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Liver transplantation in familial amyloidotic polyneuropathy (FAP). A comparative study of transplanted and non-transplanted patient's survival

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Abstract The purpose of the present study was to evaluate the impact of liver transplantation on familial amyloidotic polyneuropathy (FAP met-30) patients' survival. Forty-five FAP patients were involved in the study; 15 non-transplanted FAP patients and 30 liver-transplanted patients. All patients' records were scrutinised for information on disease duration. Preoperative nutritional status was evaluated in all patients. No difference in survival was observed for transplanted patients overall compared to historical controls. However, for cases in good nutritional status, an increased survival can be expected as a significantly increased mortality rate for malnourished patients was observed ($P < 0.05$). Increased survival has so far not been found for transplanted FAP patients. However, none of the transplanted cases has yet reached the expected survival time for non-transplanted FAP control patients, which is 14 years. A high fatality rate of malnourished patients transplanted late in the course of the disease contributed significantly to the mortality among transplanted patients.

Key words Familial amyloidosis · Inborn errors of metabolism · Liver transplantation

Introduction

Familial amyloidotic polyneuropathy type I (FAP met-30) is an inherited, fatal, systemic amyloidosis that is caused by a point mutation in transthyretin, in which valine is replaced by methionine at position 30 [1, 2, 11]. Since transthyretin is mainly produced by the liver, a liver transplantation should abolish the production of the amyloidogenic transthyretin and halt the formation of amyloid. The first liver transplantation for FAP was performed at Huddinge Hospital in 1990, and today, liver transplantation for FAP is carried out worldwide [5–7, 9, 10, 12].

The outcome of the procedure has been encouraging and is the only available treatment for FAP. The procedure halts the progress of the disease and some improvement in neurological symptoms has been reported [3, 7, 10, 15]. The patient's nutritional status improves after the procedure but the long-term outcome is still uncertain.

The aims of the study were to evaluate factors that have had an impact on Swedish transplanted patients' survival and to compare the outcome for transplanted FAP patients with historical, non-transplanted FAP patients.

Table 1 General characteristics of the 30 transplanted patients and historical controls. (*NS* Not significant)

	Controls	Transplanted	*P*
	Median (range)	Median (range)	
Number of patients	15	30	
Males/females	5/10	18/12	0.08; NS
Age at onset	41 (29–49)	39 (22–54)	NS
Males	43 (29–46)	40 (24–54)	NS
Females	41 (32–49)	37 (22–50)	NS
Time interval from onset to gastrointestinal symptoms	3 (0–14)	2 (0–5)	NS
Follow-up (years)	14 (9–23)	8 (2–14)	0.001

Patients and methods

Patients

Forty-six patients were available for analysis. One transplanted female patient was excluded from the analysis as she had an unusual, slow progression of the disease with a duration of 30 years before she underwent an unsuccessful transplantation [13], so the number of patients included in the analysis was 45, of which 30 were liver transplanted and 15 historical controls. The historical control patients have previously been used in an analysis of the natural course of the disease [14]. The clinical data of the patients are summarised in Table 1.

The transplanted patients underwent the operation during the period 1990–1995 and the evaluation was performed on 1 August 1997. All patients were evaluated at Umeå University Hospital and the diagnosis of FAP was, in all patients, based on the presence of the valine to methionine mutation of transthyretin, amyloid deposits in intestinal mucosa or skin biopsies and an axonal polyneuropathy on EMG examination.

Methods

The patient's medical records were scrutinised for data concerning onset of the disease, survival and, for transplanted patients, nutritional status at transplantation. The nutritional status was evaluated by a modified body mass index (mBMI), which was calculated by multiplying the patient's body mass index by the serum albumin (g/l) concentration to compensate for oedema [14]. Life table analysis was performed by Kaplan-Meier plots and differences in survival were analysed by the Cox-Mantel test. Differences between groups were analysed by the Mann-Whitney U-test.

Results

There was a highly significant difference in the follow-up period between controls and transplanted patients ($P < 0.001$). The mean survival time for historical controls was 14 years (range 9–24). The 10-year survival time for the group of transplanted patients was 74% compared to 73% for non-transplanted historical controls. The survival plot is shown in Fig. 1. There was no statistical difference between the two groups. However, the surviving transplanted patients have not yet reached the expected mean survival time of 14 years observed for the controls.

For malnourished transplanted patients with a mBMI below 600, a significantly increased mortality was found compared with historical controls (Fig. 2; $P < 0.05$). Of the deceased transplanted patients, six out of eight had a mBMI below 600 at transplantation. Long-standing FAP at the time of transplantation (> 7 years) was an aggravating factor, although not statistically significant ($P = 0.1$).

