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Liver transplantation in transthyretin amyloidosis: Characteristics and management related to kidney disease

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A B S T R A C T

Orthotopic liver transplantation (LT) was implemented as the inaugural disease-modifying therapy for hereditary transthyretin (ATTR) amyloidosis, a systemic amyloidosis mainly affecting the peripheral nervous system and heart. The first approach to pharmacologic therapy was focused on the stabilization of the TTR tetramer; following that new advent LT was assumed as the second step of treatment, for those patients whose neuropathy becomes worse after a course of pharmacologic therapy.

The renal disease has been ignored in hereditary ATTR amyloidosis. The low level of proteinuria or slight renal impairment does not suppose such a heavy glomerular and vascular amyloid deposition. Moreover, severity of renal deposits does not consistently parallel that of myelinated nerve fiber loss. These are pitfalls that limit the success of LT and suggest troublesome criteria for pharmacological therapy or LT. An algorithm of evaluation concerning renal disease and treatment options is presented and some bridges-to-decision are exposed. In stage 4 or 5 kidney disease, the approach remains to deliver combined or sequential liver–kidney transplantation in eligible patients. However, in the majority, hemodialysis is the only option even in the presence of a well-functioning liver graft.

In this review, we highlight useful information to aid the transplant hepatologist in the clinical practice.

1. Introduction

Amyloidosis is an uncommon disease that is characterized by abnormal extracellular deposition of misfolded protein fibrils and affecting multiple organs and tissues. Kidney disease is a common manifestation and a major contributor to morbidity in amyloidotic patients.

Diagnosis requires identification of pathologic amyloid deposition. This can be done by Congo red staining, with its characteristic apple green birefringence under polarized light. The particular precursor protein can be identified by immunohistochemical staining or mass spectrometry, which confers the greatest sensitivity and specificity for amyloid typing [1].

The major types of systemic amyloidosis are light chain associated (AL), amyloid A (AA) and the hereditary amyloidosis.

The most common type of autosomal-dominant hereditary systemic amyloidosis is associated with mutant forms of transthyretin (*TTR*). Of the pathogenic mutations, Val30Met was the first to be identified and is the most frequent known mutation found throughout the world.

The principal manifestation of most ATTR amyloidosis is peripheral neuropathy with dysautonomia. During the past few years, our knowledge on the phenotypic presentation of this devastating condition has remarkably expanded, including different neuropathic patterns [2] and patients presenting isolated or predominant kidney involvement.

Epidemiological studies from Portugal and Sweden reveal that approximately one third of the patients display varying degrees of albuminuria and renal dysfunction [3].

Nephropathy did not correlate with age, duration of disease, or severity of neuropathy. Thus, the scarcity of peripheral sensory symptoms and the lack of familial history of neuropathy, in the presence of renal disease, should not exclude ATTR amyloidosis in the differential diagnosis, even in older patients.

A family history of nephropathy and being of female gender represent a two-fold risk for kidney manifestations. The familial aggregation of renal disease suggests the influence of additional genetic factors, either alone or in combination with some environmental factors. Typically, end-stage renal disease (ESRD) patients had an onset of neuropathy ten years later than those without renal features. The progression occurs in 10% of Portuguese patients more than ten years after the onset of symptoms. Patients with nephrotic range proteinuria had a higher risk of developing ESRD [3,4].

Concerning histopathology, all patients have kidney amyloid deposits, despite the absence of albuminuria. Patients with proteinuria had a more extensive amyloid involvement than those without clinical

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renal disease. Renal dysfunction and the degree of proteinuria are correlated with heavy amyloid deposition in the glomeruli, arterioles, and medium vessels, but not with deposition in medullary tissues [3,5].

Liver transplantation (LT) has been proposed to treat this fatal disease because the liver is the principal site (over 90%) of synthesis of the mutated protein. However, the aggregate experience has shown that favorable outcomes are not always present after LT, especially concerning non-neurologic manifestations (Table 1) [6]. Over the past decade, numerous disease-modifying therapies have emerged, raising the potential for effective transthyretin amyloid therapy, namely kidney ATTR amyloidosis.

1.1. Assessment of kidney injury in patients evaluated for liver transplantation

Despite some limitations, the assay of serum creatinine is universally used to estimate glomerular filtration rate (eGFR) because of its wide availability, simplicity, and affordability [14]. The value of this assay is much lower in ATTR amyloidosis patients. They are known to have low serum creatinine levels, which are related to lower muscle mass, as weight loss and under nutrition are frequent and serious complications [15].

Cystatin C is a small peptide produced by all nucleated cells, and it has many features of an ideal marker for kidney function. It is freely filtered by the glomerulus, is not secreted by tubules, and is essentially unaffected by diet, muscle mass, or inflammation. Although cystatin C appears to be more accurate than creatinine, it is also more expensive and is not universally available, which makes it less practical for daily monitoring [14].

According to the KDIGO guidelines, the eGFR using creatinine should be reported using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. In clinical laboratories that measure cystatin C, eGFR using cystatin C and creatinine-cystatin C should be reported using the 2012 CKD-EPI equation (16).

