Indications for Liver Transplantation in Patients with Amyloidosis: A Single-Center Experience with 11 Cases

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Familial amyloidotic polyneuropathy (FAP) is an inherited disorder with the systemic deposition of amyloid fibrils containing mutant transthyretin variants. The mutant form of transthyretin amyloidosis is produced mainly in the liver. Successful liver transplantation (LTx) could eliminate the source of the variant transthyretin molecule, and is now the only known curative treatment. The aim of this study is to evaluate the results of LTx for FAP at the University of Heidelberg. Eleven patients who underwent LTx between 1985 and 2004 with the diagnosis of FAP were evaluated. Of 11 patients, seven (64%) were male and four (36%) were female. The mean age was 49.5 years (range 27-70). Met 30 (n=5) was the most common type of amyloidosis followed by Arg 50 (n=3), Val 107 (n=2), and Phe 33 (n=1). All of the patients were selected for LTx and Domino LTx was performed in six patients. The majority (80%) of the patients with type Met 30 amyloidosis are alive, whereas in other types of amyloidosis only 33% are living. This finding emphasizes better prognosis of Met 30 variant of FAP in comparison to other variants such as Arg 50, Val 107, and Phe 33. After LTx, improvement of clinical symptoms (completely or partially) was observed in six patients (55%). In conclusion, LTx is considered as the only therapeutic alternative in patients with amyloidosis accompanied by hepatic synthesis of the amyloid protein. The most important risk factors for LTx can be predicted by assessing the nutritional condition of the patient, the duration of the disease, and the amyloid variant. Therefore, precise diagnostic measures are required before listing a patient for LTx. Domino LTx is an acceptable form of LTx that can preserve the pool of organ donors. In order to stop the progression of FAP, LTx would be justified in a subgroup of patients with amyloidosis. Based on our results, we support the idea that the effectiveness of extended preoperative period before LTx or the transplantation of other transthyretin variants other than Met 30 is questionable.

Keywords: Amyloidosis, Familial amyloidotic polyneuropathy (FAP), Liver transplantation.

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The most common subtype of the familial amyloidotic polyneuropathy (FAP) is the Portuguese type, with a gene defect in nucleic acid resulting in an exchange of an amino acid in position 30 in the transthyretin, consisting of 127 amino acids. In this process valine is exchanged for methionine. This change possibly leads to an alteration in the solvent property of transthyretin. Therefore, a rigid amyloid fibril that is not ramified develops, which precipitates in the intercellular space or along fibrillar structures. This leads to a restriction of the metabolism, resulting in the impairment of organ function. Subsequently, it is aggravated in the muscles by an obstruction of the contraction and relaxation of the rigid complex of fibrils.

In Portugal and Central Europe, the onset of FAP is commonly found in patients around 30 years of age, as described by Andrade in 1952 (*1*), who reported 30 cases of FAP. However, in Sweden, the same genetic defect leads to an onset of the disease around 50 years of age. Presently it is still unclear why the same genetic alteration leads to different ages of disease onset, and what leads to the amyloid precipitation in only one organ. A diffuse involvement of multiple organs can only be observed during the later stages of the disease. Each year new variants of the transthyretin molecule are described (*5, 6*), and the altered amino acid as well as the position of the alteration may vary. Therefore a variety of amyloidoses may

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develop, presenting with different disease manifestations with respect to the onset of symptoms and the involved organs. However, not all of the genetic alterations lead to the manifestation of amyloidosis.

