Atrial Fibrillation and Central Nervous Complications in Liver Transplanted Hereditary Transthyretin Amyloidosis Patients

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Background. Central nervous system (CNS) complications are increasingly noted in liver transplanted (LTx) hereditary transthyretin amyloid (ATTRm) amyloidosis patients; this suggests that the increased survival allows for intracranial ATTRm formation from brain synthesized mutant TTR. However, atrial fibrillation (AF), a recognised risk factor for ischemic CNS complications, is also observed after LTx. The aim of the study was to investigate the occurrence of CNS complications and AF in LTx ATTRm amyloidosis patients. Methods. The medical records of all LTx ATTRm amyloidosis patients in the county of Västerbotten, Sweden, were investigated for information on CNS complications, AF, anticoagulation (AC) therapy, hypertension, cardiac ischemic disease, hypertrophy, and neurological status. Results. Sixty-three patients that had survived for 3 years or longer after LTx were included in the analysis. Twenty-five patients had developed 1 or more CNS complications at a median of 21 years after onset of disease. AF was noted in 21 patients (median time to diagnosis 24 years). Cerebrovascular events (CVE) developed in 17 (median time to event 21 years), CVEs occurred significantly more often in patients with AF (P < 0.002). AC therapy significantly reduced CVEs, including bleeding in patients with AF (P = 0.04). Multivariate analysis identified AF as the only remaining regressor with a significant impact on CVE (hazard ratio, 3.8; 95% confidence interval 1.1-9.5; P = 0.029). Conclusions. AF is an important risk factor for CVE in LTx ATTRm amyloidosis patients, and AC therapy should be considered. However, the increased bleeding risk with AC therapy in patients with intracranial amyloidosis should be acknowledged.

Hereditary transthyretin amyloid (ATTRm) amyloidosis is a fatal inherited systemic amyloidosis caused by mutations in the transthyretin (TTR) gene. Clinically, the disease is characterized by progressive peripheral somatic and autonomic neuropathy and/or an infiltrative cardiomyopathy. In addition, gastrointestinal complications and kidney impairment are commonly encountered. A few mutations are characterized by occlusalenticmal amyloidosis with symptoms from the central nervous system (CNS), but for the more common mutations, such as the TTR transthyretin mutation with valine substituted by methionine at position 30 (Val30Met), CNS complications are not part of the phenotype or expected to develop during the course of the disease. Before 1990, ATTRm amyloidosis was untreatable, and the reported median survival for Swedish patients ranged from 10 to 13 years. However, in 1990, we introduced liver transplantation (LTx) as a treatment for the disease. The foundation for the treatment was the knowledge that more than 95% of the circulating TTR is synthesized by the liver, therefore, an LTx should cease the production of circulating amyloidogenic mutant TTR and thereby halt the progression of the disease. LTx is now an accepted treatment worldwide. The overall 20-year survival rate for all transplanted patients is 55.3% after LTx, which is a considerable improvement compared to the natural course of the disease. Long-term survival, especially for early-onset ATTRm Val30Met...
amyloidosis patients (onset of disease before the age of 50 years) has proven to be excellent, whereas an inferior survival has been noted for many, but not all transplanted non-Val30Met patients.5,8

Continuous development of cardiac amyloidosis with heart failure has emerged as the major cause of death after LTx.5 It is caused by wild-type TTR deposition probably on existing amyloid deposits and leads to progressive cardiomyopathy and continued aggravation of neuropathy.9,10 This is predominantly found in non-Val30Met ATTRm amyloidosis patients and male late-onset Val30Met patients.8

Local production of variant TTR, synthesized in the retina of the eyes and the choroid plexus in the brain, is not affected by an LTx.12,13 Eye complication, such as vitreous ATTR opacities, is therefore frequently found after transplantation.14,15

In a recent investigation of liver transplanted patients, a significant increased risk of CNS complications was noted after LTx for ATTRm amyloidosis patients compared with that of non-ATTR amyloidosis patients.16 It was suggested that the marked increased overall survival enables ATTRm amyloidosis patients to develop CNS amyloid deposits from CNS synthesized mutant TTR, a complication that has not been reported in the natural history of the disease. Another report substantiated the findings by positron emission tomography (PET) using Pittsburgh component B, in which a steady increase of the tracer was found over time after LTx.17

