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Focus

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The impact of fatigue and treatment with ursodeoxycholic acid on the prognosis of primary biliary cirrhosis: an extended 9 year follow-up

Fatigue, which complicates the course of chronic liver disease [1] and of primary biliary cirrhosis (PBC) in particular [2], has been the focus of attention of hepatologists for almost three decades. Reports on the incidence of significant fatigue among PBC patients in the Western hemisphere vary between 30% and 80% and fatigue is now a well-recognized symptom in PBC patients significantly contributing to a reduced quality of life. Less is known regarding the interrelationship between fatigue and the prognosis of PBC. A previous, initial observation in a well-defined cohort of PBC patients in North-Eastern England followed for 4 years suggested that the degree of fatigue in PBC patients is associated with increased mortality and is not affected by ursodeoxycholic acid (UDCA) therapy [3]. In an earlier report, increased mortality risk among PBC patients in the UK was also linked to "non-liver causes", such as cardiac disease, and not only to end-stage liver disease and its sequelae [4]. In this context it is important to raise the question whether chronic inflammatory liver disease leads to extrahepatic and systemic effects, such as fatigue, which have an impact on the prognosis of PBC. The pathogenesis of fatigue in PBC is only partially understood and is most likely unrelated to the histological disease stage, degree of hepatic dysfunction, or autoimmune markers. However, fatigue may possibly be related to cholestasis as well as to reduced clearance of poorly defined humoral factors and increased accumulation of inflammatory cytokines such as IL-6. Either as a consequence or independently from these factors, patients may develop autonomic nerve dysfunction, hypotension, muscle dysfunction, and a disturbed sleep pattern [2].

In this issue of the journal, Jones and co-workers (see page 911) extend their original 4 year observation reported in 2006 [3] to a 9 year follow-up of a well-defined cohort of PBC patients residing in a United Kingdom community. The control population for this study was recruited prospectively through primary care physicians and was well matched. This longer follow-up enabled confirmation of some of the original observations including the poorer survival of patients with high median fatigue impact scores (FIS), the favorable impact of UDCA on survival in responders to treatment, and the lack of significant improvement in fatigue following UDCA treatment. Furthermore, the low incidence of liver-related death observed in fatigued patients who still had a higher risk for death or for liver transplantation leads the investigator to suggest that fatigue by itself may be contributing a risk factor for a poor prognosis in PBC. Indeed, using Cox regression analysis in a multivariate survival model, the severity of fatigue was shown to be independently associated with death or liver transplantation irrespective of deteriorated liver function tests. In other words, patients with a lower FIS had a better prognosis. In the "good old days" of liver transplantation, severe fatigue was considered by some transplant teams as an important indication for liver transplantation. To date, in the new MELD era, the presence of fatigue, as severe as it may be, is no longer taken into consideration in the prioritization of PBC candidates for liver transplantation. Before further consideration is given to changing the rules again, one should remember that fatigue cannot be directly correlated with the severity of liver disease and may remain stable for years before it gets worse. Further attention should be devoted to studies on the pathogenesis of fatigue and the interrelation between fatigue, chronic inflammation, and cardiac disease. Finally, this report contains a wealth of additional information not discussed in this Focus chapter, which will be of interest to clinicians who follow patients with PBC.

References

[1] Jones EA. Fatigue complicating chronic liver disease. Metab Brain Dis 2004; 19:421–429.
[2] Newton JL. Fatigue in primary biliary cirrhosis. Clin Liver Dis 2008;12: 367–383, ix.
[3] Jones DE, Bhala N, Burt J, Goldblatt J, Prince M, Newton JL. Four year follow up of fatigue in a geographically defined primary biliary cirrhosis patient cohort. Gut 2006;55:536–541.
[4] Prince M, Chetwynd A, Newman W, Metcalf JV, James OF. Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: follow-up for up to 28 years. Gastroenterology 2002;123:1044–1051.

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