Combined heart and liver transplantation for familial amyloidotic neuropathy

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Abstract

Familial amyloidotic polyneuropathy (FAP) is an inherited disease characterized by an abnormal systemic deposition of a mutant protein called transthyretin (TTR) with elective involvement of the peripheral nervous system, but often determining cardiac, gastrointestinal, and urinary tract dysfunction. FAP commonly affects the liver and the heart until end-organ failure. Transthyretin amyloidosis is today an accepted indication for orthotopic liver transplantation (OLT). Combined heart and liver transplantation (CHLT) may be an attractive and rational treatment option when both organs are contemporarily involved by this type of amyloidotic disease. Nowadays, surgical indications and techniques are far from being consolidated because only few cases of CHLT have been previously reported in literature. From November 1999 to May 2006, we performed five orthotopic combined heart and liver transplantations for FAP at our institution. Our surgical experience and clinical outcomes are herein reported. © 2007 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

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1. Introduction

Familial amyloidotic polyneuropathy (FAP) is a metabolic disease characterized by a mutant form of prealbumin called transthyretin (TTR). Circulating TTR is derived from the liver. An important distinction in two clinical forms of FAP, Met30 and NMet30, has been introduced because of different involvement of the heart and long-term results [1]. In case of NMet30 variation, it is demonstrated a deposition of the mutant form of TTR in the myocardium, evolving towards a restrictive cardiomyopathy [2]. The long-term survival after isolated liver transplantation is influenced by an evolution of the cardiomyopathy, in particular, for NMet30 variations [3].

With improvement in operative techniques, immunosuppression, and length of survival in single-organ transplantation, the indications would be extended to include multiorgan transplantation.

2. Materials and methods

From November 1999 to December 2005 six patients with FAP were referred to our institution for CHLT. The main preoperative data are shown in Table 1. A restrictive-type ventricular filling was present in all patients at echo-doppler analysis with severe cardiac impairment and signs of heart failure, despite of maximal medical therapy. In patients 1, 4, and 5, nutritional status was unaltered and weight loss was minimal, while weight loss appeared marked and nutritional status altered in patients 2 and 3; the weight loss of patient 6 was 5 kg (mBMI: 818). The modified polyneuropathy disability (PND) score was I (absence of peripheral motor impairment) in patients 1, 4, and 5; mPND score was II (serious peripheral motor impairment) in patients 2 and 3; the mPND score of patient 6 was 5 kg (mBMI: 818). The modified polyneuropathy disability (PND) score was I (absence of peripheral motor impairment) in patients 1, 4, and 5; mPND score was II (serious peripheral motor impairment and limitation of walking to 200 m) in patients 2 and 6. The patient 3 had grade IIa (one stick or one crutch required for walking) of PND score. Gastrointestinal disorders were present only in patients 2 and 3.

3. Results

The main intraoperative data of the five surgically treated patients are shown in Table 2.

There was one in-hospital death (patient 2) 60 days after CHLT. Early revision of the caval anastomosis was soon required in this patient and reoperation for bleeding was necessary in postoperative day (POD) 7. Hemodialysis was required because of renal insufficiency. One month after CHLT, the patient developed pneumonia and myocardial infarction and died of multiorgan failure (MOF) on POD 60. In patient 3, right colectomy and ileostomy was required...
ischemia. Postoperative course was characterized by orthostatic hypotension and dehydration due to vomiting and massive fluid loss through the stoma, which resolved after ileocolostomy performed 3 months later. The cardiac and hepatic functions recovered well; on the contrary, the other systemic symptoms of FAP did not ameliorate during follow-up. Unfortunately, this patient died at home of an unknown cause 20 months after CHLT.

Patients 1, 4, and 5 were discharged from the intensive care unit on the sixth, fourth, and fifth POD, respectively.

After transplantation, neither liver or heart biopsy follow-ups showed significant rejection in these patients; in particular, patient 6 is free from graft amyloid infiltration after 29 months from isolated heart transplantation.

4. Discussion

FAP is an autosomal dominant inherited form of amyloidosis associated with a mutant form of a protein called transthyretin, described for the first time by Andrade in 1952 [4]. Decreased diastolic compliance is the earliest manifestation, followed by a progressive thickening of the ventricular and atrial wall, and decreased systolic function [3].

Because transthyretin is synthesized for 98% by hepatocytes, liver transplantation has been considered the treatment of choice for FAP [5]. Amyloid fibrils in the heart are formed not only by mutated TTR but also by wild-type TTR in a proportion up to 50% [2], suggesting that wild-type TTR constitutes amyloid in the hearts of transplant recipients. FAP is divided in two main groups: Met30 and Non-Met30 mutation (Nmet30). Various investigators have reported stabilization or improvement of FAP disease after only liver transplantation in patients with Met30 mutation. Dubrey et al. [3] reported that some patients who had FAP showed continued left ventricular wall thickening after orthotopic liver transplantation (OLT), with a deterioration of ventricular function, more frequently in NMet30 patients. He also assumed that pre-existing amyloid fibrils could act as a nidus for nonhepatic sources of mutant TTR or for the deposition of normal TTR produced by transplanted liver.

Dubrey [6] analyzed the cardiac transplantation experience for amyloid heart disease of the United Kingdom. The 5-year survival after heart transplantation for FAP disease was comparable with the survival for other disease after transplantation.

Combined heart and liver transplantation (CHLT) should be indicated for several NMet30 variants with recognized risk for progressive cardiopathy [6].

Modified body mass index, duration of symptoms, polineuropathy disability score, severity of diarrhea, and orthostatic hypotension are important factors in the preoperative evaluation and for the operative indication [7,8].

We reported our experience of five consecutive CHLTs performed for amyloidogenic TTR-related cardiopathy with Glu89Gln mutation in four patients and Leu33 mutation in one patient.

Our surgical indication to perform CHLT is based on a careful distinction between Met30 and NMet30 variations. The poor prognosis after isolated liver transplantation for NMet30 disease due to progressive cardiac failure convinced us that heart and liver transplantation is the better option for these patients. The presence of a restrictive cardiomyopathy, with signs of polyneuropathy and gastrointestinal symptoms, justified suspicions of amyloidosis disease. In our patients the poor nutritional status, high polyneuropathy disability (PND) score, duration of the disease, and marked
hypotension are the most important negative prognostic factors for a good outcome after CHLT. Actually, three of the five patients who underwent CHLT are alive. We had one in-hospital death and a second patient dead after 20 month for unknown cause. Both patients were in poor conditions before the operation, with an important malnutrition status and weight loss.

Patients with preoperative compromise clinical conditions as malnutrition and advanced neuropathy should be considered at high risk for CHLT and carefully evaluated.

In patients with good preoperative conditions, the mortality and long-term survival after CHLT for FAP NMet30 could be superimposable with the results after isolated heart and liver transplantation for convectional disease [5]. Therefore, according to our experience and literature data, we believe that combined heart and liver transplantation should be a therapeutic option for patients with FAP NMet30.

References


