TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

No ocular involvement in familial amyloidotic polyneuropathy ATTR V30M domino liver recipients

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Keywords
amyloid, domino, familial amyloidotic polyneuropathy, liver transplantation, ocular, sequential.

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Conflict of Interest
The authors of this manuscript have no conflicts of interest to disclose.

Received: 1 December 2011
Revision requested: 15 January 2012
Accepted: 27 February 2012
Published online: 22 March 2012

doi:10.1111/j.1432-2277.2012.01467.x

Summary

In many transplantation centers domino liver transplantation is an established procedure, increasing the number of available liver grafts. Increasingly, grafts from familial amyloidotic polyneuropathy (FAP) patients are used. Ocular involvement is a well known manifestation of FAP, and can be vision-threatening. The aim of this study was to evaluate the risk of development of familial amyloidotic polyneuropathy ocular manifestations in domino liver recipients. Forty-four cirrhotic patients submitted to liver transplantation were studied, with an average of 6 years of follow up after the procedure. Twenty two patients had received a liver from a FAP donor (Group 1) and 22 had received a liver from a non-FAP cadaveric donor (Group 2). Both groups were similar for mean age and gender. Routine ophthalmological examinations with particular attention to amyloid deposition in the anterior segment and vitreous, peripheral retina state, lacrimal functions tests (Schirmer and tear break-up time) and pupillometry (dynamic and static) were performed. No statistically significant differences were observed in all studied ophthalmic parameters between the two groups. No FAP related ophthalmic manifestations were detected after 6 years of domino liver transplantation, but further prospective regular ophthalmological examinations are necessary to detect the eventual development of late ocular manifestations.

Introduction

Familial amyloid polyneuropathy (FAP) is an inherited, autosomal dominant, multisystemic amyloidosis. The Portuguese type of FAP, first described by Andrade in 1952, is caused by a point mutation in the transthyretin (TTR) gene with subsequent production of a mutant protein in which a valine at position 30 has been replaced by methionine (ATTR V30M) [1]. It is the most common variety of hereditary amyloidosis worldwide and its main clinical expression is a progressive autonomic and peripheral neuropathy [2,3]. Since near 90% of plasma TTR is produced by the liver [4] and the remainder produced by the choroid plexus and the retinal pigmented epithelium [5], it was expected that liver transplantation would abolish the mutant TTR production and halt the progression of the disease. In 1990, Holmgren *et al.* reported the first orthotopic liver transplantation (OLT) in a FAP patient [6]. Presently, this is the only treatment that seems to alter the natural course of the disease, and significantly palliates many underlying symptoms [7,8].

Liver transplantation is a well-established treatment for hepatic cancers, end-stage liver disease and some metabolic diseases. The shortage of donor livers is a limiting factor in the expansion of OLT [9] and many patients accepted to waiting lists die before transplantation. To increase the donor liver pool alternatives such as living donor liver grafts, increased use of marginal donors, split liver grafts from deceased donors and domino liver grafts from patients with metabolic liver disease undergoing

liver transplantation are currently used [10]. The first domino liver transplantation using a liver from an FAP patient was performed in Portugal in 1995 [11], but today livers from FAP patients and patients with other disorders [12,13] are regularly used as domino grafts [14–17]. In liver transplantation center at Centro Hospitalar do Porto – Hospital Santo Antonio, over 200 patients underwent domino liver transplantation due to liver cirrhosis (alcoholic and viral) and liver malignancies.

Several studies have reported the existence of ocular manifestations of the disease in FAP patients, some with disastrous consequences for the patient's vision. The most frequent are abnormal conjuntival vessels, *keratoconjuntivitis sicca*, pupillary abnormalities, anterior lens capsule opacification, glaucoma, vitreous opacities and vascular retinal abnormalities. Endocular complications have been mainly attributed to endocular production of mutant TTR [18–21], a hypothesis supported by the observation that ocular amyloid deposition can occur 4–5 years after liver transplantation. *De novo* amyloidosis in FAP domino liver recipients has also been described [22,23] and although some authors state that plasma TTR does not cross the pigment epithelium to the retina [24,25], there is no conclusive evidence about the passage of TTR through the blood–eye barrier to the vitreous/aqueous humor. Additionally, there is still much to elucidate relative to the fibrillogenesis pathway and kinetics of ocular deposition of TTR amyloid.

