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To cite this version:

HAL Id: hal-02305478
https://hal.sorbonne-universite.fr/hal-02305478
Submitted on 4 Oct 2019

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Domino liver transplantation: the risk of disease recurrence

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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 homocysteine levels from the donor...
rapidly dropped to normal values (< 15 µmol/L), while plasma homocysteine 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 homocysteine 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 homocysteine 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

<table>
<thead>
<tr>
<th>Diseases in which domino liver transplantation was performed</th>
<th>Transmission</th>
<th>Risk of transmission</th>
<th>Date of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unacceptable indications for donation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>RA</td>
<td>Constant</td>
<td>Immediate</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>DA</td>
<td>Constant</td>
<td>Immediate</td>
</tr>
<tr>
<td>Urea cycle diseases</td>
<td>RA</td>
<td>Reported for OTC</td>
<td>Immediate for OTC</td>
</tr>
<tr>
<td><strong>Uncertain indications for donation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>RA</td>
<td>Not yet reported</td>
<td>/</td>
</tr>
<tr>
<td>Organic aciduria</td>
<td>RA</td>
<td>Not yet reported</td>
<td>/</td>
</tr>
<tr>
<td><strong>Acceptable indications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial amyloid polyneuropathy</td>
<td>DA</td>
<td>Constant</td>
<td>7-9 years</td>
</tr>
<tr>
<td>Hereditary Fibrinogen Aα-Chain Amyloidosis</td>
<td>DA</td>
<td>Not yet reported</td>
<td>/</td>
</tr>
<tr>
<td><strong>Excellent indications for donation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>RA</td>
<td>Absent</td>
<td>/</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>CoDA</td>
<td>Absent</td>
<td>/</td>
</tr>
</tbody>
</table>

OTC: Ornithine Transcarbamylase deficiency.
References


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 hyperhomocysteinemia. Submitted to Clin Res Hepatol Gastroenterol.


