Research Article

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The effect of liver transplantation on fatigue in patients with primary biliary cirrhosis: A prospective study

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Background & Aims: The role of liver transplantation (LT) for the relief of fatigue in patients with primary biliary cirrhosis (PBC) is unclear, and while many centers exclude fatigue as an indication for transplantation, there have been no studies to prospectively evaluate the impact of LT on fatigue. We aimed at assessing the severity of fatigue in LT candidates with PBC and the impact of LT on fatigue.

Methods: In a prospective, longitudinal study, we used the PBC-40 questionnaire in 49 adult patients with PBC at listing and at 6, 12, and 24 months after LT and in two sex- and age-matched cohorts of community controls and non-transplanted PBC patients. Correlation analysis was used to assess the relationship between liver function and fatigue. ANOVA was used to compare the variation of fatigue score before and after LT.

Results: There was no correlation between MELD and fatigue before LT ($r^2 = 0.01$). Overall, the fatigue score after LT was substantially lower than before LT, falling from 40.7 ± 11.4 pre-transplant to 27.7 ± 9.5, 28.7 ± 10.1, 26.2 ± 10.1 ($p < 0.0001$) at 6, 12, and 24 months after LT, respectively. The same improvement of fatigue was observed in both low-MELD (<17) and high-MELD (⩾17) patients. Improvement in fatigue was also evident in the comparison with a "non-transplant PBC" control group (31.1 ± 11.6, $p = 0.03$). However, 44% of the total cohort, and 47% of those with low-MELD, for whom the probability of dying of LT may be higher than that of dying without LT, had moderate to severe fatigue (defined as a fatigue score ⩾29) at two years after LT.

Moreover, fatigue scores at two years were higher in the transplant PBC cohort compared to a cohort of community controls (17.8 ± 5.9, $p < 0.0001$).

Conclusions: Liver transplantation is associated with improvement in fatigue in patients with PBC. However, a substantial proportion of patients continue to suffer from significant fatigue after two years. Whether the improvement is enough to justify organ allocation in patients with fatigue alone, without liver failure, is still an open issue. Certainly, in the era of organ shortage, with many patients dying waiting for a graft, this may not represent the optimal use of donated deceased organs.

Introduction

Liver transplantation (LT) is a recognized treatment for patients with end-stage chronic liver disease. The main aim of LT is to extend life and increase patient's quality of life. Outcomes after LT continue to improve and most centers report 5-year survival exceeding 85%. Thanks to the major advances in the field of transplantation with consequent improvement in survival and increasing of the donor pool, more patients today get the opportunity to have their name added to the transplant list than in previous years, including those being transplanted for 'quality of life' (QOL) issues.

In patients with primary biliary cirrhosis (PBC), severe and intractable itching and/or fatigue may lead to poor and unacceptable quality of life [1]. The severity of these symptoms correlates poorly with the severity of liver disease [2–4]. Although the itching improves and usually resolves rapidly after LT, there is uncertainty as to the extent to which fatigue improves after transplantation [3]. Thus, for those with early disease, LT may not only expose the recipient to the risks of transplantation

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Abbreviations: AMA, antimitochondrial antibodies; AZA, azathioprine; CMV, cytomegalovirus; CNS, central nervous system; HRQoL, health-related quality of life; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MMF, mofetil mycophenolate; PBC, primary biliary cirrhosis; PRED, prednisone; QOL, quality of life; SD, standard deviation; TAC, tacrolimus; UKELD, United Kingdom Model for End-Stage Liver Disease.

without survival or symptomatic benefit, but will also deny another recipient access to transplantation.

With this background we undertook a prospective, longitudinal study to look at the effect of LT on fatigue in patients with PBC, using the PBC-40 questionnaire [5] to measure the severity of fatigue.

Patients and methods

Study patients

Patients who consecutively received LT for PBC between July 1, 2006 and June 31, 2008 at the Queen Elizabeth Hospital, Birmingham, United Kingdom, comprised the study population. Forty-nine patients with PBC were prospectively enrolled in the study. All subjects were assessed for LT and registered on the National Liver Transplant List before being invited to participate in the study.

All of these patients had definite or probable PBC defined using established diagnostic criteria (at least two of: {1} cholestatic liver function tests, {2} compatible or diagnostic liver histology, and {3} antimitochondrial antibodies (AMA) at a titre $\geqslant$1: 80) [6]. In order to assess the eligibility of patients to participate in the study, other causes of fatigue, e.g., thyroid disease, depression, anaemia, impaired renal function, and side-effects of medications, were sought at the time of recruitment.

Informed consent in writing was obtained from each patient. The study was approved by the South Birmingham Research Ethics Committee and University Hospital Birmingham NHS Foundation Trust on July 20, 2006. The study protocol was conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the appropriate institutional review committee. No donor organs were obtained from executed prisoners or other institutionalized persons.

Patients were asked to complete the questionnaire at the time of transplant listing and thereafter at four-monthly intervals until transplantation. The questionnaire completed closest to transplantation was considered as baseline. Following transplantation, questionnaires were completed at 6 months, 1 year, and 2 years post-LT. Only patients who completed QOL evaluations before and after LT were included in the patient sample for this study.

