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ORIGINAL ARTICLE

Long-term consequences of domino liver transplantation using familial amyloidotic polyneuropathy grafts

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Summary

Domino liver transplantation (DLT) using grafts from patients with familial amyloidotic polyneuropathy (FAP) is an established procedure at many transplantation centers. However, data evaluating the long-term outcome of DLT are limited. The aim of the present study was to analyze the risk of *de novo* polyneuropathy, possibly because of amyloidosis, and the patient survival after DLT. At our department, 28 DLT using FAP grafts were conducted between January 1997 and December 2005. One patient was twice subjected to DLT. Postoperative neurological monitoring of peripheral nerve function was performed with electroneurography (ENeG) in 20 cases. An ENeG index based on 12 parameters was calculated and correlated to age and/or height. Three patients developed ENeG signs of polyneuropathy 2–5 years after the DLT, but with no clinical symptoms. The 1-, 3- and 5-year actuarial patient survival in hepatocellular carcinoma (HCC) patients ($n = 12$) and non-HCC patients ($n = 15$) was 67%, 15%, 15% and 93%, 93%, 80%, respectively ($P = 0.001$). Development of impaired nerve conduction in a proportion of patients may indicate that *de novo* amyloidosis occurs earlier than previously expected. Survival after DLT was excellent except in patients with advanced HCC.

Introduction

Orthotopic liver transplantation is an established treatment for end-stage liver diseases as well as for some severe metabolic disorders and hepatic cancers. However, organ shortage is a limiting factor to meet the need for the procedure (1). Many patients with end-stage liver disease and accepted to the waiting list die before transplantation. To meet the demand, the alternatives are as follows: increased use of marginal donors, living donor liver grafts, split liver grafts from deceased donors and so-called domino liver grafts from patients with metabolic liver diseases undergoing liver transplantation. Explanted livers from patients with familial amyloidotic polyneuropathy (FAP) are often used as domino grafts, as the liver is normal apart from the production of the mutated transthyretin (TTR) variant (2). FAP is an autosomal dominant disease associated with a mutation of the *TTR* gene. TTR variant amyloid fibrils are produced mainly in the liver, and are accumulated in body connective tissues. In the peripheral nervous system, fibrils accumulate especially in the endoneurium, leading to axonal loss and neurodegeneration (3). The disease penetrance is variable, but in Sweden only 5–10% of the carriers of the mutation develop symptoms. The most frequent initial symptom of FAP is a progressive peripheral polyneuropathy with sensory and motor disturbances in hands and feet, and an autonomic neuropathy, occurring at 40–60 years of age (4). Patients typically die of cardiac complications or of severe malnutrition 10–20 years after the onset of symp-

toms of the disease. The only potentially curative treatment for FAP has been liver transplantation. The first domino liver transplantation (DLT) using a liver from an FAP patient was performed in Portugal in 1995, but today the method is used worldwide and especially in the endemic countries of FAP: Portugal, Japan, and Sweden (5–8). At our institute, the first DLT was performed in a patient with advanced hepatocellular carcinoma (HCC) in February 1997.

A few reports on the clinical course after DLT have been published. In Brazil, seven DLT recipients were followed-up. There was no evidence of peripheral or autonomic neuropathy 12–40 months after DLT, and gastrointestinal biopsies showed no signs of *de novo* amyloid deposits 4–24 months after DLT (9). In Portugal, 15 DLT recipients had skin biopsies performed 1–7 years after DLT and TTR depositions were found in a minority of patients 3 years after transplantation (10). A summary of the previous reports is shown in Table 1 (9–13). The possibility of *de novo* amyloidosis as a late complication of DLT is a worrisome issue, and more information is needed to optimize the selection of DLT recipients. The aims of the present study were to analyze the risk of *de novo* polyneuropathy and the patient survival after DLT.

Methods

Patients

At our department, 58 liver transplantations in FAP patients were performed between January 1997 and December 2005, and in 28 of these cases a DLT using the explanted FAP graft was performed. One patient (DLT no. 11 in Table 5) received a domino liver twice because of hepatitis C and liver cirrhosis. All patients received information on the nature of the FAP disease, the characteristics of the FAP liver and possible late complications after DLT. They all signed a written informed consent before undergoing the DLT procedure. The FAP patients to serve as liver donors were also thoroughly pre-operatively informed and asked if their livers could be used for transplantation to another patient. All domino donors were patients with FAP type I (Val30Met). The characteristics of the DLT recipients and the domino donors are listed in Tables 2 and 3. Our policy was to offer domino livers to patients accepted to the waiting list. However, in the beginning of our DLT program, we offered domino livers only to patients accepted to the waiting list with

Table 2. Characteristics of domino liver transplantation (DLT) recipients.