Aside from ischemic stroke (IS), transient ischemic attack (TIA), intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), additional local neurological symptoms related to cerebral amyloid angiopathy (CAA), such as aura-like episodes, have been described, which may predict an increased risk for ICH.18

Cardiac arrhythmias, such as sinoatrial or atrioventricular blocks and atrial fibrillation (AF), are common in ATTR amyloidosis,19-21 and can develop after LTx, also in patients without heart enlargement or other signs of amyloid cardiomyopathy.11 The overall prevalence of AF in ATTR cardiac amyloidosis was reported to be 64%.20 Interestingly, marked amyloid infiltration in the atrium of the heart has been found at autopsy in patients with early onset, predominantly neuropathic phenotype.22 AF constitutes a substantial risk for cerebral embolic events, and patients with AF may therefore be candidates for anticoagulation (AC) therapy.23-26

Because CNS symptoms in patients with ATTRm amyloidosis can be the result of both CAA and thromboembolic events, we investigated the relationship between CNS complications and AF in liver transplanted patients who had survived for 3 years or longer after the procedure.

**MATERIAL AND METHODS**

**Patients**

In this retrospective observational study, all liver transplanted ATTRm amyloidosis patients that were residing in the county of Västerbotten (Northern Sweden) as of October 2015 were identified. To ensure that all patients were identified, we scrutinized our registry of ATTRm amyloidosis patients at Umeå University Hospital, Sweden, and also the medical records in the central medical database of Västerbotten County. The follow-up protocol of the patients suggests a follow-up at our center 1.5 to 3 years after LTx and includes neurophysiological investigations and an evaluation of heart complications by echocardiography and Holter electrocardiography (ECG). In addition, the patients’ local hospital is encouraged to follow the patients by Holter ECG and echocardiography yearly. All patients had been followed up at Umeå University Hospital (7 patients) or Skellefteå Hospital, Sweden (36 patients). In addition, 3 patients had been treated for complications of the disease at Lycksele Hospital, Sweden. The patients’ medical records from the 3 hospitals were used to obtain relevant data.

All patients had been evaluated for LTx at Umeå University Hospital before operation and were later transplanted at the transplantation centers of Karolinska University Hospital in Stockholm, or Sahlgrenska University Hospital in Gothenburg, Sweden.

The patients included in the analysis had met the following criteria: a) residing in the county of Västerbotten as of Oct. 2015 and b) survived for 3 years or longer after LTx. The latter was to avoid bias related to complications of the transplant procedure and/or initiation of immunosuppressive treatment.

Data of the individual patients were collected from their electronic medical records and/or archived paper records when needed. From these records, relevant data, such as onset of symptoms of ATTRm amyloidosis, date of LTx and other operative records, latest check-up, and death, were recorded. The cause of death for the deceased patients was also noted. Patients with an age at disease onset of 50 years or younger were defined as early-onset cases, whereas an age at onset older than 50 years was defined as late onset. To evaluate patients over time, the patients’ latest examination before LTx was compared with the most recent recorded hospital visit or doctor’s appointment.

**CNS Complications**

Complications from the CNS were categorized as cerebrovascular events (CVE), that is, TIA, IS, ICH and SAH, or non-CVE, that is, epileptic seizures, dementia and migraine. The diagnosis settled at the treating hospital was used to classify the patients, and for each patient the first CNS event was recorded. Migraine, with or without aura, was entered as a posttransplant CNS complication if it had started after LTx or if its characteristics or frequency had changed after LTx. Information from medical records, radiological surveys, such as computed tomography (CT) and/or magnetic resonance imaging (MRI), as well as electroencephalographies were collected to identify and confirm these events and complications.

