Transplant International ISSN 0934-0874

COMMENTARY

Domino liver transplantation from familial amyloidotic polyneuropathy donors: how close is the damocles sword to the recipient?

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Received: 3 July 2007
Accepted: 10 July 2007

doi:10.1111/j.1432-2277.2007.00534.x

In 1991, a Swedish group proposed liver transplantation as the treatment of familial amyloidotic polyneuropathy (FAP) [1]. This was a therapeutic breakthrough. Until that time, FAP was a devastating disease leading patients to death in a median of 10 years after appearance of the first symptoms. No medical treatment has been shown to slow down the progression of the disease. The disease is secondary to a point mutation in the gene coding for the production of transthyretin, located on the chromosome 18. Transthyretin is a protein synthesized at 90–98% by the liver. The disease is a hereditary dominant transmitted disease. The point mutation of the gene coding for transthyretin leads to a disruption of the thransthyretin protein in amyloid fibrils. The symptoms are mainly characterized by a sensory-motor length-dependent polyneuropathy affecting first the lower limbs and then the upper limbs. This disease is, in fact, a more general disease with an autonomic neuropathy with postural hypotension, sexual impotence in men, alternating diarrhoea–constipation, dysuria and urinary incontinence. Amyloid deposits are present in the cardiac muscle leading to amyloid restrictive cardiomyopathy with conduction troubles, and are present in renal glomeruli leading to amyloid glomerulonephritis. Finally, deposits can be found in the vitreum reducing visual ability. The most frequent mutation is the Met 30 mutation present in Portuguese, Swedish and Japanese patients. However, more than 60 mutations have been described. A particular aspect of the disease is the age of appearance of the first symptoms, which occurred in general after 20 years of life. In Met 30 mutations, few cases have been described in patients between the age of 15–20 years but the majority of Portuguese cases became symptomatic between the age of 20 and 30 years. Met-30 mutations became symptomatic in Swedish patients and in French *de novo* cases later in life around the age of 50 years. Non-Met 30 mutations occurred in general later during life at 50–80 years. Unfortunately, to date, no medical treatments have been able to slow down the progression of the disease. The aim of liver transplantation was based on the hypothesis that transthyretin was mainly synthesized by the liver and that the new liver will produce proteins of donor origin. It was postulated that the production of mutated protein will be stopped and the disease will stop its progression. The first results of liver transplantation for FAP have confirmed this theory [2]. In serum, the

production of mutated transthyretin was reduced by 98%, and the normal protein is found almost exclusively in the serum. This change in the production of tranthyretin was accompanied by a dramatic decrease in the disease progression. The first clinical results showed that most of the symptoms present at the time of transplantation remain present but did not progress anymore or at a very low speed. It has been shown that the rate of nervous loss has been dramatically reduced after liver transplantation [2]. For unexplained reason, some cases of clinical deterioration have been observed mainly in non-Met 30 patients, in patients transplanted at a late stage of the disease and in old patients. Postliver transplantation progression has been shown mainly in cardiac tissue and in ocular manifestations. We have currently no explanation for the cardiac progression observed mainly in non-Met 30 patients, but ocular progression can be due to a local production of mutated transthyretin. Anyway, most patients have no progression of the disease after liver transplantation and have a good long-term survival with good quality of life. Thus, currently liver transplantation is the treatment of symptomatic FAP. Worldwide, more than 200 liver transplantations performed for FAP have been reported in the world transplant registry for liver transplantation for FAP [3]. In parallel with the development of liver transplantation for FAP, domino liver transplantation using the liver of FAP transplants recipients has been developed. The principle of domino liver transplantation is to use the liver from liver transplant recipients for another recipient [4]. Originally, FAP appeared as an excellent indication for Domino liver transplantation [4]. Indeed several points essential to the success of the domino procedure are present: (i) the liver of FAP patients is histologically normal, few amyloid deposits are present in the artery of the hilar area of some patients without any consequences; (ii) the liver is functionally normal, liver tests are normal and there is no portal hypertension; (iii) the FAP disease is usually not symptomatic during the first 20 years of life, thus a recipient of a FAP liver is supposed not to develop FAP symptoms before 20 years as a minimum [5]. In a first part of this experience of domino liver transplantation, the FAP livers were considered as marginal livers. For this reason, they were offered in priority to patients with marginal indications for liver transplantation (hepatocellular carcinoma outside the Milan criteria, HIV-positive recipients) or to patients over 60 years old. From the technical point of view, the domino procedure is a little bit more complex, but the advantage for the recipient is that the donor is frequently young and the ischemia duration short. Thus, it appears that the results were at least similar to the classical transplantation from cadaver donor and were dependent only from the indication for liver transplantation [4]. Thus recently it is has been argued that these livers could be considered as excellent livers and offered to nonmarginal recipients providing they have been fully informed of the procedure. However, the recent reports of cases of FAP symptoms developing in the recipients of FAP donors 5 to 8 years post-transplantation are worrying [6–8]. It has been shown in a report that amyloidotic deposits were present 4 to 5 years post-transplantation in the stomach without clinical symptoms [9]; this was not surprising as amyloid deposits may appear rapidly. We have shown that mutated transthyretin was present in the serum of the Domino recipients within the first day post-transplantation [4]. The detection of symptoms related to amyloid deposits as soon as 5 years post-transplantation is a surprise. In this issue of the Journal, Yamamoto *et al.* [10] described the appearance of electrophysiological signs of neuropathy in recipients of Domino liver from FAP patients. There was no development of clinical symptom, but the longer follow-up was only 5 years post-transplantation. We cannot exclude that some electrophysiological signs were related to other causes of neuropathy such as diabetes, alcohol consumption or secondary to anticalcineurins. The authors have tried to exclude other causes of neuropathy than FAP; however, in the absence of nerve biopsies showing amyloid deposits, it cannot be ruled out completely. However, at least three cases showed regular progression of electrophysiological signs suggesting to be FAP-related. The fact that no clinical symptoms occurred is reassuring, however two symptomatic cases have been reported by other teams at 7-years post-transplantation [6,8]. In our own experience, out of 80 domino transplantation performed during the past 10 years, one patient developed symptoms of polyneuropathy related to amyloid histologically proven deposits at 8-years post-transplantation. This observation suggests that in some domino recipients, symptoms of FAP disease may occur much more rapidly than expected. Is this due to more rapid nerve loss in aged patients, or to a deleterious effect of immunosuppression or to the combination of several factors affecting the nervous system post-transplantation? We should, in the near future, determine what is the exact actuarial rate of FAP symptoms in FAP-domino recipients, what are the predictive factors for development of FAP symptoms, and how should recipients of FAP liver be monitored. Anyway, it is extremely important to inform future FAP-domino recipients and to evaluate the ratio benefit/risk of such procedure. In conclusion, domino liver transplantation from FAP donors is a technically resolved procedure with excellent short and medium-term results. It is now demonstrated that FAP symptoms may occur after 5-years post-transplantation in some recipients. The true rate of FAP symptoms should be cautiously evaluated in the near future. It implies regular annual

monitoring of domino recipients using clinical and electrophysiological testing as well as regular interview to detect abnormal symptoms. It will be important to differentiate neuropathy secondary to mutated transthyretin deposits from other causes of post-transplant neuropathy, in particular, those induced by diabetes, alcohol and immunosuppressive drugs. The domino procedure should continue, however the ratio benefit/risk should be evaluated case by case and the recipient fully informed prior to the procedure. The appearance of FAP symptoms in the recipient of domino liver may be an indication for a second transplantation with a non-FAP liver.

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