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ORIGINAL ARTICLE

The long-term impact of liver transplantation on kidney function in familial amyloidotic polyneuropathy patients

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Summary

The aim of the study is to evaluate the long-term kidney function after liver transplantation (LTx) in familial amyloidotic polyneuropathy (FAP) Portuguese type patients and compare the findings with patients transplanted for chronic liver disease of other origin. We analysed the medical records of 32 FAP patients who underwent transplantation between 1990 and 1999 with a follow-up of more than 1 year after LTx. The control group consisted of 61 patients who had undergone LTx for chronic liver disease. Kidney function was measured by the glomerular filtration rate (GFR), serum creatinine and urea. There were no differences between the groups in creatinine and urea levels during the follow-up. However, during the first year after transplantation, the increase in creatinine and urea was significantly higher in the control group ($P < 0.01$). The decline in GFR after transplantation was also more pronounced in the controls ($P < 0.01$). Initially after LTx, kidney function deteriorated in both FAP and control patients, but the deterioration was more pronounced in the controls. The decline of the FAP patients' kidney function after LTx was not more pronounced than that observed in control patients, although many FAP patients' kidney function was impaired before the procedure, suggesting that LTx may halt the progression of kidney damage caused by amyloid deposition.

Introduction

Familial amyloidotic polyneuropathy (FAP) Portuguese type is an inherited, fatal, systemic amyloidosis that is caused by a point mutation in the protein transthyretin (TTR), in which valine is replaced by methionine at position 30 (ATTR Val30Met) leading to pathological amyloid formation and deposition [1]. TTR is a tetramer that predominantly is synthesized by the liver. The mechanism behind amyloid formation is not known, but it is suggested that mutated TTR is a more unstable tetramer than the wild type and that it more easily breaks down to monomers. The monomers undergo extracellular polymerization and fibril formation in the tissues with predominance for the endoneurial space of the peripheral nerves [2–4]. The disease is characterized by a painful sensory motor polyneuropathy usually starting in the lower extremities and also affecting the autonomic nervous system. In the later stages of the disease, multiple organs are affected including the heart, kidneys, intestines and eyes [5–11]. The mean survival for patients with FAP is reported to be between 9 and 13 years after the onset of symptoms [2–4,12]. As the liver is the main producer of TTR, liver transplantation (LTx) abolishes the production of the amyloidogenic mutated TTR and halts the formation of amyloid. The first LTx for FAP was performed in Sweden in 1990, and the favourable clinical outcome for the first four transplanted patients prompted several centres to perform LTx in FAP patients [13]. Today LTx is carried out worldwide and is regarded as the treatment of choice for FAP [13,14]. So far it appears to halt the progress of the disease and some improvement in neurological symptoms has been reported [13,15–17]. However, the selection of patients is important. Previous reports

indicate that LTx in severely handicapped and nutritionally depleted FAP patients does not appear to increase their survival [18]. As it is difficult to predict the prognosis in the individual FAP patient and often only minor symptoms of the disease are present at the time of decision making, the arrival at a decision regarding early LTx is difficult for both the patient and the doctor [16].

Kidney amyloidosis is a common finding in FAP patients [10] although kidney impairment is not as common as in secondary (AA) or primary (AL) amyloidosis [19]. Besides the deterioration of the kidney function caused by amyloid deposits in the glomeruli, bladder denervation leading to urinary retention is also involved in the deterioration, and bladder dysfunction has been reported to be associated with a poorer outcome [20]. Approximately 5% of the liver transplanted FAP patients reported to the FAP world transplant registry, had also been subjected to a kidney transplantation because of kidney failure [17,20]. It is logical to assume that the replacement of the liver that produces the amyloidotic variant of TTR by a liver graft producing a wild type of TTR, could potentially arrest the destruction of glomeruli by amyloid. If so, LTx may lead to an improvement of the kidney function. On the contrary, episodes of hypotension during the transplantation procedure and the risk of the patients to develop a chronic renal disease because of nephrotoxicity of the immunosuppressive therapy may hamper an improvement in renal function in FAP patients after LTx [21–25]. The aim of this study was to evaluate the long-term kidney function in FAP patients after LTx.

Patients and methods

Retrospective analyses were performed based on the medical records of 32 FAP patients who underwent LTx between 1990 and 1999 and with a follow-up of more than 1 year. A group of 61 patients with chronic liver disease, who were transplanted during the same time period (26 patients with primary sclerosing cholangitis, 26 patients with primary biliary cirrhosis and nine patients with hepatitis B virus) served as controls. Similar selection criteria were used in both groups and the controls were also matched for age. Patients transplanted because of hepatitis C were excluded because hepatitis C virus appears to have a deteriorating effect on kidney function. Likewise, patients with liver cancer were excluded because the expected survival is considerably shorter for this group of patients compared with those of FAP patients. The patient characteristics are presented in Table 1.

In the FAP group, all patients had clinical manifestations of polyneuropathy at the time of transplantation. The diagnosis of FAP in all patients was based on the presence of the valine to methionine mutation in TTR and amyloid deposits in intestinal mucosa or skin confirmed with biopsies.