Two control cohorts were identified: (a) a cohort of community "normal controls" from the primary physician register, including one sex- and age-matched individual for every case (n = 31); and (b) a "non-transplant PBC" cohort including four sex- and age-matched patients for every case (n = 124). This cohort was obtained under permission of the management committee of the UK PBC Project.

QOL assessment tools

The PBC-40 is a validated, multi-domain disease specific, patient-derived quality assessment tool with robust psychometric properties [5]. This is a 40-item scale that measures and quantifies health-related quality of life in PBC. It consists of six specific symptoms domains (cognitive, social, emotional function, fatigue, itch, and other symptoms) and is designed for self-completion. The PBC-40 fatigue domain is an established tool for the quantification of fatigue in PBC. Non-PBC controls completed the PBC-40c, a tool equivalent to the PBC-40 developed and validated for use in non-PBC subjects and which is directly comparable to the PBC-40 (unpublished data). Patients rate items on a five-point scale (1 = 'never' to 5 = 'always'), with high scores meaning greater symptoms impact and a worse quality of life. We have used ranges of severity for the fatigue domains contained in the PBC-40 as previously defined by Newton and colleagues [7]. By using these cut-off values, "no fatigue" was a score of $\leqslant$11, "mild" was a score of 12–28, "moderate" was a score of 29–39, and "severe" was a score of $\geqslant$40. We have used this specific tool to determine the effect of LT on the quality of life in PBC patients. We gained the permission to use the PBC-40 questionnaire from the authors who validated the tool.

Liver function

The Model for End-Stage Liver Disease (MELD) (3.8 [Ln serum bilirubin (mg/dl)] + 11.2 [Ln INR] + 9.6 [Ln serum creatinine (mg/dl)] + 6.4) and the United Kingdom Model for End-Stage Liver Disease (UKELD) ($5 \times \{1.5 \times \ln(\text{INR}) + 0.3 \times \ln(\text{creatinine}\ (\mu\text{mol/L})) + 0.6 \times \ln(\text{bilirubin}\ (\mu\text{mol/L})) - 13 \times \ln(\text{Na}\ (\mu\text{mol/L}) + 70\}$) were used to assess the severity of liver disease [8,9].

Sub-analysis by "low" and "high" MELD score

We also analyzed the entire PBC cohort split into two groups considering the MELD score. It has been shown that survival benefit, i.e. the risk of dying from the transplant procedure is less than the one of dying from their underlying liver disease, starts when MELD score exceed 17. Therefore, those with a MELD score <17 were considered to have "low MELD" score; those with MELD $\geqslant$17 were classified as "high" MELD score.

Statistical analysis

Data were analysed using SPSS. The correlation coefficient between fatigue score and the score of liver function (MELD, UKELD) before transplant was assessed by Spearman rank test. Fatigue scores in PBC patients before and after LT and in the control populations, and the median Δ change of fatigue scores after LT in those with low *vs.* high MELD, were compared using *t*-test and two-way ANOVA. The numbers of subjects reporting high and low fatigue scores in the high and low MELD populations were compared using the Chi-squared test. Difference was considered statistically significant when $p \leqslant 0.05$.

Results

Forty-nine patients with PBC were enrolled in the study. Twelve patients died either pre-transplant or within the first two years post-transplant. One patient was removed from the list and five patients withdrew the study at some point within the two years. Overall, 31 patients were considered for the analysis. Ninety percent of the participants were women, and the mean age was 54.3 years (standard deviation, SD ± 10.5). The main indications for transplant were liver failure (n = 17), hepatocellular carcinoma (n = 3), and symptoms (n = 10 pruritus; n = 1 lethargy). Fatigue was a co-indication in five patients with pruritus. No relevant co-morbidities were recorded for these patients. Non-hepatic causes for fatigue were excluded in this cohort.

The mean time from recruitment to transplant was 162 days (5.4 months). At the time that the questionnaires were completed before LT, the mean MELD score (unadjusted for hepatocellular carcinoma) was 14.2 ± 4.2 and mean UKELD score was 53.9 ± 4.6.

Distribution of PBC-40 scores was normal, therefore mean ± SD was used as summary statistics (Table 1). Improvement was observed in all the PBC-40 domains, except for the "Emotional" domain, where there was a slight but significant increase in the scores. Mean fatigue score before LT, at the time that the questionnaires were completed, was 40.7 ± 11.4. At 6, 12, and 24 months, following LT, fatigue scores were substantially reduced (27.7 ± 9.5, 28.7 ± 10.1, 26.2 ± 10.1; p <0.0001). Overall, 89% of patients had moderate to severe fatigue before LT. In eight transplant candidates, the time spent on the waiting list was more than 4 months; in these patients, fatigue scores at the interval closest to LT were used as baseline score. It is, however, noticeable that fatigue scores at time of listing and at each interval were very consistent (data not shown).

At 6 months after LT, 46% and 40% of patients had mild and moderate fatigue, respectively, and only 10% had severe fatigue. The reduction of severity of the PBC score remains at one and two years after LT, with 49% and 36% having mild and moderate fatigue at one year, and 50% and 38% having mild and moderate fatigue at two years, respectively; only 12% and 6% still had severe fatigue at one and two years, respectively (Fig. 1). The distress level for each item of the fatigue domain in the PBC-40 is shown in Fig. 2.

The improvement in fatigue was evident also after comparing the fatigue scores at two years after LT with those in the