Domino liver transplantation: the risk of disease recurrence

Filomena Conti, Fanny Mochel, Yvon Calmus

Domino liver transplantation: the risk of disease recurrence

Filoména Conti[1], Fanny Mochel[2], Yvon Calmus[1]

[1] AP-HP, Hôpital Pitié-Salpêtrière, Service d'Hépato-gastroentérologie, Unité Médicale de Transplantation Hépatique, Paris, France.
Sorbonne Universités, UPMC Université Paris 06, INSERM, UMR_S 938, CDR Saint-Antoine, Institute of Cardiometabolism and Nutrition (ICAN), Paris, France.

[2] AP-HP, Pitié-Salpêtrière University Hospital, Department of Genetics and Reference Center for Adult Neurometabolic diseases, Paris, France.
Sorbonne Université, UPMC-Paris 6, UMR S 1127, INSERM U 1127, CNRS UMR 7225, and ICM, F-75013, Paris, France.

Domino liver transplantation (DLT) increases the pool of liver grafts, which is highly valuable in a period of increasing organ shortage. Moreover, the liver grafts provided by this technique sustain less ischemia-reperfusion lesions than those obtained from brain dead donors, and the donors are often younger. Consequently, the results obtained with DLT are not different than those obtained after deceased donor LT, at least during the first 5 years after LT (1). Results beyond that period are scarce. The question incompletely resolved is which metabolic diseases are a reasonable source of domino liver grafts, and for which recipients. Indeed, the main limit of this procedure is the risk of transmission of the original disease to the recipient (2), a risk often poorly evaluated, with a resulting strong difficulty to give a fair information to the future recipients (3,4). The recipients chosen to receive domino livers are often older and/or patients with malignant diseases. To improve the knowledge on DLT, an international registry (the Domino Liver Transplant Registry) was created in 1999 in Sweden (http://www.fapwtr.org). By December 31 of 2017, a total of 1254 domino transplantations on 1234 patients were registered, but to date few publications have resulted from this registry (5).

In the present issue of the journal, Wei et al. (6) have used the liver of a 8-year-old boy, suffering from homocystinuria, and successfully grafted with the left liver from his father, to transplant a 41-year-old patient with cholangiocarcinoma. This is, to our knowledge, the first case of DLT using a graft from a patient with homocystinuria. One of the most interesting results of this paper is the observation that plasma homocystein levels from the donor

rapidly dropped to normal values (< 15 μmol/L), while plasma homocystein dramatically increased in the second recipient within a few weeks to levels similar to that observed in the boy before he was transplanted (> 150 μmol/L). Unfortunately, the second recipient died of cholangiocarcinoma recurrence at 11 months post-transplant. While the authors estimate that the transplantation was successful for this patient, the short-term follow-up of this patient should calls for great caution regarding the long-term evolution of this type of DLT.

Most cases of DLT have used liver grafts from patients with progressive familial amyloid polyneuropathy (FAP). FAP is a dominant autosomal disease characterized by the synthesis of an insoluble form of transthyretin (TTR) that deposits especially in peripheral and autonomous nerves. It leads to a degenerative peripheral nerve disease with symptoms onset in the 30s and death in the 40-50s (7). FAP has a prevalence of 1/1,000 to 1/10,000 in several populations such as Portugal, Sweden and Japan. Because more than 95% of the circulating TTR is produced in the liver, LT represents a curative treatment for this disease (3). It was initially thought that the transmission of the disease to a recipient would take 20 to 30 years to develop, and that the occurrence of antibodies against the mutated protein would further reduce the risk of transmission. However, we now know that the risk of recurrence may be earlier and in on a more severe form than anticipated (8). A 23 % recurrence rate has been reported after a median follow-up of 7 years (9). We have recently observed a severe recurrence of FAP, 7 years post-LT, in the form of cardiac arrhythmia requiring the implantation of a defibrillator, followed by a rapid peripheral and autonomous neural degeneration leading to death after 9 years (Calmus Y, personal communication). These data suggest that recurrence of FAP is highly variable and sometimes accelerated. Past histories of diabetes or alcoholism or other factors may play a role. In the future, less aggressive therapies, such as antisense oligonucleotides, may be available for FAP without the need for a LT (10).

The other main metabolic diseases potentially available for DLT are summarized in Table 1.

Fibrinogen Aα-chain amyloidosis involves theoretically a risk of recurrence, but which has not been observed after 8 years of follow-up in short series (11-13). It is thus potentially a good source of DLT. The other amyloid diseases, such as those induced by mutations in

genes encoding apolipoprotein A1, gelsolin and lysozyme respectively, are often associated with liver amyloid deposition, and probably not suitable for DLT (11,14).