A trend towards an increased mortality was noted for female transplanted patients compared to males, although the difference did not reach statistical signifi-

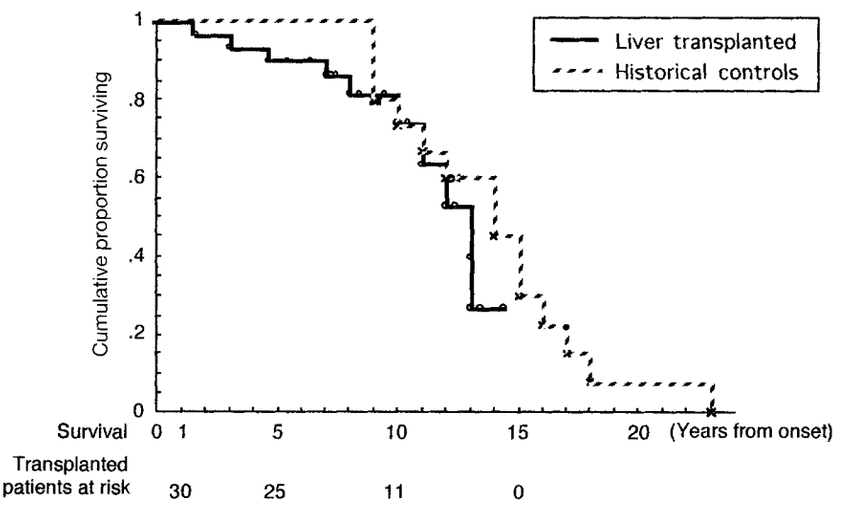

Fig. 1 Kaplan-Meier plot of survival times versus cumulative proportion of surviving transplanted and control patients. Time on the *x*-axis is from onset of disease. The end of the observation period or the patient's death is indicated for transplanted and controls by ○ and ×, respectively

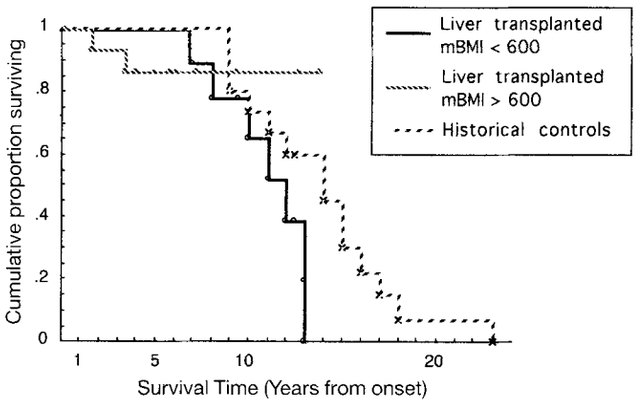

Fig. 2 Kaplan-Meier plot of survival times versus cumulative proportion of surviving transplanted and control patients. Time on the *x*-axis is from onset of disease. The patients are grouped according to their nutritional status, measured by the modified body mass index *(mBMI)*. A significantly decreased survival for transplanted, malnourished (mBMI $\leq$ 600) patients compared to controls is found ($P < 0.05$)

cance ($P = 0.06$). However, female patients' mBMI tended to be lower than that of the males ($P = 0.06$).

Discussion

For FAP patients, no alternative to liver transplantation exists [8]. However, the decision is difficult for patients especially if only minor symptoms of the disease are present. It has proved difficult to forecast the prognosis for individual FAP patients but an early onset of gastrointestinal symptoms is an aggravating factor [14]. The onset of gastrointestinal disturbances often induces a rapid deterioration of the patient's nutritional status, which diminishes the chances of survival after transplantation [16]. In the present study, no significant difference between onset of gastrointestinal disturbances was found for patients and controls. For patients transplanted late in the course of the disease, with a severely depleted nutritional status (mBMI < 600), the survival was inferior to that of the historical controls.

Severe autonomic dysfunction, measured by spectral analysis of beat-to-beat heart rate variation is another important factor that bears on the outcome by inducing blood pressure disturbances during the anhepatic phase of the transplantation [4, 17].

The increased mortality for female transplanted patients compared to males did not reach statistical difference. The trent towards an inferior nutritional status for females compared to males may contribute to the difference.

No difference was observed between transplanted and non-transplanted FAP patients. This can be explained by the relative short follow-up. The majority of successfully transplanted patients have not yet reached the mean survival time of the controls. A significant difference should evolve with further follow-up since no fatalities have been observed in the well nourished group of patients later than 6 months after transplantation.

From the present investigation it can be concluded that liver transplantation should be performed on FAP patients before they suffer severe nutritional depletion. Liver transplantation of severely handicapped and nutritionally depleted FAP patients appears not to increase their survival.

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