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Orthotopic liver transplantation in familial amyloidotic polyneuropathy is associated with long-term progression of renal disease

Ana Carina Ferreira[1], Fernando Nolasco[1], Sandra Sampaio[2], Alexandre Baptista[2], Pedro Pessegueiro[3], Estela Monteiro[1], Eduardo Barroso[1]

[1] Transplantation Unit, Hospital de Curry Cabral. Lisbon, Portugal.
[2] Nephrology Department, Hospital Distrital de Faro. Faro, Portugal.
[3] Nephrology Department, Hospital do Espírito Santo. Évora, Portugal.

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ABSTRACT

Orthotopic liver transplantation has become the treatment of choice for familial amyloidotic polyneuropathy. The aims of this study were to evaluate the renal complications post orthotopic liver transplantation in familial amyloidotic polyneuropathy and their impact.

We retrospectively studied 185 recipients who underwent 217 orthotopic liver transplants. Mean age 36.8±9.5 years, 59% males, 14.3% with renal dysfunction pre orthotopic liver transplantation. Mean follow-up 3.6±3.7 years. Thirty-two patients died. Univariate and multivariate analysis were performed, and $p<0.05$ was considered significant.

Acute kidney injury occurred in 57 patients and renal replacement therapy was needed in 16/57. In multivariate analysis, acute kidney injury was correlated with development of chronic kidney disease ($p<0.001$).

Relating to development of chronic kidney disease, 23.5% had progress to stage 3, 6% to stage 4 and 5.1% to stage 5d. According to Spearmen correlation, risk factors for chronic kidney disease development were age ($p<0.001$), renal dysfunction pre orthotopic liver transplantation ($p<0.001$) and acute kidney injury post orthotopic liver transplantation ($p<0.001$).

Mortality was correlated with age ($p<0.001$), re-transplantation need ($p=0.004$), renal dysfunction pre orthotopic liver transplantation ($p<0.001$), acute kidney injury post orthotopic liver transplantation ($p=0.04$), and chronic kidney disease stage 5 ($p<0.001$). Using binary regression, mortality was correlated with chronic kidney disease development ($p=0.02$).

In conclusion, familial amyloidotic polyneuropathy patients are disposed to renal complications that have a negative impact on the survival of these patients.

Key-Words:
Familial amyloidotic polyneuropathy; liver transplantation; mortality; renal dysfunction.

INTRODUCTION

Familial amyloidotic polyneuropathy (FAP) is a systemic amyloidotic disease, inherited in an autosomal dominant mode[1,2]. This disease is due to

a mutant gene in chromosome pair 18 that codifies transthyretin (TTR) protein[1,2]. To date, more than 80 amyloidogenic TTR variants have been described[3]. In Type I (Portuguese, Swedish and Japanese variant), the most frequent form, firstly described by Corino de Andrade[4,5], there is an amino acid substitution of methionine for valine at position 30 (V30M) of the TTR molecule[1-3,6,7]. This amino acid substitution leads to TTR protein instability that gives rise to insoluble fibres with β-sheet structures, which are deposited in the extra-cellular matrix as amyloid aggregates. However, the mutate form is not truly necessary for the amyloid deposits, since wild type is found in senile amydoidosis[2].

The Portuguese type is severe, and the amyloid deposits are diffusely distributed in the peripheral nervous system of FAP patients[1]. The symptoms start in the lower extremities, with spontaneous pains, numbness and loss of temperature sensations that extend above ankle level. Motor deficit also occurs, with loss of balance and stepping gait[3]. There is a progression of the disease with a multisystemic involvement: peripheral sensorimotor polyneuropathy, autonomic dysfunction causing orthostatic hypotension, cardiac arrhythmias, gastrointestinal dysmotility, erectile dysfunction and sphincter disturbances[1-3,8]. Renal involvement is common. All patients have amyloid deposits in the kidney, but not all will have nephropathy[1]. FAP nephropathy has special epidemiological features and only one third of the patients develop chronic kidney disease (CKD) and 10% progress to CKD stage 5d[1].