Recipients/DLT	27/28
Age (years) (mean ± SD, range)	52.4 ± 10.2 (28–73)
Gender (male/female)	14/13
No. of re-transplantations	5 (18%)
Pre-operative diagnosis, No. (%)	
Hepatocellular carcinoma	12 (42.8%)
Hepatitis C virus	10 (35.7%)
Primary biliary cirrhosis	1 (3.6%)
Primary sclerosing cholangitis	1 (3.6%)
Cryptogenic cirrhosis	1 (3.6%)
Other	3 (10.7%)
Postoperative immunosuppression, No. of patients	
Cyclosporine and steroids	5
Cyclosporine, steroids and basiliximab	6
Tacrolimus and steroids	8
Tacrolimus, steroids and mycophenolate mofetil	8
Additional OKT3 for steroid resistant rejection	2

Table 1. Previous studies reporting possible *de novo* amyloidosis after domino liver transplantation (DLT).

Authors	Contents
Bittencourt *et al.* (9)	Seven recipients of familial amyloidotic polyneuropathy (FAP) livers were followed for clinical and neurophysiological signs of FAP and also for *de novo* amyloid depositions in the gut. No signs or symptoms of *de novo* FAP nor any evidence of amyloid deposits in the gut was observed in recipients of DLT after a mean follow-up of 24 (12–40) months.
Sousa *et al.* (10)	The occurrence of amyloidosis in recipients of FAP livers was evaluated 1–7 years after DLT. Transthyretin (TTR) depositions occurred in the skin 3 years after transplantation either as amyloid or aggregates. In one of the recipients fibrillar, TTR was present in the epineurium 6 years after DLT. Nerve biopsies from DLT recipients showed no sign of FAP-related neuropathy.
Stangou *et al.* (11)	A 55-year-old man who received an FAP liver 8 years earlier reported symptoms of dysaesthesia in the lower extremities. Specimens from nerve and rectal biopsies contained TTR amyloid depositions. Overt progressive peripheral neuropathy developed in the ensuing 6 months and a re-transplantation was performed.
Goto *et al.* (12)	A 57-year-old woman who received part of an FAP liver developed sensory neuropathy 7 years after transplantation. Biopsy samples of her duodenum showed amyloid depositions. Impaired temperature sensitivity in fingers and toes was detected on neurological examination 2 years after the amyloid depositions were first detected. Nerve conduction studies revealed mild-to-moderate axonal sensory polyneuropathy without demyelination.
Takei *et al.* (13)	Biopsy of the gastroduodenal mucosa was carried out in five recipients of FAP livers. TTR-derived amyloid deposits were detected in two patients, both of whom had undergone DLT 47 months previously.

Table 3. Characteristics of DLT donors and operative procedure.

FAP donors	28
Age years (mean ± SD, range)	47.1 ± 12.2, (25–67)
Gender (male/female)	18/10
Donor-recipient blood group identity A/B/O	14/4/10
DLT recipient operation procedure	
Operation time (h) (mean ± SD, range)	9.9 ± 2.1, (5.8–14.5)
Cold ischemia time (h) (mean ± SD, range)	7.3 ± 3.5, (3.3–14.5)
Anhepatic phase (min) (mean ± SD, range)	90.1 ± 30.6, (44–175)
Blood transfusion (including cell saver blood, units) (mean ± SD, range)	14.7 ± 11.1, (2–48)

DLT, domino liver transplantation; SD, standard deviation; HCC, hepatocellular carcinoma.