**Heart Complications**

To identify the development or progression of cardiomyopathy, echocardiographic measurements of interventricular septal (IVS) thickness were evaluated and comparisons made between the pre-LTx examination and the latest available examination. Cardiomyopathy was defined as an IVS greater than 12 mm.27 To identify the presence of ischemic heart disease, defined as acute myocardial infarction or angina pectoris, the outcome of exercise ECGs and coronary angiographies was determined. In addition, data on pacemaker implantation, presence of AF, and use of AC and antihypertensive therapy were extracted from the medical records, as were the patients’ blood pressure. Hypertension was defined as a blood pressure above 140/90 mm Hg and/or concurrent medical treatment for hypertension.
Neurological Status

The patients’ neurological function was assessed by the modified polyneuropathy disability score.28

Statistical Analysis

Kaplan-Meier product limit estimation and plots were used for analysis of survival from onset of symptomatic ATTR amyloidosis until death, first CNS complication, first CVE and detection of AF. Differences between groups in the Kaplan-Meier plots were analyzed by Log Rank (Mantel-Cox) tests. To calculate the univariable and multivariable hazard ratio (HR), Cox regression analysis was used, with cardiomyopathy, AF and ischemic heart disease as covariates in the multivariate analysis. Fisher exact probability test was used to analyze categorical data between groups.

RESULTS

Eighty-two patients residing in the county of Västerbotten had undergone LTx between 1990 and 2014. Of those, 12 patients died within 3 years after LTx. Of these, 3 died within 30 days after the procedure. The remaining 9 patients died from multiorgan failure and progressive disease (n = 5), retransplantation due to bile duct stricture and subsequent liver failure (n = 1), bilateral pulmonary embolism (n = 1), bleeding complications after a liver biopsy (n = 1), and congestive heart failure (n = 1). No patient died from CNS complications. Six patients who all were alive as of October 2015 had been followed up for less than 3 years after the procedure and 1 patient was no longer residing in Västerbotten. Thus, 63 patients, all carrying the Val30Met mutation, met our inclusion criteria. The clinical characteristics of the patients are outlined in Table 1, and the clinical evaluation before LTx, 1 to 3 years after LTx and at the latest follow-up are displayed in Table 2. Median age at onset was 45 years (range, 25-66 years), and median age at LTx was 50 years (range, 27-69 years). One patient had undergone combined heart transplantation and LTx, and 2 patients combined kidney transplantation and LTx. Two patients also suffered from type 2 diabetes mellitus.

Causes of Death

Seventeen (27%) of the patients died 3 or more years after LTx, and their causes of death are presented in Table 3. Four of the deceased patients developed malignancies after transplantation. Expectedly, heart failure was the most common cause of death occurring in 6 cases, but infections, especially from the urinary tract, kidney failure, and CNS complications were other common causes of death. The overall survival is displayed in Figure 1A. The estimated median survival from onset of disease was 27 years for the 63 included patients.

CNS Complications

Twenty-five (40%) patients had developed 1 or more CNS event and of these 9 patients suffered from 2 events and 2 patients from 3 different events. Of the patients with CNS complications, 17 (27%) developed a CVE, that is, IS, TIA, ICH, or SAH as presented in Table 4. The survival without a CNS event is depicted in Figure 1B. The median time to a CNS event was 21 years after onset of disease. Migraine commenced in 1 patient 40 months after onset of disease, and the CNS complications thereafter increased successively in the population with duration of disease. In all cases the CVE diagnosis was confirmed by CT and/or by MR examination.

CVE

During follow-up, 17 patients experienced 1 or more CVE with an estimated median time to an event after onset of disease of 21 years. The development of CVEs in the study population is shown in Figure 1D.

TIA

The first recorded CVE was a TIA that occurred 83 months after onset of disease. Eight patients had TIA-like episodes, and 5 of these patients were diagnosed as having AF at the time of the event. Two patients had multiple TIA-episodes. One patient had a short episode of expressive aphasia, with subsequent debut of headache and fever, which was assessed as possible TIA or viral meningoencephalitis. This is categorized as a TIA episode in the analysis.

TABLE 1.

Demographic data of the patients included in the study

| Characteristics                           | No. patients | Percentage |
|------------------------------------------|--------------|------------|
| No. patients                             | 63           |            |
| Females, n (%)                           | 32 (51%)     |            |
| Early onset of disease*, n (%)           | 39 (62%)     |            |
| Age at onset of disease: median (range), y| 45 (25-66)   |            |
| Age at liver transplantation: median (range), y| 50 (27-69)   |            |
| Duration of disease at latest evaluation: median (range), y| 15 (5-30) |            |

* Early onset of hereditary transthyretin amyloidosis defined as onset ≤ 50 years of age, late onset as > 50 years of age.
IS
Ten patients suffered from IS, of which the first occurred 117 months after onset of the disease. One patient experienced 2 events. Another patient was diagnosed with carotid aneurysm shortly after the IS, but was not a candidate for vascular surgery. Of the remaining 9 patients with IS, 8 were diagnosed with concurrent AF. Four patients displayed older ISs on CT scan examination, for which one patient with widely spread small-vessel disease was included. These 4 patients were included in the analyses as post-LTx IS and onset was set to the date of detection.

