ELSEVIER

OUTCOMES

End-Stage Renal Disease in Familial Amyloidosis ATTR Val30Met: A Definitive Indication to Combined Liver-Kidney Transplantation

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AUTOSOMAL dominant amyloidoses characterized so far are most commonly associated with transthyretin (TTR), a plasma protein synthesized by the liver.[1] The single gene for TTR[2] is located on human chromosome 18; more than 70 TTR mutations have been documented.[3]

The most common type of hereditary amyloidosis is familial amyloid polyneuropathy type I (FAP, Portuguese type), a neuropathic form associated with a substitution of methionine for valine at position 30 of the TTR gene, TTR Val30Met.[4] The largest number of patients and families with this mutation has been identified in Portugal, but now it has been recognized worldwide.[3]

FAP in Portugal usually begins in the third or fourth decade of life with death occuring about 11 years later.[5] The clinical disease usually starts as a sensory neuropathy in the lower extremities, but autonomic and gastrointestinal features may occur early. Motor neuropathy usually manifests itself later with cardiac conduction disturbances frequently leading to the need for artificial pacing. Vitreous deposits of amyloid have been reported, most particularly in Swedish families.[6] Cachexia has been described as a significant factor in mortality.[3] Orthotopic liver transplantation (OLT) is widely recommended for patients affected by FAP; it is recognized as the only specific treatment for this disease.[7] Virtually all TTR is produced by the liver, and, therefore, OLT halts the supply of variant amyloidogenic TTR (ATTR).

Amyloid proteins have different organ specificity, leading to variations in clinical features. Classically, nephropathic and nonneuropathic autosomal dominant amyloidoses are associated with apolipoprotein A-I and A-II, fibrinogen Aα-chain, and lysozyme.[8] Renal amyloidosis also has been described in FAP.[9] In Portugal, approximately one third of FAP patients have clinical renal features with varying degrees of proteinuria and renal failure. The progression to end-stage renal disease (ESRD) occurs in 10% of Portuguese patients, more than 10 years after the onset of symptoms (Lobato et al, unpublished data). Although dialysis may prolong life, it does not prevent the progression of systemic amyloid involvement; death occurred, on average, at 22 months after renal replacement therapy. The cause was infection in one half of the patients (Lobato et al, unpublished data).

The first successful renal transplantation in a patient with renal amyloidosis was reported in 1968,[10] but until now this treatment has been associated with poor graft and patient survival.[11] Most published series concerning renal transplantation in amyloidosis deal with familial Mediterranean fever or other forms of reactive amyloidosis (AA type).[12] The results of kidney transplantation in ATTR have not been described.

In patients with FAP undergoing dialysis, the potential advantages of simultaneous liver-kidney transplantation instead of isolated kidney transplantation are to avoid the progression of systemic manifestations and the recurrence of renal amyloidosis. The obstacles to renal transplantation

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0041-1345/03/$–see front matter
doi:10.1016/S0041-1345(03)00331-2

in these patients are the presence of postural hypotension, advanced motor deficits, neurogenic bladder, and decubitus ulcers related to the long duration of the disease.

We report here on two Portuguese patients with familial amyloid neuropathy, TTR Val30Met, who underwent combined liver-kidney transplantation for ESRD caused by amyloidosis. Both patients have been followed up for more than 18 months after surgery. We analyzed their clinical course and main complications after the procedure.

PATIENTS AND METHODS

Selection of Patients

The reported patients were selected from a cohort of 22 subjects with FAP, all carrying the TTR Val30Met mutation and receiving dialysis during 1999. The two patients had family history of FAP, TTR amyloidosis in renal biopsy specimens shown by congophilic deposits with green birefringence under polarized light, and positive immunolabelling by anti-TTR monoclonal antibodies. Our conditions for combined liver-kidney transplantation were as follows: (1) ability to walk without aid or no more than one crutch to walk; (2) absence of permanent bladder catheter, (3) absence of neurogenic or decubitus nonhealing ulcers; (4) absence of dialysis-related syncope or persistent vomiting due to autonomic neuropathy; and (5) general conditions suitable for kidney and liver transplantation.

Immunosuppressive Protocol

Induction therapy included rabbit antithymocyte globulin (ATG; 3 mg/kg/d), cyclosporine (6 mg/kg/d), azathioprine (2 mg/kg/d), and prednisolone (500 mg intravenously followed by tapering doses until 0.5 mg/kg/d oral at day 6 after transplantation). Cyclosporine was adjusted to obtain trough blood levels between 150 ng/mL and 250 ng/mL (whole-blood, fluorescent polarization immunoassay) for the first 8 weeks. The long-term immunosuppressive regimen included cyclosporine maintaining trough blood levels between 100 and 150 ng/mL (using the same measurement technique), azathioprine (0.5–1 mg/kg/d), and prednisolone (10 mg/d during the first 2 years, 5 mg/d thereafter).