advanced HCC. After 2000, we expanded our domino recipient inclusion criteria also to include waiting list patients over the age of 40 with liver cirrhosis induced by hepatitis C virus (HCV) and/or Hepatitis B virus (HBV), patients with chronic graft failure after previous liver transplantation and all patients older than 60 years of age regardless of indication. The recipient age at the time of transplantation ranged from 28 to 73 years (mean 52.4 years). Fourteen were males and 13 were females. The underlying disease in the 23 first time transplant DLT recipients was: 11 patients with HCC (of whom four patients with HCV, two patients with HBV, one patient with both HCV and HBV, one patient with HCV and Laennec's cirrhosis, and one patient with Alagille's syndrome, one patient with HCC combined with cholangiocellular carcinoma and one patient without liver cirrhosis), nine patients had liver cirrhosis because of HCV without HCC (one of these patients also had Laennec's cirrhosis and one patient also had HIV) and finally one case each with primary sclerosing cholangitis, primary biliary cirrhosis, and cryptogenic cirrhosis. Five DLTs were performed as re-transplantations. The indications in these cases were liver failure with biliary obstruction, liver cirrhosis with recurrence of HCV (This patient received a domino liver twice.), liver dysfunction because of hepatic artery pseudoaneurysm, late recurrence of HCC in the liver graft, and liver cirrhosis with *de novo* autoimmune hepatitis. Detailed clinical data on the HCC patients are given in Table 4.

All patients were given standard postoperative immunosuppressive treatment. No prophylactic vitamin treatment for polyneuropathy was given as there was no evidence that the FAP patients benefited from this. Patient characteristics are summarized in Table 2. The postoperative follow-up period for the surviving DLT recipients at the end of November 2006 was 12–85 months (mean 36 months).

Evaluation of late neurological complication

Postoperative neurological monitoring of peripheral nerve function was performed with electroneurography (ENeG) according to our postoperative follow-up protocol and was carried out with conventional neurophysiological technique using surface electrodes. Six parameters of motor nerve conduction were recorded in the median, peroneal, and tibial nerves and six parameters of sensory nerve conduction were recorded in the median, superficial radial and sural nerves. The parameters were chosen to reflect both axonal and myelin functions in upper and lower extremities. Any isolated nerve lesion, such as carpal tunnel syndrome, was identified and the corresponding parameters were excluded by the computer program. An ENeG index based on the parameters was calculated as the mean deviation in SD from normal values and correlated to age and/or height, using a computer program developed at our institute (14). The diagnoses of slight, moderate, and severe neuropathy were conducted according to the ENeG index (0 to -0.72 = normal, -0.72 to -2 = slight neuropathy, -2 to -4 = moderate neuropathy and less than -4 = severe neuropathy). In the first nine patients, nerve conduction monitoring was performed at 1 and 6 months and thereafter yearly if the patient's medical condition was stable. After October 2000, the monitoring was scheduled yearly. New abnormal neurological findings discovered after 2 years were considered as late occurring complications.

Statistical analysis

Overall actuarial survival was calculated from the date of DLT until death from any cause. Statistical analyses were performed by using the STATISTICA software program (Statsoft Inc., Tulsa, Oklahoma, USA). The Kaplan–Meier method and the log-rank test were used to calculate the survival rates and differences in survival curves. A P-value of <0.05 was considered to be statistically significant.

Results

Evaluation of late neurological complication after DLT

Table 5 summarizes the late complications in the DLT recipients. No DLT recipients presented clinical symptoms of peripheral motor and/or sensory dysfunction preoperatively. Twenty DLT recipients were evaluated by repeated ENeG to assess the peripheral nerve function. Seven patients are not reported because five patients died within 2 years of DLT and for two patients the follow-up time was too short to be conclusive. Six patients (DLT No. 12, 14, 17, 21, 23, and 28) had normal ENeG results 1, 1, 2, 2, 1 and 1 year after DLT, respectively. Abnormal

Table 4. Characteristics of hepatocellular carcinoma (HCC) patients.