ICH
Of the 3 patients with an ICH, one patient’s hemorrhage was related to a minor head trauma and concurrent anticoagulant therapy. The other 2 were spontaneous ICHs, both lethal, of which one was a pons bleeding occurring during AC.
therapy and the other in conjunction with cytopenia due to chemotherapy for a T-cell lymphoma.

SAH
Two patients had traumatic SAH without detectable aneurysms, one of which had concurrent anticoagulant therapy.

Non-CVE Central Nervous Complication
A total of 12 patients (14%) developed non-CVEs after LTx.

Epileptic Seizures
Seven patients developed epileptic seizures after LTX, however, 1 patient was diagnosed with epilepsy since the age of 3 years. Another patient suffered from generalized seizures assessed as postapoplectic after a traumatic SAH. The remaining 5 patients were included in the analysis as epileptic seizures.

Dementia
Three patients developed dementia. One patient had a family history of Alzheimer disease and the remaining 2 patients were diagnosed with vascular dementia based on the findings on CT examinations. All were included in the analysis.

Migraine
Nine patients had migraine, but 3 of these had suffered from migraine before LTx without any changes in symptoms or frequency and were therefore not included.

Heart Complications
AF, CVE, and AC therapy
In Figure 1C and Table 2, the development of AF is displayed. Twenty patients were diagnosed with AF during the follow-up, and the estimated median time to diagnosis was 24 years after onset of disease. One additional patient had AF 1 year before onset of symptomatic ATTRm amyloidosis and was not on AC therapy at the time of LTx 8 years later. This patient was included in the analysis. The occurrence of AF was related to their amyloid cardiomyopathy. Only 5 patients without cardiac hypertrophy developed AF compared with 18 patients with hypertrophy (P = 0.004). However, no such relationship was found for ischemic heart disease (P = 0.17).

A significant increase of CVE in patients with AF compared with those without was noted and are shown in Figure 2 (95% confidence interval [CI], 1.50-11.86 and 0.084-0.667, respectively [P < 0.002]). Thirteen of the patients with AF were late onset patients. Among 17 patients with CVE, AF was not detected in six (3 with TIA episodes, 2 with cerebral infarctions and 1 with traumatic SAH). For the remaining 11 patients, AF was detected at the time of their CVE, and 9 of these patients were put on AC therapy. Warfarin was the drug used for AC in all patients.

Of the 18 patients with AC therapy due to AF, 5 suffered from an additional CVE. Two patients had an ICH and 1 an SAH as outlined above. AC therapy was discontinued in the patient with a traumatic ICH. Two patients suffered from an additional IS after initiation of AC therapy. CVEs including ICH and SAH were significantly less common in patients during AC therapy (P < 0.04, Figure 3). There was no difference in CVE distribution in relation to sex, hypertension or age at onset of ATTRm amyloidosis.

Table 5 displays the outcome of Cox regression analysis of risk factors for CVE. AF, cardiomyopathy, and ischemic heart disease were all significant predictors of CVE in the univariate analysis. However, in the multivariate analysis, AF was the only remaining regressor with a significant impact on CVE (HR, 3.8; 95% CI, 1.1-9.5; P = 0.029).

Development of Cardiomyopathy
There was a statistically significant increase in IVS thickness with 2.6 mm (95% CI, 1.511-3.618), suggesting a progress of cardiomyopathy over time in transplanted ATTRm amyloidosis patients.

Ischemic Heart Disease
Six patients (10%) of the evaluated transplanted ATTRm amyloidosis patients were diagnosed with ischemic heart disease. Of these, 2 patients experienced ischemic heart disease before the onset of symptomatic ATTRm amyloidosis and LTx (1 acute myocardial infarction with subsequent coronary artery bypass surgery and 1 with angina pectoris). No patient developed myocardial infarction after LTx.