Antimicrobial Prophylaxis

Immediate posttransplantation antimicrobial prophylaxis consisted of teicoplanine (6 mg/kg/d every 72 hours for 1 week), aztreonam (500 mg every 8 hours for 3 days), trimethropim (160 mg) and sulfamethoxazol (800 mg) every 24 hours, and nystatin mouth wash for 6 months. Antiviral therapy with ganciclovir 500 mg every 12 hours for 3 months was used to prevent cytomegalovirus infection. One year after transplantation, we started antimicrobial prophylaxis for urinary tract infection (UTI) with oral first generation cephalosporin or amoxacillin every 24 hours.

Clinical Procedures and Evaluation

The patients were offered combined liver and kidney transplantation using a single cadaveric donor who was ABO blood group compatible of 0 HLA match and with a negative crossmatch. A ureteral stent was placed at the time of renal transplantation and removed between the second and the third week after surgery. Our policy was to remove the urinary catheter at 1 or 2 weeks after removal of the ureteral stent, to avoid precocious urinary tract obstruction due to a neurogenic bladder in the presence of a stent.

Patients were discharged from the hospital when they were able to walk (alone or with aid) and to feed themselves. Daily physiotherapy was initiated 1 week after surgery and carried out during the first hospital stay; physiotherapy was maintained twice per week in the first 3 months after transplantation.

An accurate examination of the skin was performed routinely after transplantation. Superficial wounds, particularly in the extremities, were treated with topical clorhexidine and fusidic acid adjunctive.

Patients were categorized according to a modified disability scoring system[13] before transplantation and at the end of follow-up: score I, sensory disturbances in the extremities but preserved walking capacity; score II, difficulties walking without the need for a walking stick; score IIIA, one walking stick or one crutch required for walking; score IIIB, two walking sticks or crutches required; and score IV, patients in a wheelchair or bed-confined.

The symptoms of autonomic neuropathy were systematically questioned. Measurements of blood pressure and pulse rate in the recumbent and standing positions were recorded on each visit. Urinalysis with screening of proteinuria and bacteriuria were assessed at all visits. Criteria for antimicrobial therapy in UTIs included all positive cultures with more than 10^5 bacterial colonies during the first 6 months, and symptomatic bacteriuria thereafter (pyuria and fever). One single urethral catheterization was recommended in case of a UTI with urinary residue.

Evaluation of amyloid involvement within the vitreous humor of the eye and two-dimensional and M-mode echocardiography were performed at least 6 months before transplantation and during the follow-up.

RESULTS

Patients' Characteristics

Patient 1. Patient 1 was a 44-year-old woman when first evaluated in 1994 and is of Portuguese ancestry. She had sinus bradycardia, hypertension, and nephrotic syndrome. Sensory neuropathy of the lower limbs and constipation began 1 and 2 years later, respectively. Renal biopsy specimen revealed extensive TTR amyloidosis. She had a strong family history of FAP (proved TTR Val30Met) and renal failure. Two years after presentation, a cardiac pacemaker was needed. Recurrent UTI and urinary incontinence were present since 1996; postvoid residual urine was estimated at 100 mL. The renal impairment progressed to ESRD and the patient commenced hemodialysis in December 1997. She became progressively fatigued, with alternating diarrhea-constipation and nocturnal fecal incontinence. Weight loss was estimated at 2 kg. Before transplantation she was score I for motor neuropathy, and, by this time, she showed palsy of dorsiflexion of the toes. Combined liver-kidney transplantation was performed in January 2000.

Patient 2. Patient 2, a man of Portuguese origin, was found to have sexual impotence at 32 years of age (1986). Inquiries revealed a younger sister with a peripheral neuropathy; TTR Val30Met mutation was identified in both. One year later he admitted constipation and disturbed micturition. Hyposthesia of the lower limbs began in 1991 and later diarrhea; when he was 37 years old. Difficulty in walking slowly progressed until one crutch was necessary in 1998 at which time he experienced daily and nocturnal

Table 1. Clinical Characteristics of Patients With FAP-I Who Underwent LKT

	Patient 1	Patient 2
Age at LKT (y)	50	46
Duration of disease at LKT (y)	6	14
Time on dialysis before LKT (mo)	25	12
Serum creatinine at 1 year after LKT (mg/dL)	1.4	1.0
Serum creatinine at end of follow-up (mg/dL)	1.3	1.3
Aspartate aminotransferase/serum alkaline phosphatase at end of follow-up (U/L)	35/31	29/67
Posttransplantation proteinuria	Absent	Absent
Hemoglobin at end of follow-up (g/dL)	11.8	14.4
Serum albumin before/after LKT (g/dL)	3.4/3.5	3.6/3.7
Hospital admissions related with infections	3	1
Time of follow-up after LKT (mo)	27	18
Outcome	Alive	Alive