Without treatment, the patients die after eight to ten years, following the development of muscular atrophy, severe autonomic neuropathy and malnutrition[9,10]. Because more than 90% of the mutant protein is produced by the liver, orthotopic liver transplantation (OLT) has been proposed to treat this disease. The first OLT for treatment of FAP patients was performed in 1990 by Holmgren[11]. Follow-up of these patients was successful, and it is considered to date an effective treatment in clinical management of the disease[12-14].

After OLT, kidney disease is a very important problem, and this complication significantly compromises patient outcome[15-17] and increases mortality risk[18-20]. Several factors, such as the presence of renal dysfunction pre OLT, the use of calcineurin inhibitors and the development of hypertension or diabetes could exacerbate kidney function[15,18,19].

The aims of this study were to evaluate the incidence of renal complications post OLT in patients with FAP, to identify possible risk factors and to determine the impact on patient survival.

PATIENTS AND METHODS

Study design

This was a retrospective study of 185 FAP patients submitted to 217 OLT in our unit over a fifteen-year time period. Data were collected at day 0, 1, 7 and 21, at 6 months, 12 months and yearly after transplantation, up to the end of the study.

Clinical data included age, gender, weight, presence of diabetes mellitus, hypertension, hepatitis B and C infection, immunosuppression and need for acute renal replacement therapy (RRT). Laboratory data included serum creatinine (Scr) values and/or glomerular filtration rate (GFR), estimated by Cockcroft-Gault equation.

Renal dysfunction before transplantation (RD pre OLT) was defined by GFR ≤60ml/min or Scr ≥1.5 mg/dl. There were no records concerning proteinuria/microalbuminuria in patients' clinical files.

Acute kidney injury (AKI) was defined according to the RIFLE criteria[21] as a persistent decrease in renal function for at least three days using the worst value for renal function in that period.

At the end of follow-up and depending on the last value of GFR, renal function was classified according to the K/DIGO Clinical Practice Guidelines[22].

Patients submitted to simultaneous liver and kidney transplants were excluded from this study.

Biochemical analysis

Biochemical analysis was performed using standard laboratory methods.

Immunosuppression protocols

Over the fifteen-year period, different immunosuppressive protocols were used. Induction protocols with ATG or basiliximab were rarely employed until 2007. Steroids were usually applied in all patients for the first months (20 mg/day), and slowly diminished up to twelve months. The association of ciclosporin and azathioprine were used in the majority of recipients up to 2003, and, since then, tacrolimus and MMF have been used. Since 2001, sirolimus has been used in a limited number of recipients. The use of ciclosporin, tacrolimus, sirolimus, azathioprine or MMF was considered as a dichotomous variable (yes or no).

Statistical analysis

Data are presented as mean±SD values for normally distributed variables or as frequencies for categorical variables. Independent variables were compared using the Mann Whitney and the chi square tests. Correlations between variables were studied with Spearman correlation test for univariate analysis, and by binary regression for multivariate analysis (confidence interval of 95%), with forward method. All tests were performed using the SPSS system 15.0 (SPSS Inc., Chicago, IL) and a p< 0.05 was considered statistically significant.

RESULTS

Table I shows the clinical characteristics of our population. Up to 2007, 217 FAP patients were transplanted in our unit, with a mean follow-up of 3.6±3.7 years, with 28.6% (n=62/217) having more than five years and 8.8% (n=19/207) more than ten years of follow-up. These patients were predominantly young males, with a global mean age of 36.8±9.5 years. Arterial hypertension was present in only 17 patients and a minority was diabetic (n=2) or HCV (n=2) infected patients. There was no HBV infection among these patients. Re-transplantation was needed in 14.7% (n=32), due predominantly to thrombotic complications.

