OPEN

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

Niklas Wange,[1] Intissar Anan, MD, PhD,[1] Bo-Göran Ericzon, MD, PhD,[2] Johanna Pennlert,[1] Björn Pilebro,[1] Ole B. Suhr, MD,[1] and Jonas Wixner[1]

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.

(*Transplantation* 2018;102: e59–e66)

Received 29 April 2017. Revision received 1 September 2017.

Accepted 16 September 2017.

[1] Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden.

[2] Department of Transplantation Surgery, Karolinska University Hospital, Huddinge, Sweden.

The present work was funded by a grant from the Swedish Heart and Lung foundation and the patients' organisation FAMY and FAMY Norbotten and the AMYL foundation.

The authors declare no conflicts of interest.

N.W. did the data acquisition, analysis and interpretation of the data, and the writing of the article. O.B.S. initiated the working hypothesis, participated in data acquisition, interpretation of the data, and the writing of the article. J.W., B.P. and J.P. participated in the analysis and interpretation of the data and writing of the article and gave valuable input on the content and design. I.A. contributed by data acquisition, revising the article, and gave valuable input on the content and design and B.G.E. contributed by revising the article and gave valuable input on the content and design. All authors were active in reviewing and finalising the article.

Correspondence: Ole B Suhr, MD, Department of Medicine, Umeå University Hospital, SE 901 85 Umeå, Sweden. (ole.suhr@umu.se).

ISSN: 0041-1337/18/10202-e59

DOI: 10.1097/TP.0000000000001975

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 occulomeningeal 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.[1]

Before 1990, ATTRm amyloidosis was untreatable, and the reported median survival for Swedish patients ranged from 10 to 13 years.[2,3] 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.[4] LTx is now an accepted treatment worldwide.[5] 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.[2,6,7] 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.[11]

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 Pittsburg 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 focal 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 (56 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.

TABLE 1.

Demographic data of the patients included in the study

No. patients	63
Females, n (%)	32 (51)
Early onset of disease[a], 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)

[a] Early onset of hereditary transthyretin amyloidosis defined as onset ≤ 50 years of age, late onset as > 50 years of age.

TABLE 2.

Clinical data of the patients at the evaluation before liver transplantation, at the first posttransplant evaluation and at the latest follow-up

	Pre-LTx[a]	First post-LTx	Latest follow-up
Duration from LTx: median (range), mo	8 (1-17)	25 (15-72)	121 (37-262)
mPND score[b] (n)			
0	4	3	1
I	36	29	21
II	17	21	12
IIIA	3	3	7
IIIB	1	6	12
V	2	1	9
Cardiac hypertrophy (septal thickness, >12 mm)	16	24[c]	32[d]
Pacemaker	6[e]	9	29
AF	1	5	21
Hypertension at evaluation (blood pressure > 140/90 mm Hg)	10	9[f]	10[g]

[a] Liver transplantation.
[b] mPND-score, polyneuropathy disability score where 0 denotes no neurological impairment; I: sensory disturbances but preserved walking capacity; II: difficulties in walking but the patient does not require a walking stick; IIIA: 1 stick or crutch required for walking; IIIB: 2 sticks or crutches required; IV: patient in wheelchair or confined to bed.
[c] Septal thickness not measured in 2 patients and not included for 1 heart/liver transplanted patient.
[d] Septal thickness not included for 1 heart/liver transplanted patient.
[e] Including 3 patients with prophylactic pretransplant pacemaker insertions.
[f] Including 5 patients with normal blood pressure at pretransplant evaluation.
[g] Including 4 patients with normal blood pressure at previous evaluations.

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 3.

