education, and race, all which could influence results. The study data were able to answer an important question: It appears that advanced liver disease and comorbid conditions are more strongly associated with fatigue than is the hepatitis B infection itself. This observation, which confirms prior studies of cirrhotic patients [9], should help inform the design of future studies of advanced fibrosis patients.

Where should we go from here? Additional correlational studies in other countries would be important in understanding fatigue in the context of regional and cultural differences into disease burden insight. Future studies should also include the collection of mental health information and current medications for those conditions, which can impact patient-reported outcomes. Moreover, comparisons to other well-validated tools that specifically assess fatigue in liver disease [3] (Fatigue Severity Scale and Fatigue Impact Scale) would have added another dimension to this data analysis. Additional studies of the mechanisms that influence fatigue in chronic liver diseases are also important to pursue, including evaluation of the effect (and treatment) of sleep disturbances [11] combined with testing for the presence of autonomic dysfunction [3].

Fatigue remains an important issue in patients with chronic liver disease, now including patients with chronic HBV infection by the HBRN. There is an increasing awareness of patient-oriented outcomes as important components of treatment and clinical research [12]. This research should spur further investigation into fatigue and other patient-reported outcomes in patients with chronic liver disease, especially in the context of longitudinal change with treatments.

Compliance with ethical standards

Conflict of interest None

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