Table I

Clinical characteristics of the population

Variable	OLT (n=217)
Age (yr)	36.8±9.5
Gender	
Male	128 (59%)
Female	89 (41%)
Diabetes (%)	0.9% (2)
Arterial Hypertension (%)	7.8% (17)
Hepatitis C virus infection (%)	0.9% (2)
Hepatitis B virus infection (%)	0%
Renal dysfunction pre transplantation	14.3% (31)
Acute kidney injury	26.3% (57)
Chronic kidney disease	34.6% (75)
Stage 3	23.5% (50)
Stage 4	6% (13)
Stage 5	5.1% (11)
Re-transplantation (%)	14.7% (32)
Mean follow-up time (yr)	3.6 ±3.7
Mortality (%)	14.7% (32)
Immunosuppression (%)	
With Ciclosporin	44.5%
With Tacrolimus	49.2%
With Sirolimus	6.3%

OLT (orthotopic liver transplantation).

Renal dysfunction before transplantation

RD pre OLT was known in 14.3% (n=31) of the recipients. These patients were older (r=0.3; p<0.0001) and this finding was more frequent in women (r=0.3, p<0.0001) and in hypertensive patients (r=0.2; p=0.01). There was no correlation between the presence of RD pre OLT and diabetes or HCV infection.

Using Spearman correlation, RD pre OLT was associated with F criteria of AKI classification (r=0.2, p=0.02), CKD development (r=0.5, p<0.001): stage 3 (r=0.4; p<0.001), stage 4 (r=0.2; p=0.03), stage 5d (r=0.2; p=0.01), with RRT requirement (r=0.2; p=0.003) and with mortality (r=0.2; p=0.002). For multivariate analysis, adjusting for age, gender, and for AKI post transplant, it was significantly correlated with development of CKD (p<0.001).

Acute kidney injury (AKI)

AKI was observed in 57 (26.3%) patients (Table II), predominantly in women (r=0.2; p=0.02). Acute RRT was needed in 16/57 patients (r=0.4; p<0.001). Only a minority recovered their renal function, with a GFR ≥60ml/min (r=-0.5; p<0.001): 25 (43.8%) developed CKD stage 3 (r=0.3; p<0.001), 9 (15.8%) developed CKD stage 4 (r=0.3; p<0.001), and 8 (14%) of these patients are on haemodialysis (r=0.2; p<0.001); 13 (22.8%) patients died

Table II

Clinical characteristics of the population according to the presence or absence of AKI or CKD

	AKI (n=57)	No AKI (n=160)	CKD (n=75)	No CKD (n=142)
Mean age (yr)	37.5±10.1	36.6±9.3	40.2±10.4	35.1±8.6
Male gender (%)	45.6% (26)	63.8% (102)	45.3% (34)	66.2% (94)
Diabetes (%)	0%	1.3% (2)	2.7% (2)	0%
Arterial hypertension (%)	14% (8)	5.6% (9)	12% (9)	5.6% (8)
Hepatitis C virus infection (%)	0%	1.3% (2)	0%	1.4% (2)
Renal dysfunction pre OLT (%)	21.1% (12)	11.9% (19)	37.3% (28)	2.1% (3)
Acute kidney injury (%)	100%	0%	52% (39)	11.3% (16)
CKD	73.7% (42)	20.6% (33)	100%	0%
Stage 3	43.9% (25)	16.3% (26)	68% (51)	
Stage 4	15.8% (9)	2.5% (4)	17.3% (13)	
Stage 5	14% (8)	1.9% (3)	14.7% (11)	
Re-transplantation (%)	21.1% (12)	12.5% (20)	20% (15)	12% (17)
Mean follow-up time (yr)	3.3±3.6	3.7±3.7	4.3±4.3	3.2±3.3
Mortality (%)	22.8% (13)	11.9% (19)	25.3% (19)	9.2% (13)

AKI (acute kidney injury); CKD (chronic kidney disease).

(r=0.1; p=0.04) In multivariate analysis, adjusting for age and for presence of renal dysfunction before OLT, AKI correlated with development of CKD (p<0.001).

Chronic kidney disease (CKD)

According to KDOQI definitions, 34.6% (n=75/217) of the recipients developed CKD, with 51 patients (23.5%) attaining a stage 3, 13 patients (6%) a stage 4 and 11 patients (5.1%) attaining a stage 5d (Table II).