The possibility of *de novo* amyloid deposition in recipients of livers from FAP patients remains a serious concern [19] and longitudinal studies are required to carefully evaluate the risk of ocular manifestations due to 'acquired' FAP in domino liver recipients. The aim of this study was to evaluate the long-term ocular consequences of domino liver transplantation using amyloidotic polyneuropathy grafts, particularly the occurrence of *de novo* ocular amyloidosis.

Patients and methods

Patients

Forty-four randomly selected non-consecutive liver transplanted patients with previous alcoholic cirrhosis were studied. Twenty two patients received a FAP ATTR V30M liver graft (Group 1) and 22 received a non-FAP cadaveric graft (Group 2). Both groups had similar gender distribution (18 men and 4 women in each group), mean age (58.6 ± 7.3 years vs. 56.4 ± 8.5 years, $P = 0.32$) and time of follow-up after liver transplantation (6.1 ± 1.8 years vs. 6.5 ± 2.8 years, $P = 0.44$) (Table 1). None of the patients studied had signs or symptoms of FAP and the immunosuppressive therapy was similar between groups. Three patients from Group 1 and 2 patients from Group 2 had diabetes mellitus. Four patients from Group 1 and 5 of Group 2 had arterial hypertension. Patients under therapy with potential effects on sympathetic or parasympathetic pupillary function or submitted to previous ocular surgery were excluded.

Table 1. Characteristics of the patients.

	Patients	Age (years-old)	Gender (M/F)	Time of OLT (years)	Eyes (*n*)
Group 1	22	58.6 ± 7.3	18/4	6.0 ± 1.8	44
Group 2	22	56.4 ± 8.5	18/4	6.5 ± 2.8	44

The study was approved by the Ethic Committee of Centro Hospitalar do Porto, and informed consent was obtained from all patients according to the declarations of Helsinki 2000 and Istanbul 2006.

Methods

All patients were submitted to ophthalmic evaluation in the same room, with the same equipment and by the same senior ophthalmologist at the Ophthalmology Department of Hospital Santo Antonio – Centro Hospitalar do Porto. The examinations were performed between 9:00 AM and 1:00 PM.

The near vision was evaluated as previously described by the authors [26].

Slit lamp examination evaluated the presence of conjunctival microaneurysms, opacification of the anterior capsule of the lens and the state of the iris (presence of amyloid deposits at the pupillary border and irregularity in the pupillary border).

Lacrimal function was evaluated using a Schirmer test without anesthesia and tear break-up time (TBUT) testing. Schirmer test was performed by placing a small filter paper strip (Schirmer-Plus manuf. by Dina-Hitex spol s r.o., Czech Republic) in the temporal one-third of the lower eyelid and closing eyes for 5 min. The paper was then removed and the wet part of the strip was measured in millimeters. To measure TBUT, an eyedrop of Fluotest® (fluorescein 2.5 mg/dL + hydrochloride oxybuprocaine 4 mg/dL – Fort Worth, TX, USA) was applied to the inferior conjunctiva. The precorneal tear film was examined with a slit lamp cobalt blue filter and the elapsed time, in seconds, was recorded before the initial breakup, rupture of the tear film or formation of dry spots.

Glaucoma was identified by the presence of optic nerve and visual field abnormalities associated with an intraocular pressure level equal to, or higher than 22 mmHg, or was inferred from ongoing treatment with ocular hypotensive eyedrops.

To evaluate the vitreous and the retina status, the pupil was dilated with one drop of topical tropicamide at 1%

and observation carried out after 30 min with a non-contact 90 D lens.

Pupillometry, or pupillography, are very useful non-invasive tests to study the autonomic nervous system function, with the advantage of requiring minimal patient cooperation [27]. The pupil diameters under standard light conditions [28] and several dynamic parameters are well correlated with the autonomic function and neuropathy [29]. Pupillometry has been proposed as a simple and sensitive tool to detect subclinical autonomic dysfunction [30,31]. To evaluate the differences in pupillary autonomic neuropathy between the two groups, the pupil reflexes were measured with a Pupillometer (Metrovision® Pérenchies, France) [27] in twenty eyes from each group. It uses invisible near infra-red illumination (950 nm), with an accuracy of measurement of pupil diameter of 0.1 mm and a sampling frequency of 30 Hz. Static and dynamic pupillometry was carried out after 30 min of dark-adaption. Static pupillometry evaluated the diameter of each pupil under scotopic (0.1 cd/m^2), mesopic (1 cd/m^2), low photopic (10 cd/m^2) and high photopic (100 cd/m^2) conditions. Dynamic pupillometry was performed after a standardized light stimulus from a light emitting diode with a duration of 200 ms and a brightness of 10^4 cd/m^2. The parameters evaluated as reflecting sympathetic and parasympathetic pupillary modulation were: light reflex amplitude (mm), latency of contraction (ms), duration of contraction (ms), velocity of contraction (mm/s), latency of dilatation (ms), duration of dilatation (ms) and velocity of dilatation (mm/s) [32,33].