Domino liver transplantation (DLT) No.	Sex	Age	Pre-DLT diagnosis	Histological diagnosis	Primary lobe of HCC	No. of tumor noduli	Tumor size (max diameter cm)	Within Milan criteria	Presence of liver cirrhosis	Presence of vascular invasion	Presence of capsular invasion	Adjuvant cancer therapy	Outcome	Survival after DLT (months)	Cause of death	Tumor recurrence in
1	M	33	HCC with Hepatitis B virus (HBV)	Moderately differentiated HCC	Right lobe	4	3.5	No	Yes	No	Yes	–	Dead	12	Cancer recurrence	Bone
2	F	34	HCC with Alagille's syndrome	Moderately differentiated HCC	Right lobe	2	8	No	Yes	Yes	No	Transcatheteric hepatic arterial embolization	Dead	3.2	Cancer recurrence	Lung
4	M	50	HCC with hepatitis C virus (HCV)	Moderately differentiated HCC	Right and left lobe	Multiple	11	No	No	No	No	Combined stem cell tx and chemotherapy	Dead	2.5	Pneumonia	Spleen, pancreas, and liver hilum
5	F	55	HCC with HCV	Well-differentiated HCC	Right lobe	1	7	No	Yes	No	No	–	Dead	22.1	Cancer recurrence	Lung
8	M	56	HCC with HCV and alcoholic cirrhosis	Well-differentiated HCC	Left lobe	1	4	Yes	Yes	No	No	–	Dead	82.6	Cardiac complication	
12	M	47	HCC with HBV	Well-differentiated HCC	Right lobe	4	9	No	Yes	No	No	–	Dead	8.9	Cancer recurrence	Lung
15	F	41	Recurrence of HCC after orthotopic liver transplantation	Moderately differentiated HCC	Right and left lobe	3	14	No	No	No	No	–	Dead	14.2	Cancer recurrence	Lung, liver
16	M	57	HCC with HCV and HBV	Moderately differentiated HCC	Right and left lobe	Multiple	5.1	No	Yes	Yes	No	Combined stem cell tx and chemotherapy	Dead	35.7	Multiorgan failure	
18	M	56	HCC	Well-differentiated HCC	Right and left lobe	Multiple	19.4	No	No	Yes	No	Combined stem cell tx and chemotherapy	Dead	10.9	Cancer recurrence	Pancreas, bone
20	F	60	HCC with HCV	Moderately differentiated HCC	Right lobe	2	1.7	Yes	Yes	Yes	No	Transcatheteric hepatic arterial chemoembolization	Dead	26.7	Cancer recurrence	Lung
21	F	28	HCC with cholangiocellular carcinoma	HCC and cholangiocellular carcinoma	Right and left lobe	3	2.4	No	No	No	No	Combined stem cell tx and chemotherapy	Alive	29.9		Lung
28	F	68	HCC with HCV	Poorly differentiated HCC	Right lobe	1	1.7	Yes	Yes	Yes	No	–	Alive	12.3		

Table 5. Patients followed up with electroneurography (ENeG) after domino liver transplantation (DLT).

DLT No.	Age	Patient status	Post-DLT months for updated ENeG	Initial ENeG Index/updated ENeG index	ENeG findings (index value) and comments
1	33	Dead	7	+0.05/0	Low-amplitude motor response in the right median nerve (C7, C8 and Th1) because of metastasis. Normal at 6 months
2*	34	Dead	60	+0.12/−0.83	Slight polyneuropathy, deterioration compared to the result at 36 months (−0.23)
3*	52	Dead	60	−3.11/−2.60	Moderate polyneuropathy, deterioration compared to the result at 24 months (−1.42). The initial score at 6 months was −3.11 but improved
5	55	Dead	12	−2.24/−1.17	Slight polyneuropathy, deterioration compared to the result at 7 months (−0.80). The initial score at 1 month was −2.24 and also clinical symptoms but improved
6	58	Alive	72	−1.10/−9.00	Advanced generalized polyneuropathy because of Guillain-Barré syndrome
7	60	Alive	60	−1.00/−0.79	Slight polyneuropathy at 36 months (−1.00) but improved slightly at 60 months (−0.79)
9	58	Dead	1	−3.80	Moderate polyneuropathy, possibly because of diabetes and HIV
10	46	Alive	72	−3.40/−2.11	Moderate polyneuropathy, no significant difference compared to findings at 36 months (−2.15)
11*	50	Dead	24	+0.02/−1.13	Slight polyneuropathy, deterioration compared to normal findings at 12 months. DLT transplanted twice.
12	47	Dead	13	−0.50	Normal
13	43	Alive	12	−1.20	Slight polyneuropathy
14	57	Alive	12	−0.41	Normal
16	57	Dead	12	−2.87	Moderate polyneuropathy
17	52	Alive	24	−1.06/−0.26	Normal. The initial score at 1 year was −1.06 but improved
21	28	Alive	24	−0.10/−0.30	Normal
22	64	Alive	12	−1.50	Slight polyneuropathy
23	57	Alive	12	−0.50	Normal
24	73	Alive	12	−0.80	Slight polyneuropathy
25	52	Alive	12	−1.50	Slight polyneuropathy
28	68	Alive	12	−0.70	Normal

*Possible *de novo* neuropathy.