Table 1. Patient characteristics.

	FAP ($n = 32$)	Control ($n = 61$)
Age at time of transplantation (years)	44 (25–64)	48 (22–70)
Sex (female/male)	14/18	33/28
Follow-up (years)	4.5 (1–9)	5 (1–11)
Basic immunosuppression (CyA/FK)	21/11	35/26
Kidney failure (dialysis)	2	4
Patients alive/dead	24/8	51/10

All patients underwent orthotopic cadaveric LTx and received an ABO compatible graft. Immunosuppressive therapy was based on cyclosporine A or tacrolimus in combination with steroids. The evaluation was based on the latest data obtained before transplantation, on the 1-year post-transplantation control and on the latest data obtained from patients followed for 4 years or longer (in the FAP group 18 patients with a median follow-up of 6.8 years, range 4–9.2 years; in the control group 35 patients with a median follow-up of 7.4 years, range 4–11.5).

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 concentration (g/l) to compensate for oedema [12]. Renal function was evaluated as glomerular filtration rate [GFR; plasma clearance of ^{51}Cr-EDTA, adjusted for the body surface area (ml/min/1.73 m^2)], and measurements of serum creatinine (μmol/l) and urea (mmol/l). GFR at 4+ years evaluation was available in nine FAP patients and in 27 controls.

Blood pressure, immunosuppressive regimen and the number of episodes requiring rejection treatment were also analysed.

Statistics

The ANOVA test was employed throughout the study. Differences in increase or decrease in parameters between groups were tested with the Mann–Whitney *U*-test. Survival analysis was performed using Kaplan–Meier and Cox regression methods. Data are presented as median (range). The differences were considered significant when $P < 0.05$.

Results

There were no differences between the groups regarding patient age at the time of transplantation, patient sex,

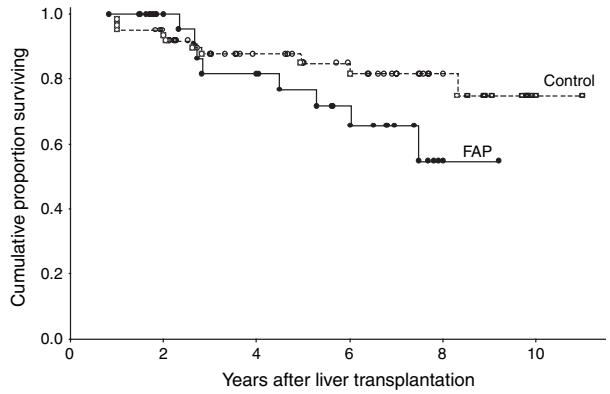

Figure 1 Analysis of survival in FAP (•) and control (○) patients who survived more than 1 year after liver transplantation.

patient survival, basic immunosuppressive therapy, episodes of kidney failure treated with haemodialysis and patient survival [Table 1; Fig. 1].

No difference was found in serum creatinine and urea levels between the groups during the follow up. A significantly higher increase in creatinine and urea was seen in controls than in the FAP patients [creatinine increase of 40 (−35 to 489) vs. 19 (−88 to 79) (Table 2) and urea increase of 4 (−7 to 79) vs. 2 (−46 to 10), respectively, $P < 0.01$]. The observed increase in creatinine was reflected by a correspondingly more pronounced decrease in GFR in the controls [GFR decrease of −33 (−94 to 13) vs. −18 (−77 to 1), respectively, $P < 0.01$; Fig. 2]. A more marked decline in GFR for controls was also found at the 4+ years evaluation [−45 (−75 to −3) vs. −21 (−57 to 4), respectively $P < 0.01$].

Arterial blood pressure behaved differently after transplantation in the two groups. Despite a tendency of higher systolic pressure before transplantation in the FAP patients [125 (85–185) than in the controls 120 (80–140); $P < 0.08$], the systolic blood pressure increased significantly more in the control group than among the FAP patients during the first year after transplantation [20 (−60 to 60) vs. 7 (−60 to 45), respectively, $P < 0.01$; Table 2). After the first year after LTx, a continued increase in the systolic blood pressure was observed among control patients while it remained stable in the FAP group [10 (−40 to 40) and −10 (−40 to 25), respectively, $P < 0.01$]. Similar changes were noted for the diastolic blood pressure, although the diastolic blood pressure was higher among FAP patients than among the controls before transplantation [80 (50–110) vs. 70 (40–90), respectively, $P < 0.01$; Table 2].

Before transplantation, FAP patients had significantly higher mBMI than control patients [811 (382–1114) and 563 (326–1000), respectively $P < 0.01$; Table 2]. During

Table 2. Serum creatinine, modified body mass index (mBMI), arterial systolic and diastolic pressure in FAP and control patients before, 1 year after and 4 years or more (4+) years after liver transplantation (LTx).