Primary hyperoxaluria is an autosomal recessive metabolic disorder that is characterized by a defect in the alanine-glyoxylate aminotransferase, encoded by a gene that is expressed only in the liver. This deficiency results in liver oxalate overproduction, hyperoxaluria, calcium oxalate depositions, nephrocalcinosis, and end-stage renal failure. Renal transplantation should always be associated with LT to avoid the rapid destruction of the renal graft. In the reported cases of DLT using livers from primary hyperoxaluria patients, renal failure constantly developed in the recipient, often within a few months (11).

Recipients of DLT from patients with homozygous familial hypercholesterolemia develop hypercholesterolemia despite intensive lipid-lowering therapy including statins and ezetimibe. Short-term follow-up (up to 7 years) has not shown cardiac or arterial lesions (15). Extra-hepatic LDL receptors probably allow a significant uptake and metabolism of cholesterol, limiting the development of the disease, but long-term cardiovascular follow-up is clearly needed in those patients.

Acute intermittent porphyria (AIP) is an autosomal dominant disorder affecting the third enzyme from the heme biosynthetic pathway. The liver is the source of the heme precursor, aminolevulinic acid, which is the major cause of neurological attacks in AIP. Liver transplantation is a potentially effective treatment for severely affected patients with recurrent life-threatening neurovisceral attacks despite optimal medical therapy with human hemin. DLT from patients with AIP caused acute typical metabolic attacks in the recipients (16).

Maple Syrup Urine Disease (MSUD) is an autosomal recessive metabolic disorder caused by impaired activity of the branched-chain α-keto acid dehydrogenase complex, which results in an accumulation of branched-chain L-amino acids (valine, leucine and isoleucine) and α-keto acids. The clinical course is marked by episodes of ketoacidosis with neurotoxic effects. The treatment consists in reduced intake of protein, especially branched-chain amino acids. However, brain damage or death can occur during acute uncontrolled metabolic crises. DLT has been performed with the liver of patients with MSUD, with excellent results (17,18).

Blood analyses of the recipients showed no accumulation of branched amino acids, despite the absence of dietary limitations, suggesting sufficient extra-hepatic enzymatic activity. This is very different from inherited metabolic diseases for which the defective enzyme is predominantly hepatic. Likewise, inadvertent cases of DLT using liver grafts from patients with ornithine transcarbamylase deficiency led to hyperammonemia and coma in the recipients (2). On the other hand, DLT was recently performed in two patients with organic aciduria. The recipient of the propionic acidemia liver has maintained his propionic acid levels within normal ranges over 2 years post-transplant, while the recipient of the methylmalonic aciduria liver did develop elevated methylmalonic acid levels in plasma and urine with an uncertain long-term outcome (19,20).

Urea cycle diseases are probably not good candidates to DLT. Inadvertent cases of DLT using liver grafts from patients with Ornithine Transcarbamylase (OTC) deficiency has led to hyperammonemia and coma (2).

In the case of homocystinuria, long-term results, beyond the 11 months of the present report, are needed. High plasma homocystein levels in the recipient, exceeding 150 μmol/L, suggest that the disease will ultimately occur in the recipient: (1) homocystinuria fully develops early in the life, often between 5 and 10 years of age; (2) plasma homocystein levels higher than 100 μmol /L are associated with significant neurological and embolic risks (21).

Table 1. Diseases in which domino liver transplantation was performed and risk of disease transmission

	Transmission	Risk of transmission	Date of recurrence
Unacceptable indications for donation			
Primary hyperoxaluria	RA	Constant	Immediate
Acute intermittent porphyria	DA	Constant	Immediate
Urea cycle diseases	RA	Reported for OTC	Immediate for OTC
Uncertain indications for donation			
Homocystinuria	RA	Not yet reported	/
Organic aciduria	RA	Not yet reported	/
Acceptable indications			
Familial amyloid polyneuropathy	DA	Constant	7-9 years
Hereditary Fibrinogen Aα-Chain Amyloidosis	DA	Not yet reported	/
Excellent indications for donation			
Maple syrup urine disease	RA	Absent	/
Familial hypercholesterolemia	CoDA	Absent	/

OTC: Ornithine Transcarbamylase deficiency.

References

1. Geyer ED, Burrier C, Tumin D, Hayes D Jr, Black SM, Washburn WK, Tobias JD. Outcomes of domino liver transplantation compared to deceased donor liver transplantation: a propensity-matching approach. Transpl Int. 2018;31:1200-1206.

2. Schielke A, Conti F, Goumard C, Perdigao F, Calmus Y, Scatton O. Liver transplantation using grafts with rare metabolic disorders. Dig Liver Dis. 2015;47:261-70.