ENeG was recorded in 14 patients at the time of the updated evaluation. The time from the date of DLT to the initial abnormal results in these patients ranged from 1 to 60 months.

Three patients developed neurophysiological signs of progressive polyneuropathy 5, 5 and 2 years after DLT, respectively. DLT No. 2 with a pre-operative diagnosis of HCC and Alagille syndrome had a normal ENeG at 5 months, 1, 2, and 3 years after DLT. However, the patient had abnormal ENeG (ENeG index −0.83) 5 years after DLT. The general condition of this patient was stable and no clinical symptoms of neuropathy were observed at the time. No additional evaluation could be conducted due to the patient's death. DLT No. 3 with pre-operative diagnosis of HCV suffered postoperative complications with intra-abdominal bleeding and bile leakage that required reoperation and temporary hemodialysis. Initial ENeG at 6 months postoperatively showed a moderate polyneuropathy with ENeG index −3.11 possibly because of the postoperative complications. At 1 year after DLT, the ENeG index was −2.21, and at 2 years after DLT the ENeG index had further improved to −1.42. However, an updated ENeG 5 year after DLT showed signs of deterioration and moderate polyneuropathy with an ENeG index of −2.60. No additional evaluation could be conducted due to the patient's death. DLT No. 11 who received DLT twice with pre-operative diagnosis of HCV had a normal ENeG (ENeG index 0.02) 1 year after DLT, but showed signs of abnormality (ENeG index −1.13) 2 years after DLT without clinical neurological symptoms. No additional evaluation could be conducted due to the patient's death.

The seven patients who had abnormal results on the ENeG index already shortly after the operation and thus did not develop *de novo* polyneuropathy are described in detail. DLT No. 1 had normal ENeG except for decreased

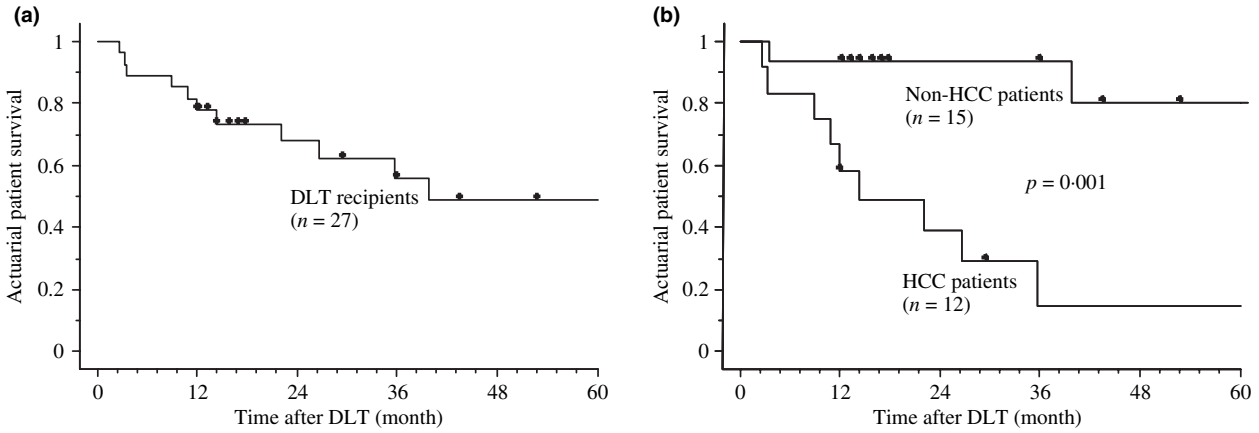

Figure 1 (a) Overall survival of patients receiving domino liver transplants. (b) Overall survival of domino liver transplantation in hepatocellular carcinoma (HCC) patients and non-HCC patients. A significant difference in survival was observed between the two groups ($P = 0.001$).