The Portuguese type of FAP commonly begins with sensory deficits in the lower extremities, with preference to a loss of temperature sensitivity. A painful polyneuropathy might result, with increasing atrophy of the muscles (*7*). The involvement of the autonomic nervous system (*8*) can lead to a large group of functional impairments leading to life-threatening situations such as cardiac arrhythmia, impairment of orthostatis and cachexia. In rare cases cardiac involvement could be the first manifestation of FAP. In cases, in addition to the involvement of the nerves, thickening of the intestinal wall by amyloid precipitations can be observed. There are most probably two mechanisms leading to cardiac and intestinal damage. Therefore, cardiac problems such as arrhythmia as well as muscular pumping deficiency might develop (*9*). With respect to the gastrointestinal tract, malabsorption, motility disorders such as constipation or diarrhea, and bleeding often develop (*10*). Renal disorders, recurrent urinary tract infections as well as erectile dysfunction can be also observed. Synthesis of transthyretin, which served as a transport protein, is performed predominantly in the liver, only about 5% are synthesized in the retina and the choroid plexus (*11*). In other FAP variants, the protein underlying the amyloid is also synthesized extrahepatically, as in the APO-AI amyloidosis of the small intestine (*12*).

DIAGNOSIS OF FAP

As in all rare diseases, it is important to think about amyloidosis when examining a patient with corresponding symptoms. In the early course of the disease, the family history is of high importance. Because FAP is an autosomal dominant disease, one parent must have suffered from FAP; however, this might not have been diagnosed as FAP. A detailed examination of the patients according to a fixed scheme can lead to an exact description of the disease pattern. This assessment includes neurological, cardiopulmonary, gastrointestinal, nephrologic, ophthalmologic staging, and amyloid scintigraphy (*16*). Histological demonstration of amyloid can be performed with special staining as well as with immunohistochemistry, which is used to identify the type of the amyloid fibers (*13*). This can be accomplished in almost all cases with modern antibodies (*14*). Should it be shown that the patient suffers from familial amyloidosis, the primary molecule should be evaluated and specified (*15*). After the results of all evaluations are complete a decision on the type and the time of therapy can be made.

THERAPEUTIC CONCEPT OF FAP

The therapeutic approach to eliminate the pathologic transthyretin by dialysis has not been successful (*17*). Presently it is still under evaluation whether the solvent property of the pathologic transthyretin can be altered by alkalization of the intracellular space in combination with sufficient hydration, as observed in experimental in vitro models. It is highly unlikely that a cure of the disease could be found in the near future, however the onset of the disease could be delayed (*18*). LTx has become an accepted treatment modality with a worldwide acceptance. The number of transplant cases has increased over the past decade and has reached a plateau of 60 transplantations per year (*25*). The replacement of the diseased liver through LTx results in abolishing the synthesis of the pathological transthyretin and stopping disease progression. The precipitated amyloid fibrils cannot be eradicated; however, major clinical symptoms will occasionally be recovered by LTx (*19,21*). In cases with extensive disease, progression of the FAP can be observed even after LTx because healthy transthyretin molecules precipitate next to the present amyloid fibrils (*20*). However, the exact time point when amyloidosis is irreversible cannot be predicted. It is supposed that cardiac involvement might impair reversibility more than other involvements (*22*). To stop the progression of FAP, LTx can only be justified in a subgroup of patients with amyloidosis. In these patients, the protein consisting of amyloid fibers, is synthesized within the liver. Almost all of these patients suffer from a hereditary form of amyloidosis.