	Before LTx	1 year after LTx	4+ years after LTx
Creatinine			
FAP	80 (51–182)	100 (67–240)	106 (58–569)
Control	76 (49–193)	119 (68–583)	131 (80–454)
mBMI			
FAP	811 (382–1114)	895 (486–1301)	875 (385–1183)
Control	563 (325–1000)	927 (477–1462)	907 (613–1150)
Arterial systolic blood pressure			
FAP	125 (85–185)	125 (100–170)	120 (100–160)
Control	120 (80–140)	135 (60–185)	140 (100–175)
Arterial diastolic blood pressure			
FAP	80 (50–110)	80 (60–110)	80 (55–90)
Control	70 (40–90)	85 (60–115)	85 (65–100)

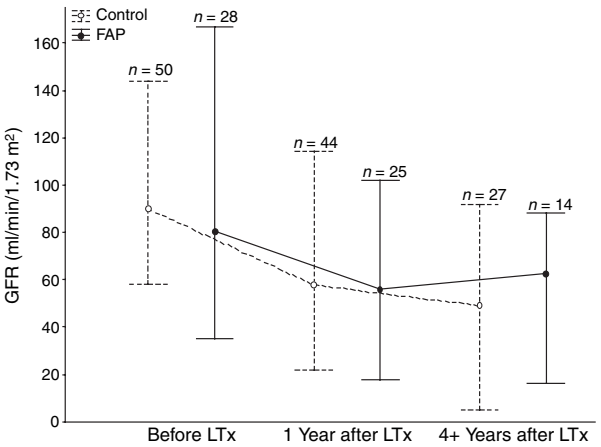

Figure 2 Renal function monitored with glomerular filtration rate (Cr EDTA) in FAP (•) and control (○) patients who survived more than 1 year after liver transplantation.

the first year after transplantation a significantly higher increase in mBMI was observed in the control group compared with FAP patients [368 (−308 to 1108) vs. 63 (−392 to 438), respectively, $P < 0.01$). After the first year after LTx mBMI remained stable in both groups.

An analysis of the basic immunosuppressive regimen and the number of rejection episodes did not reveal any significant differences between the groups.

Discussion

Previous studies have shown that up to 70% of liver transplant recipients develop renal insufficiency in the early postoperative period [26]. Although renal function often deteriorate with time after LTx [23], a stabilization in function has been observed in patients with a

long-term follow-up [27]. Our study demonstrates a significant decline in kidney function during the first year after LTx both in the FAP patients and in the matched control group. After the observed initial kidney damage, the function appeared to stabilize in both groups. However, in contrast to our expectations the kidney damage appeared to be more pronounced in the controls as indicated by the higher increase in creatinine and corresponding decrease in GFR during the first year after transplantation. This may in part be explained by a higher increase of mBMI in the control group than in the FAP patients. The immunosuppressive therapy seems less likely to be the cause for this difference, because the target blood trough levels of tacrolimus or cyclosporine were similar in both groups. The more marked decrease in GFR among the controls than in the FAP patients supports the assumption that LTx may have a beneficial effect on the kidney damage caused by amyloid kidney deposits. The observed changes in GFR in the control group closely correlate with previously reported data [27], and the better preserved GFR in the FAP group seems to be specific for this group of patients. For ethical reasons, kidney biopsies were not routinely performed in our patients, therefore a histopathological proof of diminished amyloid deposition in the kidney or differences between the groups with regard to the toxic effects of immunosuppresion on the kidneys cannot be provided. As there is a significant decline in renal function in FAP patients after transplantation, these patients should be evaluated for combined liver–kidney transplantation if their preoperative creatinine clearance is consistently lower than 25–30 ml/min/1.73 m^2, in conformity with the evaluation of other liver transplant candidates having longstanding renal dysfunction [28].

The FAP patients in this study had higher mBMI values before transplantation than the controls, but during the first year the mBMI among control patients increased more than that in the FAP patients. This could be the result of the fact that FAP patients with a low mBMI have an increased mortality after LTx [12,17]. Patients with very low mBMI died within the first year after transplantation and they were excluded from the study according to the study protocol. Furthermore, FAP patients are today transplanted at an early stage of the disease, before they develop marked malnutrition [18].

Poorly controlled blood pressure is known to have a significant impact on the kidney function after transplantation. A relatively stable blood pressure was observed in the FAP patients in contrast to the control patient's blood pressure that increased steadily after transplantation. This is likely to have contributed to the more pronounced loss of kidney function observed in controls when compared with FAP patients. Detailed protocol evaluation of the antihypertensive treatment was not performed in the present study, but the same principles of antihypertensive treatment were applied in both groups. The relatively stable blood pressure after transplantation in FAP patients may also have been an effect of the autonomic neuropathy that is a known complication of FAP.

In conclusion, during the first year after LTx, kidney function deteriorates in FAP patients like it does in other liver transplanted patients. However, although FAP patients often have an impaired kidney function as a complication of their disease, the loss of kidney function after LTx was comparable and in some aspects less than that in other liver transplanted patients. Our results indicate that LTx in FAP patients may have a beneficial effect on their kidney function in the long-term, because of the cessation of amyloid formation and deposition within the kidneys.

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