motor response of the right median nerve because of a vertebral metastasis of HCC. DLT No. 5 with pre-operative diagnosis of HCC and HCV had a moderate polyneuropathy already 1 month after DLT with clinical symptoms and an ENeG index of −2.24. The index improved to −0.77 at 7 months after DLT, and worsened insignificantly to −1.17 at 1 year after DLT. No additional evaluation was possible because of the patient's death. DLT No. 6 had an advanced acute generalized polyneuropathy (Guillain-Barré syndrome) 5 months after DLT. DLT No. 9 who had a pre-operative diagnosis of HCV, HIV, and insulin-demanding diabetes mellitus had a moderate polyneuropathy at 1 month after DLT with an ENeG index of −3.80. No additional evaluation was carried out due to the patient's death. DLT No. 10 showed moderate polyneuropathy 2 months after DLT (ENeG index −3.41), which gradually improved to −2.11. DLT No. 13 with HCV had a slight polyneuropathy (ENeG index −1.2) at 12 month after DLT. This patient had post-transplantation diabetes with paresthesia in both feet at 27 months after DLT. DLT No. 16 with a pre-operative diagnosis of HCC and HCV suffered complications because of graft-versus-host disease (GVHD) and cytomegalovirus (CMV) infection and a deterioration in general condition. He showed moderate polyneuropathy at 12 months after DLT with an ENeG index of −2.87. No additional evaluation was conducted because of the patient's death.

Three other patients in stable general condition (DLT No. 22, 24, and 25) had ENeG findings indicating slight polyneuropathy (ENeG index −1.5, −0.8 and −1.5, respectively) already 1 year after DLT. DLT No. 7 had abnormal ENeG results 3 years after DLT (ENeG index −1) but improved slightly 5 years after DLT (ENeG index −0.79) without clinical neurological symptoms.

Considering all the above, it may be concluded that at least three patients (DLT No. 2, 3 and 11) developed findings compatible with *de novo* polyneuropathy by ENeG and its diagnostic criteria.

Patient survival

Thirteen patients (10 of whom had HCC) out of 27 DLT recipients died. The causes of death were recurrence of HCC ($n = 7$), cardiac complications ($n = 2$), pneumonia ($n = 1$), brain infarction ($n = 1$), multiorgan failure ($n = 1$), and the patient who was subjected to DLT twice died of circulatory collapse during the re-transplantation ($n = 1$). The time of death for the 10 HCC patients is shown in Table 4. The three non-HCC patients died at 3 months (cardiac complication), 40 months (re-transplantation), and 61 months (brain infarction) after the transplantation.

Overall, the 1-, 3- and 5-year actuarial survival was 82%, 56%, and 49%, respectively (Fig. 1a). We also analyzed the survival in patients with HCC and those without HCC separately (Fig. 1b). In HCC patients, the 1-, 3- and 5-year actuarial survival was 67%, 15%, and 15%, respectively compared with 93%, 93%, and 80%, respectively in non-HCC patients ($P = 0.001$, Fig. 1b). Kaplan–Meier analysis showed an overall 1- and 3-year disease-free survival for HCC patients of 42% and 21%, respectively.

Discussion

The DLT procedure using FAP liver grafts for transplantation is today spread worldwide. The Domino Liver World Transplant Registry (DLWTR, http://www.fapwtr.org) was established in 1999, and until November 2005, 461 DLTs had been performed in 16

countries. Almost half of the cases were carried out in patients with malignant liver disease. As shown in Table 2, 43% of our cases had hepatic malignancy and 18% were re-transplantations. These proportions are similar to reports from other centers reporting to the DLWTR.

The DLT procedure by its nature raises a specific ethical problem. The FAP liver graft to be transplanted produces a pathogenic protein, the TTR variant in the DLT recipient. The justification to use such a graft is that the life expectancy for the recipient is less than the estimated time for the occurrence of clinical *de novo* amyloidosis, caused by the accumulation of amyloid produced by the transplanted FAP liver. However, the risk of transmitting *de novo* amyloidosis to the DLT recipients of FAP livers cannot be neglected and is of serious concern. Stangou *et al.* (11) have recently reported the transmission of FAP disease to one patient with symptoms in the lower extremities occurring 8 years after DLT. Furthermore, other authors have reported subclinical TTR deposits in the skin in five DLT recipients either as amyloid or aggregates 3 years after DLT (10). In our study, 14 patients had abnormal ENeG findings. Among them, three patients developed abnormal peripheral nerve conduction on ENeG as a possible sign of *de novo* amyloidosis. Ten patients had abnormal nerve conduction already within 1 year after DLT, and it is unlikely that these early postoperative abnormalities of nerve conduction were due to *de novo* amyloidotic polyneuropathy. These patients require further repeated yearly evaluations.