Clinical data of 17 patients who died more than 3 years after liver transplantation

Sex	Age at onset, y	Survival from disease onset, y	Survival from LTx[a], y	PND[b] score at LTx	Causes of death
Female	30	30	22	IV	Alzheimer[c]
Male[d]	36	21	14	IIIB	IS—recurrent septicaemia (urinary tract)
Male	49	12	8	IIIA	Septicemia (urinary tract)
Male	54	11	5	IIIA	Kidney failure—uremia
Female [d]	50	22	19	I	Meningoencephalitis
Female	44	12	5	II	Sepsis/chronic leukemia
Male	52	13	6	IIIA	Septicaemia (urinary tract)
Male	63	15	10	II	ICH
Male	66	12	10	0	Dementia/heart failure
Male	52	15	12	II	Heart failure
Male	36	19	14	II	Heart failure
Male	31	27	20	II	ICH—lymphoma
Male	49	12	8	II	Heart failure
Female	48	18	11	IIIB	Septicemia—kidney failure
Female	60	14	9	I	Colon cancer
Male	63	12	10	I	Heart failure
Male	67	8	5	I	Heart failure

[a] Liver transplant.
[b] Polyneuropathy disability score where 0 denotes no neurological impairment; I: sensory disturbances but preserved walking capacity; II: difficulties in walking but the patient does not require a walking stick; IIIA: 1 stick or crutch required for walking; IIIB: 2 sticks or crutches required; IV: patient in wheelchair or confined to bed.
[c] Diagnosis by symptoms, family history and MR examination.
[d] Liver and kidney transplanted.

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

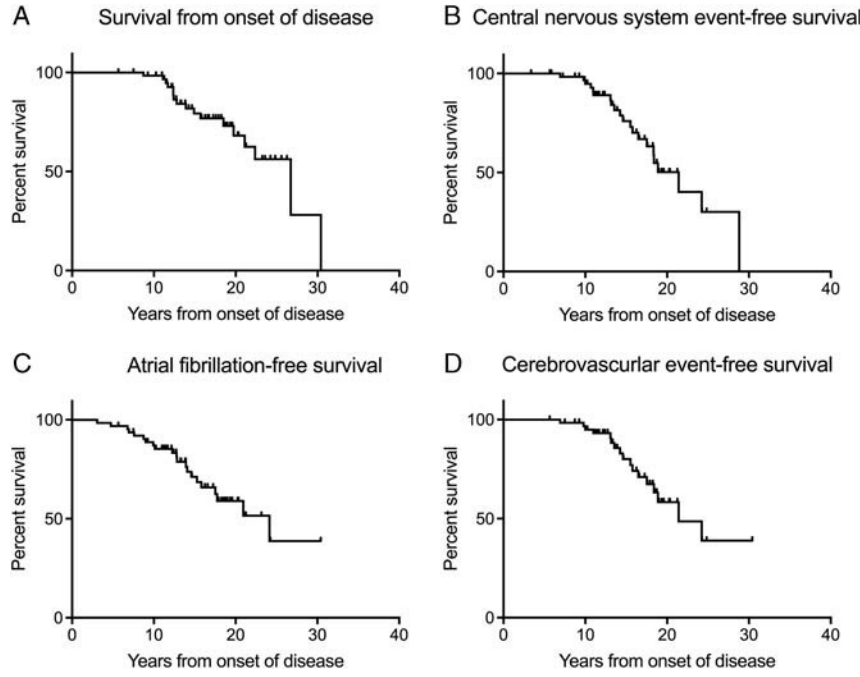

FIGURE 1. Kaplan-Meier plot of survival (A), development of CNS complications (B), development of AF (C), and development of cerebrovascular events, that is, TIA, IS, ICH or SAH (D). All are measured in years from onset of disease.

TABLE 4.

CNS complications reported in the 63 liver transplanted patients that were followed for more than 3 years

	Number of Patients (%)
CNS events	25 (40%)
Cerebrovascular events	17 (27%)
IS	10 (16%)
TIA	8 (13%)
ICH	3 (5%)
SAH	2 (3%)
Noncerebrovascular events	12 (19%)
Epileptic seizure	5 (8%)
Dementia	3 (5%)
Migraine	6 (10%)

Percentages are calculated from the total population of 63 patients.
Nine patients suffered from 2 different CNS-events and 2 patients had 3 different events. An individual patient is included only once per event (row).