Albuminuria, as a tool to detect individuals with undiagnosed renal amyloidosis and an early sign of progressive renal disease, should be evaluated. According to KDIGO guidelines, it must be determined by urine albumin-to-creatinine ratio (UACR), preferably in an early morning urine sample [16].

A Portuguese study prospectively evaluating 22 asymptomatic gene carriers and 32 patients with neuropathy concluded that screening albuminuria may be important to assess disease onset and to recommend LT in individuals at risk [4]. The same group recommended the systematic and regular measurement of urinary albumin excretion in asymptomatic gene carriers and patients, as a non-invasive method for evaluating renal ATTR amyloidosis [4].

Early detection of organ dysfunction caused by amyloid deposits has particular emphasis in ATTR amyloidosis, as it may determine prognosis and allocation in LT programs. Thus, improved methods for detecting onset of kidney amyloid deposits, even before clinical disease, are needed to allow earlier treatment. The first description of the contribution of urinary proteins, other than albumin, as non-invasive and cost-effective markers to anticipate renal ATTR amyloidosis revealed that urinary excretion of tubular proteins is related to severity of kidney injury [17]. The combined excretion of low and high molecular weight proteins was exclusively found in patients who progressed to ESRD. Therefore, periodic screening of subclinical tubulopathy using these urinary biomarkers appears to be a simple and non-invasive means of identifying ATTR amyloidosis patients at risk of kidney disease, including impending decline in kidney function [17].

A revision of the results of LT for ATTR amyloidosis in Swedish patients found no indication for kidney biopsy to be performed routinely in these patients before LT [18]. That position was based on the advantages of serum amyloid P scintigraphy, the risk of hemorrhage, and the patchy distribution of amyloid in renal tissue with a dubious clinical interpretation [18]. However, a series of 14 renal biopsies was performed systematically in Portuguese ATTR amyloidosis patients without complications [5].

Later, the Japanese group, based on a study of 13 patients, recommended renal biopsy for determining the indications and contraindications for LT in ATTR amyloidosis patients [19]. Five of them presented proteinuria ≥300 mg/day with a mean value of 1.2 g. In all, creatinine clearance was greater than 30 mL/min per 1.73 m^2. Only ten of these patients had neurologic criteria to LT, and one died in the postoperative period. After a mean follow-up of 27 months, the patients with moderate to severe amyloid deposits in glomeruli had the worst outcome, evaluated by morbidity and mortality. Kidney biopsy was helpful in determining the chronicity. Furthermore, kidney biopsy may be helpful in determining whether or not an LT candidate would be better served by a simultaneous liver–kidney transplant (LKT).

Fig. 1 represents an algorithm for evaluation of renal impairment in patients under assessment for LT.

1.2. Renal dysfunction after liver transplantation

Renal dysfunction after LT is common and may have an acute or chronic presentation. Calcineurin inhibitors (CNIs) acutely induce reversible vasoconstriction, increasing renovascular resistance. Progressive obliterative arteriolopathy and chronic interstitial fibrosis with glomerulosclerosis develop in LT patients in a dose-dependent, time-dependent fashion, and have limited potential for reversibility [20].

Although CNIs have been associated with post-LT nephrotoxicity, their role may be overestimated, and other contributing etiologies should remain in a clinician's differential diagnosis.

The major determinant of post-transplant renal failure is the presence of pre-transplant renal disease [20].

A retrospective study of 185 Portuguese ATTR Val30Met amyloidosis patients, submitted to 217 LT over a fifteen-year time period, revealed that renal dysfunction pre-LT and acute renal failure post-LT were risk factors for chronic renal disease development [21]. Renal dysfunction pre-LT (defined as eGFR ≤60 ml/min or serum creatinine ≥1.5 mg/d) was seen in 31 recipients (14.3%), and acute renal failure was observed in 57 patients (26.3%). According to KDOQI definitions, with a mean

Table 1
Impact of liver transplantation on non-neurologic manifestations of ATTR amyloidosis.

Organ envolvement	Origin of patients	Number of LT patients	Follow-up time	Conclusion	Reference; year
Cardiac	Swedish	21	12–27 months	Increased septal and left ventricular wall thickness; increased left atrial dimension	2002 [7]
	French	31	24 ± 15 months	Magnitude of the cardiac sympathetic denervation remained stable; Cardiac amyloid infiltration progressed	2006 [8]
	Japanese	12	7.5 ± 3 years	Mean left atrial diameter and interventricular septal thickness significantly increased	2008 [9]
			40 months	12.5% developed vitreous opacities	
			18 months	8% developed glaucoma	
Ocular	Swedish	48	No reported	33% developed deposits on the anterior surface of the lens; 21% developed scalloped papillary margins	2008 [10]
	Japanese	22	7	36% developed vitreous opacities; 18% developed glaucoma	2010 [11]
	Portuguese	32	No reported	Ocular manifestations not influenced by LT	2015 [12]
Gastric	Swedish	22	No reported	No significant improvement of gastric emptying; in patients with longstanding disease (≥4 years) is unchanged after LT	2003 [13]