Only <10% of the Swedish Val30Met mutation carrier population develop the clinical FAP disease and symptoms (15). In contrast, a higher percentage of our DLT recipients seem to develop objective ENeG findings of early polyneuropathy, although not yet clinically evident FAP disease.

The occurrence of polyneuropathy after liver transplantation is not unusual. Factors such as diabetes and poor general condition because of uremia, HCV, alcoholic liver disease or Guillain-Barré Syndrome affect nerve function and may lead to polyneuropathy. Neurotoxicity by calcineurin inhibitors is a well-known side effect, but peripheral polyneuropathy is rare and related to high blood concentrations (16, 17). Unfortunately, screening for polyneuropathy post-transplantation is not always performed. Thus, we know little about such changes in DLT and non-DLT liver transplant recipients. Biopsies of the gastrointestinal tract, skin, muscle and nerves in DLT recipients can be used to diagnose *de novo* amyloidosis, but do not necessarily provide information on clinically manifested polyneuropathy.

The ENeG index in this study summarizes 12 nerve conduction parameters and facilitates comparison between recordings with respect to overall peripheral nerve function. It can detect subclinical pathology in peripheral nerves before clinical symptoms of neuropathy have developed (14). It is a sensible and reliable tool to monitor generalized neuropathy in individuals over time.

Our analysis showed that the overall survival of HCC DLT recipients was significantly lower compared to non-HCC DLT recipients. Only three out of 12 DLT recipients for HCC fulfilled the Milan criteria, which are known to influence the survival significantly after liver transplantation in nondomino liver graft recipients (18). Understandably, liver transplantation in patients with advanced hepatic cancer will at present yield poor results, because of the underlying severe disease and the high recurrency rate in these patients. We were, of course, quite aware of this reality and the poor prognosis in these patients. For several years, we have tried to improve the results in patients with advanced hepatic cancer by using adjuvant chemotherapy as well as combining stem cell transplantation and liver transplantation (Table 4) (19). Patients with advanced hepatic cancer are accepted to our usual waiting list and compete with other indications for donor livers, and therefore at several occasions domino livers have been used in these patients. In view of the fact that domino livers constitute good grafts, we believe that these livers should be offered to patients accepted to the waiting list, and we want to emphasize that our waiting list was not expanded to find use for domino livers. Domino livers from FAP patients constitute excellent grafts, as they are healthy aside from the production of the variant TTR. However, complications caused by the accumulation of amyloid in various organs may occur earlier and more frequently than expected from the natural FAP course. FAP patients who begin to develop symptoms live at least 10 years after the onset before they die from the disease. We previously predicted that <10% of the DLT recipients would, with time, develop FAP disease, and that symptoms would start later than 15 years after the DLT procedure. Taking the present findings and earlier reports into consideration, this may have been too optimistic. The selection of potential recipients must therefore be careful, but with the large number of patients waiting for liver transplantation and the relatively small number of FAP livers available for DLT, it seems possible to select DLT recipients from the waiting list in whom the risk of developing FAP disease post-transplantation is minimized. Examples of such potentially suitable patients are elderly patients (>60 years), HCV patients (>40 years) running a high risk of recurrent hepatitis and patients with hepatic cancers. If a DLT patient demonstrates *de novo* amyloidosis, re-transplantation with a nondomino liver should be considered.

In this study, we have only analyzed the Val30Met mutated variant, which is only one out of many different

mutations. The risk of transferring the original disease by DLT may differ with other TTR variants.

In conclusion, we found electroneurographic signs indicating impaired nerve conduction in several of the DLT recipients. The cause is not clear, but in three of 28 patients disease transmission by the FAP liver graft cannot be ruled out. Nevertheless, we believe that with a careful selection of potential recipients, the DLT is of value and the treatment modality should be continued. The DLT procedure can contribute significantly in relieving the organ shortage. We are also convinced that the follow-up after DLT should include ENeG in addition to clinical examination. We are presently conducting a prospective study including biopsies to address the question of amyloid deposits.

Authorship

SY[1] performed the main role in designing the study, collecting and analyzing the data and writing the article. TI, ML, HG, and GS contributed to design the study, collect the data, and analyze the results. GS evaluated the ENeG, contributed in the design of the study and in writing the article. HEW and BE had a significant role in the design of the study, in analyzing the data and in supervising the first author, as well as in writing the article.

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