Editorial

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Is fatigue in primary biliary cirrhosis cured by transplantation?

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The name primary biliary cirrhosis (PBC) was coined when the disease was mostly diagnosed in its late cirrhotic stage [1]. Today, PBC must be considered a historic misnomer, as the disease nowadays presents usually many years or decades prior to the development of cirrhosis, and with timely diagnosis and adequate treatment, the majority of patients never reach the stage of cirrhosis [2–4]. It is considered an autoimmune disease characterized by non-suppurative destructive cholangitis, and it is thus considered a disease of the small intra-hepatic bile ducts. However, there may be a second reason why PBC is a misnomer: probably the disease is not only confined to the liver, but may have extra-hepatic manifestations. In addition to the immune-mediated inflammation in the liver, patients may suffer from a number of extra-hepatic manifestations as varied as Sicca-syndrome, arthralgias and, most of all, fatigue.

Fatigue is a complex symptom characterized by the feeling of exhaustion, lethargy, and discomfort. Fatigue affects 40–80% of PBC patients [5,6]. Fatigue is not only common, for most patients it also constitutes the primary clinical problem, as about 50% of the patients affected describe fatigue as the most bothersome symptom of their disease [7]. In addition to this enormous impact on quality of life, new data suggest an influence on survival in PBC, as well [8].

In order to meet this highly challenging problem in PBC, effective therapeutic strategies for patients affected by fatigue would be highly desirable. However, to date there is no specific treatment for fatigue in PBC [9]. Even though different drugs have been tested in clinical trials, favorable effects have only been shown for Modafinil, such as decreased somnolence and night sleep as well as increased energy levels [10,11], and for methotrexate [12], albeit only described in small case series without adequate placebo controls. In addition to the limited effectiveness, side-effects will limit therapeutic options frustrating both patients and their treating physicians.

The lack of effective therapeutic options for fatigue is explained by our lack of understanding of the underlying pathophysiology. What is the relation to the liver, and to the liver disease? Fatigue, but also other extra-hepatic symptoms in PBC such as Sicca syndrome, calls into question that PBC is only a disease of the liver. None of these symptoms correlate in any measurable way with hepatic disease activity, nor do they correlate with disease stage. In particular, no association could be found between fatigue and the histological stage or degree of hepatocellular dysfunction [5,7,8,13]. It is therefore highly questionable that these are simply extra-hepatic manifestations of a purely hepatic disease. They may, however, be different facets of a more systemic disease. Understanding the pathophysiology of these disease manifestations, and developing new treatment options out of this understanding, is what PBC patients are probably most hoping for.

Liver transplantation is not only an excellent, life-saving treatment option for end-stage liver disease in PBC, it is also an experiment into the pathophysiology of the disease, both hepatic and extra-hepatic. If indeed fatigue is independent of liver disease, transplantation is unlikely to affect fatigue. On the other hand, if fatigue is cured by liver transplantation, this symptom is likely to be a secondary manifestation of hepatic inflammation. This seems to be a simple and important question to answer, but so far it has never been studied systematically. In the current issue of the *Journal of Hepatology*, Carbone *et al.* try to give an answer to this question. In their prospective study, 49 patients with PBC undergoing transplantation were included, however, only 31 could be included in the final analysis. Two control cohorts were identified, one healthy control group and one non-transplant PBC group, both age- and sex-matched. Evaluation of the severity of fatigue was done using the PBC-40, an established questionnaire assessment tool for quality of life including fatigue in PBC [14]. Fatigue was assessed prior to transplantation as well as 6, 12, and 24 months after the operation. Subgroup analyses were performed regarding MELD and UKELD score.

The question, both clinically and scientifically, was straightforward: can liver transplantation cure fatigue in PBC? Disappointingly, the answer to the question appears more complex than one would have expected: fatigue is clearly improved in this cohort by liver transplantation, but persists to a considerable degree in many of the transplanted PBC patients. In particular, in the transplanted PBC cohort, the number of patients with moderate or severe fatigue was reduced from

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Abbreviation: PBC, primary biliary cirrhosis.

89% before liver transplantation to less than 50% two years afterwards; a significant decrease, which was independent of hepatic decompensation prior to transplantation. However, in a relevant number of patients, significant fatigue persisted after liver transplantation and remained clearly higher than in the healthy control group. These mixed results might be due to a variety of factors: the group of patients studied was small, and had a considerable drop-out rate, mainly due to death (n = 12) or to the fact that patients withdrew from the study after transplantation (n = 5), which might have lead to a certain bias. Furthermore, advanced cirrhosis prior to transplantation could have caused various degrees of minimal to manifest hepatic encephalopathy. It may have been very difficult to measure fatigue in encephalopathic patients, and even though the authors tried to control for that, minimal encephalopathy might have escaped their assessment.

Most importantly, the authors failed to include an important control group, which would have been patients transplanted for other liver diseases. We know very little about fatigue following liver transplantation, and the high fatigue scores in transplanted PBC patients in this study could have been at least partly due to factors unrelated to PBC, but related to liver transplantation. The key question is, whether patients transplanted for PBC suffer from significantly more (and different kind of) fatigue than other transplant recipients. Such a finding would strongly support the concept of an extra-hepatic pathogenesis of fatigue in PBC.

Evidence for an extra-hepatic mechanism in the development of fatigue in PBC has grown in the recent years and different mechanisms for fatigue in PBC have been put forward. These include autonomic nervous system dysfunction, progesterone metabolites, psychological elements, mitochondrial dysfunction, cytokines and adipokines as well as structural cerebral abnormalities [9]. In this context, magnetic resonance imaging demonstrated parenchymal changes in the globus pallidus as well as white matter lesions in patients with PBC. Interestingly, these abnormalities correlated to some extent with the severity of fatigue [15,16]. Data from a trans-cranial magnetic stimulation study demonstrated CNS abnormalities in both non-transplanted and transplanted patients [17]. This suggests persistent organic brain injury as a possible factor in persistent fatigue in PBC.

Another possible mechanism of fatigue in PBC might be alterations of the neuroendocrine axis. It can well be that PBC is a more generalized small duct disease manifesting usually in the largest gland of the body, the liver, but also in salivary glands and possibly in some other ductular structures, including neuroendocrine organs.

Thus, we are left with half an answer: liver transplantation is likely to improve fatigue in advanced PBC, but some fatigue is likely to remain. This is a sufficiently encouraging piece of news for PBC patients waiting for transplant. It is also sufficiently clear to exclude transplantation as a therapeutic option for severe fatigue in the absence of advanced cirrhosis. However, it does not sufficiently answer the key scientific question, if fatigue is an extra-hepatic symptom of hepatic inflammation, or a manifestation of an extra-hepatic disease. In this respect, further studies of the pathophysiology on this important issue are needed, including assessment of structural CNS involvement as well as the role of the neuroendocrine axis. Liver transplantation saves the lives of patients with advanced PBC, and it may improve their symptomatic fatigue, but only to some degree. The key for a cure of fatigue in PBC probably lies outside of the liver.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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