In univariate analysis, RD pre OLT (r=0.5; p<0.001) and AKI post OLT (r=0.5; p<0.001), as mentioned, were risk factors for CKD development in all three stages. Age (r=0.3; p<0.001) was also a risk factor for CKD development, especially in stages 4 and 5d (r=0.2; p=0.003; r=0.2; p=0.008; respectively), and acute RRT requirement (r=0.4; p<0.001), specially in stage 5 (r=0.8; p<0.001). Arterial hypertension was found to be a risk factor for CKD stage 4 (r=0.3; p<0.0001), and diabetes a risk factor for stage 5 (r=0.2; p=0.001). CKD was associated with increased mortality (r=0.2; p=0.001), and this observation had particularly impact on patients with CKD stage 5d (r=0.4; p<0.001). There were no correlations between immunosuppression protocols and CKD other than a beneficial effect of tacrolimus (r=-0.2; p=0.03) on chronic renal dysfunction.

In multivariate analysis, and adjusting for age, RD pre OLT, and AKI post OLT, CKD correlated with mortality (p=0.02).

Table III

Multivariate analysis for CKD development

	CKD development			
	β	CI 95%	p	R2
RD pre OLT	3.5	8.2 to 127.6	<0.001	
Age	0.7	1 to 1.1	0.003	0.6
Gender	0.2	0.5 to 2.8	0.6	
AKI post OLT	2.8	6.5 to 37.7	<0.001	
AKI	2.8	6.5 to 38.8	<0.001	
Age	0.7	1 to 1.1	0.002	0.6
RD pre OLT	3.5	8.2 to 131.2	<0.001	

CKD (chronic kidney disease); AKI post OLT (acute kidney injury post orthotopic liver transplantation);
RD pre OLT (renal dysfunction pre orthotopic liver transplantation).

Mortality

By the end of follow-up, 32 (14.7%) FAP patients died, with a mean follow-up of 1.8±3.2 years (r=-0.3; p<0.001). Follow-up time was shorter in older patients

Table IV

Multivariate analysis for mortality

	Mortality			
	β	CI 95%	p	R2
CKD development	1.9	1.2 to 38.2	0.02	
Age	0.004	0.9 to 1	0.2	0.3
AKI post OLT	0.6	0.5 to 6	0.4	
RD pre OLT	1	0.9 to 9.2	0.08	

AKI post OLT (acute kidney injury post orthotopic liver transplantation); CKD (chronic kidney disease);
RD pre OLT (renal dysfunction pre orthotopic liver transplantation).

(r=-0.2; p=0.009) and in re-transplanted patients (r=-0.3; p=0.001).

According to our results, in univariate analysis mortality was associated with age (r=0.3; p<0.001) and need for re-transplantation (r=0.2; p=0.004).

Mortality was also linked to renal dysfunction, including renal dysfunction pre OLT (r=0.3, p<0.001); AKI post OLT (all classes: r=0.2; p=0.04; F class: r=0.1; p=0.03) and CKD development (all stages: r=0.2; p=0.001; stage 5: r=0.4; p<0.001).

Using binary regression, mortality was correlated with CKD development (p=0.02).

DISCUSSION

Liver transplantation is expected to cause a partial regression or stabilisation in the majority of symptoms in FAP patients. In fact, the neurological symptoms stabilise, but there is usually no significant improvement[13]. In addition, OLT must be performed early, prior to the development of malnutrition, which is associated with high morbidity and mortality[10]. Nephropathy, as demonstrated by the presence of microalbuminuria or overt proteinuria, develops concomitantly with progression of the neurological disease, but occasionally may be present from the beginning and may affect one third to 75% of the patients[23]. Recently, it has been shown that patients with normal renal function and low levels of proteinuria have slow progression to ESRD, irrespective of the duration of their neuropathy[24].

Renal dysfunction appears to be an important issue after OLT transplantation, as it is associated with higher mortality. Our study evaluates the long-term impact on renal function in 185 FAP patients submitted to 217 OLT procedures. There was a male preponderance, as is usual in FAP patients, and the mean age was 36.8±9.5 years. In Portugal mean age of onset of the disease is 33.5±9.5 years[2] and this difference probably reflects listing time.