Statistical analysis was performed with the PASW 18 statistical software package. Normally distributed data are presented as mean ± standard deviation. Group comparisons used the Student's *t*-test or a chi-square test, as appropriate. A P value < 0.05 was regarded as statically significant.

Results

The results are summarized in Table 2. None of the evaluated patients, domino or non-domino liver recipients presented conjunctival microaneurisms, glaucoma, vitreous amyloidosis or visible amyloidotic retinal angiopathy. Neither visible amyloid deposition on the anterior surface of the lens or on the iris nor scalloped iris was observed in any patient.

The average add power in group 1 was 1.84 ± 0.44 diopters and in group 2 was 1.89 ± 0.49 D, a non statistically significant difference ($P = 0.69$).

Also, no statistical difference was observed in mean Schirmer test results between groups (12.54 ± 6.34 mm in Group 1 and 14.19 ± 7.11 mm in Group 2, $P = 0.28$). Mean TBUT was also similar in both groups, 4.73 ± 2.23 s (Group 1) vs. 5.54 ± 2.86 s in (Group 2), $P = 0.19$.

The results of pupillometry are presented in Table 3. No significant differences were observed in parameters of static and dynamic pupillometry. In all standard conditions of light, the difference in pupil diameters between groups was not significant. Dynamic parameters such as sympathetic parameters (diameter, velocity of dilation, latency of contraction) or parasympathetic parameters (reflex amplitude, constriction velocity, latency of dilation) showed no statistically significant differences.

Discussion

The first report of domino organ transplantation described the reuse of a heart graft taken from a patient undergoing heart-lung transplantation [34]. A similar procedure was described by Moreno *et al.*, who referred a case where the liver taken from a liver recipient who suffered brain death was reused [35].

Livers explanted from FAP ATTR V30M patients have normal function, except for the production of an amyloidogenic mutant TTR. Initial estimates of the risk of disease transfer were based on the natural course of FAP disease. The age of onset of FAP ATTR V30M ranges from the 20 s to early 40 s, and the progression of the disease takes 15 years until death supervenes [13]. It was expected that liver grafts from FAP patients would function in recipients without amyloid deposition for a long period of

Table 2. Incidence of ocular manifestations.

	Group 1	Group 2	
Near vision (add power – diopters)	1.84 ± 0.44 D	1.89 ± 0.49 D	$P = 0.69$
Conjuntival microaneuryisms	0	0	
Amyloid deposition (lens/iris)	0/0	0/0	
Pupillary irregularity border	0	0	
Lacrimal funtion			
Schirmer test (mm)	12.54 ± 6.34	14.19 ± 7.11	$P = 0.28$
TBUT (s)	4.73 ± 2.23	5.54 ± 2.86	$P = 0.19$
Glaucoma	0	0	
Vitreous amyloid	0	0	
Amyloidotic retinopathy	0	0	

Table 3. Static and dynamic pupillometry.

	Group 1	Group 2	
Scotopic (mm)	4.35 ± 0.86	4.14 ± 0.62	$P = 0.79$
Mesopic (mm)	2.93 ± 0.52	2.95 ± 0.58	$P = 0.95$
Photopic low (mm)	2.25 ± 0.42	2.35 ± 0.47	$P = 0.55$
Photopic high (mm)	1.87 ± 0.31	1.96 ± 0.33	$P = 0.43$
Reflex amplitude (mm)	1.65 ± 0.35	1.53 ± 0.29	$P = 0.29$
Latency of contraction (ms)	353.53 ± 32.24	357.77 ± 28.22	$P = 0.69$
Duration of contraction (ms)	650.92 ± 72.53	645.47 ± 75.91	$P = 0.83$
Velocity of contraction (mm/s)	4.79 ± 0.78	4.42 ± 0.97	$P = 0.23$
Latency of dilation (ms)	997.37 ± 71.25	1002.20 ± 72.79	$P = 0.85$
Duration of dilation (ms)	1471.89 ± 84.84	1487.73 ± 77.27	$P = 0.58$
Velocity of dilation (mm/s)	1.66 ± 0.27	1.55 ± 0.35	$P = 0.26$

time. With careful selection of candidates it seemed a reasonable option to use livers from FAP patients to transplant patients with a short life expectancy.

