ELSEVIER

Characterization of End-Stage Renal Disease After Liver Transplantation in Transthyretin Amyloidosis (ATTR V30M)

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ABSTRACT

Transthyretin (TTR) amyloidosis, an autosomal-dominant disease, is characterized by peripheral and autonomic neuropathy—familial amyloidotic polyneuropathy (FAP). End-stage renal disease (ESRD) occurs at 10 years after the onset of neuropathy. Orthotopic liver transplantation (OLT) is the usual treatment of choice. We evaluated FAP patients, ATTR V30M, before and after OLT who started dialysis within 3 months after surgery. The 11 patients had an age at the onset of neuropathy of 31.9 ± 6.3 years with a mean evolution of disease to OLT of 4.54 ± 2.5 years. The glomerular filtration rate was <60 mL/min in 2 patients, 2 displayed nephrotic range proteinuria, and 3 had microalbuminuria. Elective pacemaker implantation was necessary in 8 subjects. Post-OLT 3 patients developed proteinuria, 2 of whom showed increasing nephrotic syndrome. Dysautonomia worsened leading to bladder catheterization in 6. In patients with previous normal renal function and proteinuria <3 g/d, the evolution of neuropathy to the first dialysis was 14.6 ± 4.2 years versus 7.5 ± 1.1 among the other subjects. Overall, dialysis was implemented at 7.4 ± 4.9 years after surgery. There was no liver graft dysfunction. The heart evaluation post-OLT showed the following: 3 patients with de novo dysrhythmias requiring pacemaker implantation and 3 with N-terminal pro-natriuretic peptide levels >10,000 pg/mL. Death occurred in 4 subjects at an average of 26 months after initiation of dialysis. Concerning ESRD, there was no clear benefit of transplantation in the early stages. Patients with normal renal function and lower levels of proteinuria showed slower progression to ESRD, irrespective of their duration of neuropathy.

FAMILIAL amyloidotic polyneuropathy (FAP) is a systemic form of disease inherited in an autosomal-dominant manner. The disorder is associated with a transthyretin (TTR) variant. More than 100 amyloidogenic point mutations have been described so far in the TTR genes. The V30M mutation, which is a substitution of valine for methionine in position 30, is the most prevalent one worldwide; Portugal is the major focus of this type of amyloidosis (ATTR V30M).[1]

The disease is characterized by peripheral sensorimotor neuropathy with dysautonomia usually beginning in the third or fourth decade of life. The most frequent clinical picture includes dysesthesias, sensory loss involving lower and upper limbs, weight loss, constipation alternating with diarrhea, and motor impairment. Bladder dysfunction is associated with complicated infections and the need for an indwelling urinary catheter. Later, foot-drop, wrist-drop, muscular weakness, and postural hypotension lead to severe disabling, infected trophic ulcers in bedridden patients. Classically, non-neurological manifestations include involvement of the kidney, heart, and eye. In the natural course of disease, death occurs at 11 years after development of neuropathy.[2]

Renal manifestations of ATTR V30M, like other amyloidoses, show various levels of proteinuria and renal insufficiency. A stage of microalbuminuria can precede the neuropathy, representing incipient nephropathy. In Portugal, approximately one third of the patients display varying degrees of

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albuminuria and renal dysfunction.[3] The progression toward end-stage renal disease (ESRD) occurs in 10% of patients, usually at more than 10 years after the onset of symptoms; it is followed by death in about 2 years. Typically, ESRD patients had an onset of neuropathy 10 years later than those without renal features. A family history of nephropathy and female gender represent two-fold risk for kidney manifestations.[4] The characteristic histopathology reveals large amyloid depositions in the medullary zone and kidney tubules. Despite the absence of albuminuria, all patients have kidney amyloid deposits. More extensive glomerular and vascular involvement is only present among patients with renal manifestations.[5]

In FAP the majority of patients are spared of significant cardiomyopathy; heart involvement is particularly characterized by conduction disturbances leading to the need for artificial pacing. Dry eyes with corneal ulcers and vitreous opacities worsen the quality of life.[2]