Abbreviation: LKT, combined liver-kidney transplantation.

diarrhea. Proteinuria was detected during the year 6 of the disease, but by year 10 he had hypertension, urinary incontinence, nephrotic syndrome, and renal failure. Renal biopsy specimen showed vascular and mesangial amyloid deposits (ATTR) with advanced glomerulosclerosis. He reached end-stage renal failure and initiated hemodialysis in October 1999. Insertion of a cardiac pacemaker in the presence of first-degree atrioventricular block was performed in preparation for transplantation. Intermittent self-catheterization for optimal bladder drainage was initiated after 2 episodes of pyocystis in 2000; no urinary reflux was shown. Three months after dialysis was initiated, he developed a crisis of vomiting. The weight loss since disease onset was 9 kg (17%). His score for motor neuropathy was IIIA. He underwent simultaneous liver-kidney transplantation in October 2000.

Table 1 summarizes the clinical characteristics and outcomes after combined liver-kidney transplantation.

Posttransplantation Management and Morbidity

The early postoperative period was uneventful; the patients were admitted to the intensive care unit and discharged after 48 hours. Perioperative blood transfusions were 8 and 2 u for patients 1 and 2, respectively. The allografts had immediate function, although one short hemodialysis session was necessary to correct severe metabolic acidosis in patient 1. The native livers were found to be normal with scarce vascular amyloid deposits.

Both patients developed septicemia in the first week after transplantation (pulmonary and central catheter related) and urinary Candidiasis in the second week. No special problems were related to the management of surgical wounds. There were no episodes of rejection of either the renal or liver grafts. The patients were discharged with good graft function at 4 and 3 weeks after transplantation, respectively.

Patient 1 presented with a skin infection of the right foot after an accidental water burn in the second month after transplantation, which required surgical debridement, antibiotics, and skin graft. Patient 2 developed a maleolar neurogenic ulcer during the first hospital admission, which completely healed with local care.

The postvoid residual urine volume was evaluated after urinary catheter removal; intermittent catheterization was performed if that volume exceeded 150 mL, or when ureteral dilation or hydronephrosis of the renal graft was present. Both patients developed recurrent UTI. There were four hospital readmissions, all caused by infections (UTI and skin), exclusively during the first posttransplantation year. The antimicrobial prophylaxis for UTI decreased the episodes of bacteruria and associated febrile episodes did not recur. Episodes of low blood cyclosporine levels were found to be related to transient uncontrollable diarrhea. We did not observe posttransplantation hypertension or hyperlipidemia. Treatment with human recombinant erythropoietin was suspended at 2.5 months after transplantation.

Table 2. Echocardiographic Measurements Before and After LKT

	Patient 1 Before LKT/After 24 mo	Patient 2 Before LKT/After 14 mo
Left ventricular end-diastolic diameter (N < 54 mm)	55/55	52/50
Posterior left ventricular wall thickness (N < 11 mm)	10/13	14/12
Interventricular septum (N < 11 mm)	12/13	13/13
Aortic root dimension (N < 39 mm)	24/27	34/37
Left atrial dimension (N < 38 mm)	44/45	49/48

Abbreviations: LKT, combined liver-kidney transplantation; N, normal value in adults.

FAP Manifestations After Combined Liver-Kidney Transplantation

The clinical motor score and sensory deficits remained unchanged. Transient postural hypotension appeared concomitant with some UTI episodes during the first year after transplantation. We verified a progressive amelioration of bladder emptying; at the end of follow-up the postvoid urine volume was <50 mL. At the last observation, the patients continued to experience alternating diarrhea and constipation. A vomiting crisis appeared in patient 2 in the presence of a UTI. Both patients gained weight, 8 kg for patient 1 and 4 kg for patient 2. An active life was possible for patient 1, although with fatigue. Patient 2 ameliorated his social life and tolerance to effort.

Echocardiographic studies, before transplantation and after 24 and 14 months of follow-up, for patients 1 and 2 respectively, are detailed in Table 2. A "speckled" appearance of the myocardial wall was not observed and diastolic left ventricular function was considered normal. None of the patients showed vitreous opacities, glaucoma, or other ocular complications before or after transplantation.

DISCUSSION

ATTR Val30Met With ESRD is an Indication for Combined Liver-Kidney Transplantation

We have shown that simultaneous liver-kidney transplantation is useful for treatment of ESRD associated with the TTR Val30Met mutation. Technical problems during the liver or kidney transplantation have not been observed, neither have they required a long stay in the intensive care unit.