Immunosuppression and Hypertension
The vast majority of our patients received tacrolimus for immunosuppression with or without concurrent low-dose
Risk factors for cerebrovascular events in liver transplanted hereditary transthyretin amyloidosis patients

| Risk Factor                | Univariate, HR (95% CI) | P     | Multivariate, HR (95% CI) | P     |
|---------------------------|-------------------------|-------|---------------------------|-------|
| Sex (male/female)         | 0.9 (0.3-2.4)           | 0.853 | ND                        |       |
| Early/late onset          | 1.8 (0.6-5.5)           | 0.302 | ND                        |       |
| Cardiomyopathy            | 3.2 (1.1-10.0)          | 0.041 | 2.8 (0.7-11.3)            | 0.202 |
| Hypertension              | 1.8 (0.5-6.7)           | 0.380 | ND                        |       |
| AF                        | 4.4 (1.6-12.0)          | 0.004 | 3.8 (1.1-9.5)             | 0.029 |
| Ischemic heart disease    | 3.1 (1.3-23.7)          | 0.019 | 3.2 (0.7-14.2)            | 0.124 |

HR for CVE with time set from onset of disease to CVE, and sex, age at onset (≤50 vs > 50 years), cardiomyopathy (IVS thickness, > 12 mm), hypertension after LTx, AF, and presence of ischemic heart disease as regressors.
in patients with oculoleptomeningeal forms of ATTRm amyloidosis, which might warrant brain imaging with gadolinium-enhanced MRI or PET with amyloid specific tracer. This was performed systematically in the report by Sekijima et al who found amyloid deposition in the CNS, as measured by Pittsburgh component B-PET, approximately 10 years before onset of transient focal neurological episodes, which occurred approximately 16.8 years after onset of the disease. However, cardiac arrhythmia, such as AF, was not reported.

Non–vitamin K antagonist oral anticoagulants (NOACs) have been advocated for stroke risk reduction and generally display a lower risk for ICH than warfarin. Studies have compared NOACs with warfarin in patients with ATTR amyloidosis, but given the lower risk of ICH, it is tempting to use them instead of warfarin in this group of patients. An additional approach is percutaneous left atrial appendage occlusion, which appears to be able to achieve a relative stroke risk reduction of 60% in patients with contraindications, or increased risk for ICH during AC therapy.

Given the high risk of both AF and associated CVEs in liver transplanted ATTRm amyloidosis patients, intensified screening for AF seems like the most appealing option, especially since eleven of our patients’ AF was diagnosed after they suffered from a CVE in spite of regular Holter ECG examinations. An improved surveillance should enable preventive AC therapy or left atrial appendage occlusion as indicated. Because standard 24-hour (Holter) EKGs appear not to be sufficient to detect AF, intermittent thumb-EKG recordings might be a better solution, especially for patients with intermittent AF. We are currently performing thumb-EKG recording during a 3-week period in all patients with disease duration of more than 9 years in addition to ECG and Holter ECG.

Our study is limited by the lack of information concerning the status of the patients’ amyloid disease stage at the time of CNS events, and also of investigations specifically aimed to diagnose intracerebral amyloid and CAA. Even though all patients with CVEs were investigated by CT and/or MR examination, the examinations were not directed toward amyloid deposits or CAA. In 1 patient, the CT examination suggested microvascular disease, that is, CAA, but the suggested MR examination was not carried out because the patient carried a pacemaker. In another patient, who died of IS, an autopsy was performed, but the gross examination of the brain showed no macroscopic evidence of amyloid deposition, but unfortunately, no histopathological examination was performed. In no other deceased patient was an autopsy performed.

In summary, CNS complications are being increasingly recognised in long-term survivors with ATTRm amyloidosis, and symptoms of CAA can be hard to distinguish from thromboembolic events. We found a high frequency of AF in our liver-transplanted ATTRm Val30Met amyloidosis patients, which was the only significant predictor of CVEs in a multivariate analysis. The risk of CVEs, bleedings included, was lower in the group of patient with AC therapy. We therefore suggest active screening for AF and that AC therapy should be considered in all patients with ATTR amyloidosis and AF. However, assessment of bleeding risk including the possibility of a CAA must be taken into consideration. Given the risks for ICH noted in CAA, NOACs or percutaneous left atrial appendage occlusion are probably the treatments of choice in these patients.

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