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 were 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

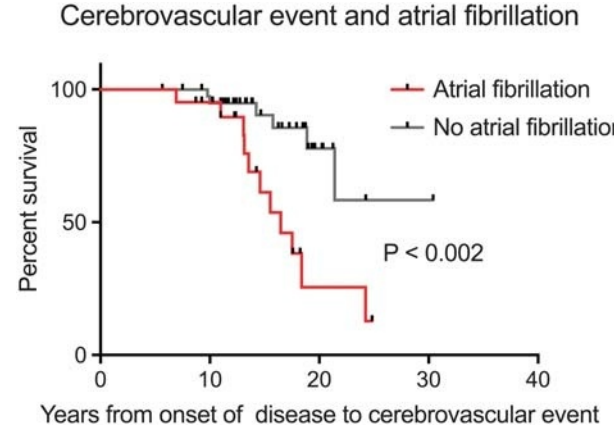

FIGURE 2. Development of cerebrovascular events in patients with (red line) and without (black line) AF.

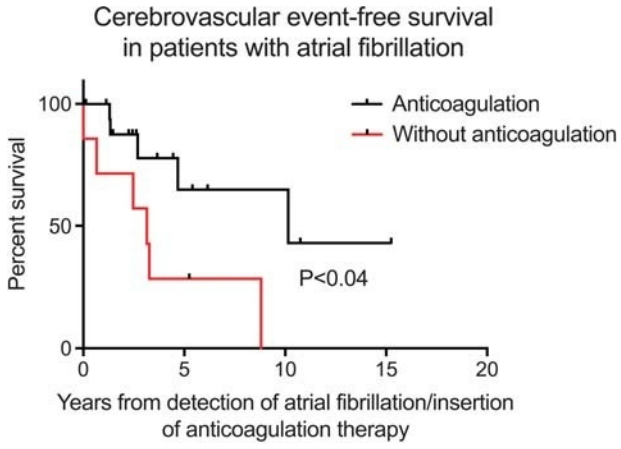

FIGURE 3. Development of a cerebrovascular event, that is, TIA, IS, ICH or SAH for patients with AF during periods with or without AC therapy.

prednisolone, and the latter was often discontinued during the observation period. We were unable to find any relationship between hypertension and immunosuppression regime. Hypertension was not more common among patients on steroids compared with those without ($P = 0.33$).

DISCUSSION

ATTR CNS complications and CAA are conditions for which we currently have no treatment. None of the existing drugs or those in clinical trials pass the blood-brain barrier, at least not in the doses currently used. However, the risk of cerebral embolism caused by AF can be reduced by AC therapy.[23] Our investigation disclosed 2 important complications in liver transplanted ATTRm amyloidosis patients—a high frequency of CNS complications that steadily increased with time after onset of disease, and a high frequency of AF, which is a generally acknowledged risk factor for IS and TIA. The development of AF was correlated to the presence of amyloid cardiomyopathy. However, 19% of the patients developed non-CVEs, which may be attributed to complications from CAA.

In the series published by Maia et al,[16] focal neurological episodes occurred in 31% (27/87) of ATTRm Val30Met amyloidosis patients after an average disease duration of 14.6 years, which is considerably shorter than our figure of 21 years. However, the occurrence of AF was not reported, although 2 (3.3%) of 60 patients without focal neurological episodes were on AC treatment, and antiplatelet treatment was given to 9 (33.3%) of 27 patients with and 11 (18%) of 60 patients without focal neurological episodes.

Current European Society of Cardiology guidelines on the management of AF[29] recommend thromboembolic risk assessment by the CHA(2)DS(2)-VASc scoring system before the initiation of AC treatment. The scoring system takes into account numerous factors including age, sex, previous CVE, and heart failure, but amyloid heart disease is not accounted for.[29] Because patients with cardiac amyloidosis are generally at high risk for thromboembolism, a careful clinical assessment of high-risk characteristics specific to cardiac amyloidosis, advanced left ventricular diastolic dysfunction, lower left appendage emptying velocities, elevated heart rate, and increased right ventricular wall thickness should be applied even in the absence of AF.[30] Unfortunately, the echocardiographic findings in our patients were not detailed enough to be included in the analysis. In ATTR cardiomyopathy, however, these are factors regularly associated with increased LV wall thickness that, although significantly related to CVE in the univariate analysis, did not remain so in the multivariate analysis. It should be noted that amyloid deposition in the myocardium is present even without echocardiographic evidence of amyloid cardiomyopathy or positive findings on amyloid scintigraphy using 99m-Tc-DPD scintigraphy.[31,32] In addition, strain analysis has disclosed abnormal strain rate in ATTRm amyloidosis patients, with normal heart dimensions compared with healthy controls.[33]