In general, patients with amyloidosis undergoing renal transplantation tolerate complications poorly and are at high risk of dying within the first 3 months.[14] Deaths after isolated liver transplantation in FAP often occurred within 6 months after surgery (57%).[15] Therefore, although our follow-up did not exceed 27 and 18 months, respectively, an important finding was the absence of early death, encouraging us to continue this therapy. Combined liver-kidney transplantation has been used for diseases that lead to end-stage failure of both organs, or in inherited metabolic disorders in which the primary defect is hepatic and leads to renal damage.[16] This approach to systemic hereditary amyloidosis was detailed in two patients but both also had progressive liver dysfunction: one with fibrinogen α-chain Glu526Val mutation, and another with apolipoprotein AI Gly26Arg mutation.[17,18] In familial amyloidosis related to TTR Val30Met mutation, liver amyloid deposits are scarce and progressive hepatic failure absent; OLT was done only to reduce the supply of amyloid fibrils.

In both patients, there was immediate graft function and an absence of rejection episodes. Abdominal pain and muscle weakness after renal transplantation have been reported in patients with amyloidosis, associated with high doses of cyclosporine.[19] Induction therapy with ATG and long-term triple immunosuppressive regimen provide an option that allows early low cyclosporine doses and diminishing risks of rejection.

Early Posttransplantation Complications are Urinary and Skin Infections

Autonomic neuropathy causing urinary retention or incontinence represents an additional problem in kidney transplantation. The neurogenic bladder may exert deleterious effects on the renal graft. In patients with FAP with isolated liver transplantation, the origin of lethal septicemia was urinary in 71%, and urinary incontinence was associated with higher transplant mortality.[15] Our policy of systematic evaluation of bacteriuria, intermittent self-catheterization in patients with incomplete voiding, surveillance of skin wounds, and long-term antimicrobial prophylaxis may explain the low number of hospital admissions related to infections. Urinary Candidiasis was observed early in the posttransplantation period, therefore prompt removal of ureteral stents is advisable. On the other hand, no other sources of infection were observed except the urinary tract and the skin.

Potential Benefits of Combined Liver-Kidney Transplantation in FAP

In patients with ESRD and FAP who underwent combined liver-kidney transplantation, we expect neither recurrence of amyloidosis in kidney graft nor deterioration of neuropathy. Although kidney transplantation has been described for severe amyloid TTR nephropathy,[15] the outcome of the renal transplantation was not specified.

The recurrence rate of amyloidosis in the renal allograft, based on evidence from biopsy specimens, may reach 26% in patients who survive beyond 12 months after transplantation.[12] The recurrence of renal ATTR after liver-kidney transplantation in FAP is not expected: several reports consistently confirm a rapid and steady decrease of circulating mutated TTR in the serum after liver transplantation.[12,20] Meanwhile, the progression of cardiomyopathy after liver transplantation among patients with FAP, TTR Val30Met, has been attributed to deposition of wild-type TTR-amyloid.[21] The amyloid fibrils in the hearts of patients with FAP (including ATTR Val30Met), which died of terminal cardiac failure after liver transplantation, were composed of wild-type TTR and variant TTR at a ratio of 1:1.[22] The kidney allograft, unlike the heart, is a genetically different organ without previous deposits, and thus recurrence of amyloidosis seems less probable.

In our experience, 50% of patients with FAP on regular hemodialysis die during the first year of therapy, and neuropathy progresses in all subjects (unpublished data). In ATTR liver-kidney recipients no deterioration of the motor deficit has been observed at present. Autonomic nervous dysfunction is a well-recognized complication of ESRD, whatever the etiology. A recent study failed to show complete normalization of the autonomic nervous system testing after kidney transplantation; however, there was a tendency to improve with the longevity of normal renal function.[23] Then, in FAP, the renal transplantation may represent an extra benefit for dysautonomy.

The long-term prognosis of patients with renal amyloidosis would appear to be dependent on the presence of cardiac amyloidosis and amyloidosis of the adrenals.[12] In both patients, echocardiographic findings before transplantation showed abnormal values in the left atrial dimension and in the interventricular septal thickness whereas signs of cardiomyopathy were present, the disorder did not represent a problem during the early posttransplantation period. In one patient, the left atrial dimension was increased and the thickness of the septal and left ventricular dimension increased after transplantation, as was previously described in the Swedish study with isolated OLT.[21] Curiously, that was the patient with a shorter duration of disease and a lower score for motor neuropathy. More follow-up will be necessary to clarify whether those findings have a deleterious impact on renal graft function or patient survival.

In conclusion, the available data in selected patients, suggest that combined liver-kidney transplantation is recommended for ESRD in FAP TTR Val30Met. Early treat-

ment of UTI and skin infections after transplantation is mandatory to diminish early mortality. Autonomic dysfunction of the bladder represents an additional problem, but does not contraindicate transplantation. Recurrence of amyloidosis in the renal graft is not expected.

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