3. Tincani G, Hoti E, Andreani P, Ricca L, Pittau G, Vitale V, et al. Operative risks of domino liver transplantation for the familial amyloid polyneuropathy liver donor and recipient: a double analysis. Am J Transplant 2011; 11: 759-766.

4. Schenck D, Mazariegos GV, Thistlethwaite JR Jr, Ross LF. Ethical Analysis and Policy Recommendations Regarding Domino Liver Transplantation. Transplantation. 2018;102:803-808.

5. Ericzon BG, Larsson M, Herlenius G, Wilczek HE; Familial Amyloidotic Polyneuropathy World Transplant Registry. Report from the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR) and the Domino Liver Transplant Registry (DLTR). Amyloid. 2003;10 Suppl 1:67-76.

6. Wei Qu; Zhu Zhi-jun, MD; Li-Ying Sun; Lin Wei; Ying Liu; Zhi-gui Zeng. Successful living donor liver transplantation for hyperhomocysteinemia and domino liver transplantation from hyperhomocsyteinemia. Submitted to Clin Res Hepatol Gastroenterol.

7. Plante-Bordeneuve V, Carayol J, Ferreira A, et al. Genetic study of transthyretin amyloid neuropathies: carrier risks among French and Portuguese families. J Med Genet 2003;40:e120.

8. Vollmar J, Schmid JC, Hoppe-Lotichius M, Barreiros AP, Azizi M, Emrich T, Geber C, Schad A, Weyer V, Otto G, Heise M, Mittler J, Birklein F, Lang H, Galle PR, Zimmermann T. Progression of transthyretin (TTR) amyloidosis in donors and recipients after domino liver transplantation-a prospective single-center cohort study. Transpl Int. 2018 Nov;31:1207-1215.

9. Mnatsakanova D, Živković SA. Iatrogenic amyloid polyneuropathy after domino liver transplantation. World J Hepatol. 2017;9:126-130.

10. Adams D, Hawkins PN, Polydefkis M. Oligonucleotide Drugs for Transthyretin Amyloidosis. N Engl J Med. 2018;379:2086.

11. Kitchens WH. Domino liver transplantation: indications, techniques, and outcomes Transplantation Reviews 2011; 25: 167-177.

12. Popescu I, Dima SO. Domino liver transplantation: how far can we push the paradigm? Liver Transpl. 2012;18:22-8.

13. Stangou AJ, Banner NR, Hendry BM, et al. Hereditary fibrinogen A-chain amyloidosis: phenotypic characterization of a systemic disease and the role of liver transplantation. Blood 2010;115:2998-3007.

14. Shaz BH, Lewis WD, Skinner M, et al. Livers from patients with apolipoprotein A-I amyloidosis are not suitable as domino donors. Mod Pathol 2001;14:577-80.

15. Popescu I, Habib N, Dima S, Hancu N, Gheorghe L, Iacob S, et al. Domino liver transplantation using a graft from a donor with familial hypercholesterolemia: seven-yr follow-up. Clin Transplant. 2009;23:565-70.

16. Dowman JK, Gunson BK, Bramhall S, Badminton MN, Newsome PN. Liver transplantation from donors with acute intermittent porphyria. *Ann Intern Med* 2011;154: 571-572.

17. Badell IR, Hanish SI, Hughes CB, Hewitt WR, Chung RT, Spivey JR, Knechtle SJ. Domino liver transplantation in maple syrup urine disease: a case report and review of the literature. Transplant Proc. 2013;45:806-9.

18. Mazariegos GV, Morton DH, Sindhi R, Soltys K, Nayyar N, Bond G, et al. Liver transplantation for classical maple syrup urine disease: long-term follow-up in 37 patients and comparative United Network for Organ Sharing experience. J Pediatr; 2012;160:116-21.

19. Moguilevitch M, Delphin E. Domino Liver Transplantation from a Child with Propionic Acidemia to a Child with Idiopathic Fulminant Hepatic Failure. Case Rep Transplant 2018 14:1897495.

20. Khanna A, Gish R, Winter SC, Nyhan WL, Barshop BA. Successful Domino Liver Transplantation from a Patient with Methylmalonic Acidemia. JIMD Rep 2016;25:87-94.

21. Morris AA, Kožich V, Santra S, Andria G, Ben-Omran TI, Chakrapani AB, Crushell E, Henderson MJ, Hochuli M, Huemer M, Janssen MC, Maillot F, Mayne PD, McNulty J, Morrison TM, Ogier H, O'Sullivan S, Pavlíková M, de Almeida IT, Terry A, Yap S, Blom HJ, Chapman KA. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis 2017;40:49-74.