In our study, kidney dysfunction established by glomerular filtration rate, not by the presence of proteinuria/microalbuminuria, was present in 14% by the time of OLT. Of note, this proportion may be certainly higher, as renal functional status in FAP patients can be underdiagnosed, due to malnutrition and reduced muscular mass, and this contributes to false lower Scr levels. However, it may be used to follow changes of renal function, as the BMI remains constant after OLT. Patients with RD pre OLT were predominantly female gender. Other groups have also shown that female gender is a risk factor for the development of CKD in FAP patients[1,2]. Significantly, patients presenting with RD pre OLT were at higher risk of developing AKI and CKD after OLT, and had a higher risk of mortality.

These findings impose a question: renal function pre OLT predicts an increased risk of postoperative renal failure, infection and death. This item, in many of these studied patients, is overestimated. We can conclude that in some patients a hidden risk with major consequences exists. Perhaps some patients would benefit from liver-kidney transplantation (LKTx), as haemodialysis dependence is higher in RD pre OLT patients. In this case, simultaneous LKTx has potential advantages; it avoids the progression of systemic manifestations of amyloidosis, avoids recurrence of renal amyloidosis and avoids the need for haemodialysis, providing a long-term substitution therapy for renal failure[25,26]. There are published articles recommending combined LKTx for CKD stage 5d in FAP TTR Val30Met[25,26].

There is little published data, and appropriate criteria for simultaneous LKTx both in acute and chronic kidney diseases are being studied. The Consensus Conference on Simultaneous Liver Kidney Transplantation Review Board has proposed the following indications[27]: 1) end stage renal disease and symptomatic portal hypertension; 2) liver failure and CKD below 30 ml/min; 3) AKI with Scr 2 mg/dl and dialysis for more than 8 weeks; 4) liver failure and CKD with more than 30% of glomerulosclerosis / fibrosis. Looking at these criteria, combined LKTx in FAP should be proposed to some patients on the topic of their renal function pre OLT. Nevertheless, it is important to note that patients with amyloidosis undergoing renal transplantation tolerate complications poorly and are at high risk of dying within the first three months, and autonomic neuropathy causing urinary retention is an additional difficulty in kidney transplantation[26]. As it is a complex surgical procedure, immediate post transplantation time is crucial to its good outcome. In the long-term, hepatitis C virus

infection, panel reactive antibody › 20% and female donor gender are contributing factors for unfavourable outcomes[28].

AKI was observed in 26.3% of the patients after OLT. The development of AKI was a poor prognosis factor, as it was correlated with CKD. Indeed almost 74% remained with CKD.

Overall, CKD affected 34.6% patients. Hypertension, diabetes, need of RRT, RD pre OLT and AKI were risk factors for the development of different stages of CKD. Immunosuppressive protocols may impact on renal function; in reality one of the most important causes for CKD post OLT is calcineurin inhibitor toxicity, and this emphasises the need for calcineurin inhibitor minimisation protocols post transplant. In this population, mortality was correlated with CKD stage 5. Mortality was additionally correlated with age, re-transplantation and with renal dysfunction prior to OLT and with AKI, mainly with severe AKI, defined by F class.

Despite these results there are some limitations to our study. Firstly, renal dysfunction was only acceded by Scr, as there were no records regarding proteinuria, and this is an important tool to access nephropathy. Secondly this is a retrospective study, with all those drawbacks.

In conclusion, CKD development after OLT was observed in one third of our population and renal failure was associated with mortality. These results reinforce the need for early OLT for better outcome and inevitable referral to the nephrologists when there is impairment of renal function. As mortality was higher when there was renal dysfunction, we can conclude that renal complications are important prognostic tools in these patients.

Conflict of interest statement. None declared.

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Correspondence to:
Dr Ana Carina Ferreira
Hospital de Curry Cabral
Rua da Beneficência 8
1069 Lisbon, Portugal
E-mail: karinadacostafer@hotmail.com