After several reported cases of *de novo* amyloidosis, it is now evident that disease transfer occurs after domino liver transplantation. In 2005 Stangou *et al.* [36] published the first case of FAP symptoms in a domino liver recipient 8 years after liver transplantation, indicating that amyloid deposition or FAP symptoms appeared in domino recipients much sooner than expected. There is a possibility of accelerated fibrillogenesis in adults due to the enhancement of several mechanisms involved in amyloid formation and/or to the downregulation of inhibitory pathways [19]. The earlier than expected appearance of disease after domino liver transplantation could be associated with the complex post transplantation inflammatory and infectious status, with several rejection episodes. Moreover, surgical trauma, previous disease damage and immunosuppression could also trigger the formation of amyloid [37]. Another possible cause to the premature development of the disease in domino liver recipients is an enhanced deposition of mutant TTR in a favourable environment characterised by the presence of wild-type TTR deposits.

In spite of the demonstration of the passage of mutant transthyretin trough the blood–nerve barrier [19] and trough the blood–cerebrospinal barrier [38], no conclusive data exists about the passage through the blood–ocular barrier.

In FAP, endocular complications are the most feared ocular changes, that may lead to permanent blindness. After 6 years of liver transplantation, no evidence has been found of amyloid deposition in the anterior capsule of the lens or in the iris, scalloped iris, vitreous amyloid, amyloidotic retinal angiopathy or glaucoma. This could be due to the inability of the mutant TTR to cross the blood–eye barrier in significant amounts, insufficient to cause detectable changes, or to limited time of follow-up. A longer follow-up of these patients is needed to detect possible late ophthalmic complications caused by continuous systemic production of mutant TTR. However, for now, it seems that there is no risk of amyloidotic oculopathy in FAP ATTR V30M liver recipients.

All patients evaluated in this study were transplanted due to end-stage alcoholic liver disease. In cirrhotic patients, autonomic dysfunction is very frequent, but its pathogenesis remains poorly understood [39]. It is characterized by an autonomic nervous system imbalance: a relatively decreased parasympathetic activity and increased sympathetic tone [39–43]. The patients' age, the waiting time for liver transplantation and the age of onset of liver disease were similar in both groups, variables that could possibly change the autonomic balance. All studied parameters related to autonomic dysfunction such as Schirmer test, TBUT and static and dynamic pupillometry did not present statistically significant differences between the two groups, suggesting a similar evolution of autonomic changes, not related with the production of mutant TTR. However, further studies with longer follow-up are necessary to detect possible autonomic changes in these liver transplanted patients.

Assaying the presence or absence of mutant TTR in the aqueous humor, and/or vitreous, in these patients, will allow us to determine if the blood–eye barrier effectively prevents, or not, the passage into the eye of the mutant TTR produced by the FAP liver. It is important to remember, however, that even in the absence of TTR transport through the blood–eye barrier, autonomic ocular manifestations can still occur since they are independent of that barrier function.

We only evaluated ATTR V30M liver transplant recipients. Other TTR mutants have diverse amyloidogenic potentials. It is possible that the risk of inducing *de novo* amyloidosis is different when other TTR mutations are present.

Patients with end-stage hepatic disease with only a few months of life expectancy are the usual candidates for domino liver transplantation. The use of livers from FAP

patients allows the treatment of two patients with a single cadaveric donor, and increases the survival and quality of life of patients with end-stage liver disease. Domino liver transplantation has proven its value, especially, in northern Portugal, where the high proportion of FAP patients on the waiting list for liver transplantation compounds a serious shortage of donor livers [13]. The emergence of *de novo* amyloidosis mandates lifetime screening for FAP disease symptoms in these patients. On the other hand, ocular manifestations, if they occur, are probably very late in life and do not represent a contraindication to domino liver transplantation.

Authorship

MB: designed study; performed study, collected data, wrote paper. EM: analysed data. IB and PPC: wrote paper. PT: designed study.

Funding

No funding.

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