The World Transplantation Center for hereditary amyloidosis in Umea has registered 890 patients with amyloidosis treated by LTx until September 30, 2004 (*24*). Using this database the pre- and postoperative risk can be calculated. Additionally, the operated patients can be observed and the course of the disease can be analyzed. Therefore, main risk factors such as the nutritional index of the patients, calculated in Sweden as a modified Body Mass Index (mBMI), the time period of the symptoms, the involvement of the autonomic nervous system and the type of the amyloidosis could be found (*25*). There is a strict time frame for LTx in patients with FAP, in which transplantation is indicated. Since complete regression of the disease cannot be accomplished, no severe functional deficits should be present to preserve a somewhat sufficient quality of life (*23*). Clinical manifestations improves approximately in one third of the cases after LTx. Gastrointestinal involvement responds in 50%, while the response rate after LTx for FAP patients with cardiovascular involvement is 20% (*25*). Cardiovascular involvement seems to be a particularly ominous sign, maybe requiring additional selection criteria than only mBMI and duration of disease (*25*). Because the waiting list for LTx is long, the extended waiting period results in significant problems. In patients with rare variants of transthyretin, the speed of disease progression is unknown. In patients with more frequent FAP (Met 30) the clinical course of disease progression cannot be predicted. Often, LTx is performed in a later stage of disease progression, where patients already suffer from irreversible organ malfunction. In some cases of massive cardiac and renal involvement, combined organ transplantation is performed by leading transplantation centers. However, sufficient experience is not available thus far. Since manifestations of FAP develop relatively late in age, domino LTx as an intelligent method which can be performed in the elderly with a short life expectancy (*26*). Therefore, the pool of organ donors can be extended. This approach is performed in a variety of centers since 1990 (*27*). Data of these patients were also collected in Umea and, until now, no further amyloid precipitation can be observed in these patients. However, the observation time is still relatively short (*28*).

TABLE 1. Patient characteristics

Patient	Sex	Age (years)	Type of amyloidosis	Modified body index	Domino liver transplantation	Improvement of clinical symptoms	Survival	Follow-up period (years)
1	M	27	Met 30	980	No	Yes	Yes	8
2	F	43	Met 30	694	No	Yes	Yes	8
3	M	70	Val 107	843	No	No	No	1
4	M	62	Met 30	929	No	No	Yes	7
5	M	70	Val 107	908	No	No	No	0
6	F	41	Arg 50	528	Yes	Partial	No	5
7	M	64	Met 30	1211	Yes	No	No	0
8	F	39	Arg 50	1219	Yes	Partial	Yes	4
9	F	35	Arg 50	851	Yes	Partial	No	0
10	M	31	Phe 33	438	Yes	Yes	Yes	1
11	M	63	Met 30	967	Yes	No	Yes	0.5

Results of the Heidelberg Transplantation Center

Based on our results, we support the idea that the effectiveness of extended preoperative period before LTx or the transplantation of other transthyretin variants other than Met 30 is questionable. According to published experiences in the literature, and to expand the donor pool we performed six successful domino LTx to date. Patients' characteristics are shown in Table 1.

Of 11 patients, seven (64%) were male and four (36%) female. The mean age of the patients was 49.5 years (range 27-70). The age range of the female patients was very limited (between 35 and 43 years). Met 30 (n=5) was the most common type of amyloidosis followed by Arg 50 (n=3), Val 107 (n=2), and Phe 33 (n=1). All of the patients were candidates for LTx and Domino LTx was performed in 6 patients. The majority (80%) of the patients with type Met 30 amyloidosis are alive, while in other types only 33% are alive. This finding emphasizes better prognosis of Met 30 variant of FAP in comparison to other variants such as Arg 50, Val 107, and Phe 33. After LTx, improvement of clinical symptoms (completely or partially) occurred in 6 patients (55%).

In conclusion, LTx is considered the only therapeutic alternative for patients with amyloidosis with predominantly hepatic synthesis of the amyloid protein. Symptoms of amyloidosis result from organ involvement that can be shown in different ways based on the molecular variant of the disease and the age of disease onset. The newly described variants add some symptoms to the most common symptom of polyneuropathy. Extensive cardiomyopathy, gastrointestinal symptoms, urological complications as well as ophthalmological problems have been identified as other possible symptoms. The most important risk factors for a transplantation can calculated by assessing the nutritional condition of the patient, the length of the disease time period, the amyloid variant and the diagnosis of autonomic nerve damage. Therefore, precise diagnostics are required before listing a patient for LTx, as well as regular follow-up examinations while a patient is on the waiting list. Domino LTx is an acceptable form of transplantation that can preserve the pool of organ donors.

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