Believing that the liver is the main source of circulating TTR (amyloid precursor), orthotopic liver transplantation (OLT) has been introduced as a treatment for FAP. Early data on transplant recipients showed that OLT stabilized neuropathy. To optimize the prognosis, surgery is advisable in the early stages of the disease when the first symptoms appear. A good nutritional status is recommended to improve long-term survival.[6] However, the aggregate experience has shown that favorable outcomes are not always present after OLT. Recipients may display continued deposition of normal TTR in cardiac tissue, recurrent vitreous opacities, and glaucoma as well as lack of improvement of sensorimotor neuropathy.[7,8]

Liver transplantation programs have restrictions regarding inclusion of FAP patients with renal insufficiency on the waiting list. Theoretically, the development of proteinuria de novo after OLT is improbable; albuminuria may improve.[5] Renal dysfunction among recipients of a nonrenal organ complicates medical management, leading to increased morbidity and mortality. The incidence and progression of this complication vary widely because there is a lack of a standardized definition of chronic renal failure after transplantation. The occurrence of renal dysfunction depends on the type of transplanted organ, the immunosuppression, and the pretransplantation kidney function. Other diseases like hypertension, dyslipidemia, diabetes mellitus, hepatitis, and perioperative renal injury can contribute to kidney disease.[9] In FAP, remission of proteinuria and deterioration of renal function after OLT have been documented, albeit with limitations of knowledge concerning ESRD. The aim of this study was to determine the clinical characteristics, outcomes, and approaches to renal replacement therapy for FAP patients with ESRD after OLT and the prognostic factors associated with the condition.

PATIENTS AND METHODS

We retrospectively evaluated FAP Portuguese patients, all of whom displayed the TTR V30M mutation, who underwent OLT and started dialysis 3 months after surgery. Amyloid deposits in biopsy specimens were demonstrated in all patients. Our study did not include subjects who underwent renal replacement therapy before OLT. When patients reached ESRD, hemodialysis was proposed to all.

Table 1. Demographic Data, Symptoms, and Outcomes During the Follow-Up Period

Patient No.	Gender (M/F)	Age at Onset of Neuropathy (y)	Duration of Symptoms at OLT (y)	Duration of Symptoms at First Dialysis (y)	Outcome
1	M	26	6	10	Dead
2	F	26	7	8	Alive
3	M	24	3	11	Alive
4	M	37	3	9	Dead
5	M	27	6	18	Dead
6	F	34	4	12	Dead
7	M	28	6	20	Alive
8	F	35	3	7	Alive
9	M	39	5	6	Alive
10	M	45	2	11	Alive
11	M	30	5	20	Alive

Abbreviations: M, male; F, female.

Demographic, clinical, and laboratory data were collected based on medical records. Specifically, we evaluated age at onset of neuropathy, family history, duration of symptoms, course of motor neuropathy (walking ability), bladder catheterization, and cardiac conduction disturbances. Glomerular filtration rate (GFR) was estimated using the Cockroft-Gault formula. Modified body mass index (mBMI) was calculated for the living patients according to the following formula: (weight [kg]/length [m^2]) $\times$ albumin (g/L). We also registered urgent or elective dialysis as well as date and cause of death.

The immunosuppressive therapy was based on a calcineurin inhibitor (CNI), azathioprine or mycophenolate mofetil/mycophenolic acid, and prednisone. The same nephrological team followed the patients before and after dialysis.

RESULTS

Pretransplantation Characterization

The 11 patients, including 8 men and 3 women, all had family history of neuropathy with 7 of them having relatives with nephropathy. Their mean age of onset of neuropathy was 31.9 $\pm$ 6.3 years, with a mean duration of symptoms until transplantation of 4.54 $\pm$ 2.5 years. In all cases, peripheral neuropathy was the first feature of FAP (Table 1).

Prior to OLT the patients were able to walk without help; only 1 required intermittent bladder catheterization and 8 underwent elective pacemaker placement. Concerning the renal evaluation, 2 patients had abnormal GFRs (50 mL/min and 35 mL/min, respectively), 2 had nephrotic range proteinuria, and 3 had microalbuminuria (Table 2). No underlying conditions were observed to be associated with chronic renal disease, such as diabetes mellitus, hypertension, and hepatitis.

In 4 patients, a renal biopsy had been performed without complications. TTR amyloid deposits were mainly present in the medullary zone with scarce involvement of vascular and tubular structures.