AC exacerbates the hemorrhagic tendency, which has been considered problematic due to the increased risk of brain hemorrhage seen in patients with CAA, especially in those with transient focal neurological episodes.[18] There are tools for determining bleeding risk in patients treated with AC, for example, HAS-BLED,[34] but these are not validated in patients with ATTRm amyloidosis.

In our series, 29% of the CVEs were bleedings, but only 3 (18%) were in patients on AC therapy and only 1 (6%) was a spontaneous bleeding. In our multivariate analysis, AF was the only remaining significant predictor of CVE, which implicates that thromboembolic events are the predominant risk factor for CVEs in this study population. Further, the overall risk of CVE (bleedings included) was significantly reduced with AC therapy, indicating that the risk of brain hemorrhage is not unreasonably high. We are therefore convinced that AC treatment should be initiated in most, if not all, patients with ATTR amyloidosis and AF, regardless of the CHADS-VASc score.

Still, CAA increases the risk of ICH and cerebral microbleeds in long-term survivors with ATTRm Val30Met amyloidosis and

TABLE 5.

Risk factors for cerebrovascular events in liver transplanted hereditary transthyretin amyloidosis patients

	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 occuloleptomeningeal forms of ATTRm amyloidosis,[16,17,35] 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[17] who found amyloid deposition in the CNS, as measured by[11] Pittsburg 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.[36-38] No 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.[39,40]

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 an 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.[41] We are currently performing thumb-ECG 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 depositions 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.

ACKNOWLEDGMENTS

The authors acknowledge The Centre for Hereditary Amyloidosis at Umeå University Hospital, and their patients. Albert Crenshaw, Ph.D. for editing the language.

REFERENCES

1. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve*. 2007;36:411–423.
2. Andersson R. Familial amyloidosis with polyneuropathy. A clinical study based on patients living in northern Sweden. *Acta Med Scand Suppl*. 1976;590:1–64.
3. Suhr O, Danielsson A, Holmgren G, et al. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. *J Intern Med*. 1994;235:479–485.
4. Holmgren G, Ericzon BG, Groth CG, et al. Clinical improvement and amyloid regression after liver transplantation in hereditary transthyretin amyloidosis. *Lancet*. 1993;341:1113–1116.
5. Ericzon BG, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? *Transplantation*. 2015;99:1847–1854.
6. Coutinho P, da Silva AM, Lima JK, et al. Forty years of experience with type I amyloid neuropathy. Review of 483 cases. International congress series no 497. In: Glenner GG, e Costa PP, de Freitas AF, eds. *Amyloid and amyloidosis*. Amsterdam-Oxford-Princeton: Excerpta Medica; 1980:88–98.
7. Mariani LL, Lozeron P, Theaudin M, et al. Genotype-phenotype correlation and course of transthyretin familial amyloid polyneuropathies in france. *Ann Neurol*. 2015.
8. Suhr OB, Larsson M, Ericzon BG, et al. Survival after transplantation in patients with mutations other than Val30Met: extracts from the FAP World Transplant Registry. *Transplantation*. 2016;100:373–381.
9. Liepnieks JJ, Zhang LQ, Benson MD. Progression of transthyretin amyloid neuropathy after liver transplantation. *Neurology*. 2010;75:324–327.
10. Yazaki M, Tokuda T, Nakamura A, et al. Cardiac amyloid in patients with familial amyloid polyneuropathy consists of abundant wild-type transthyretin. *Biochem Biophys Res Commun*. 2000;274:702–706.
11. Okamoto S, Zhao Y, Lindqvist P, et al. Development of cardiomyopathy after liver transplantation in Swedish hereditary transthyretin amyloidosis (ATTR) patients. *Amyloid*. 2011;18:200–205.
12. Ando Y, Terazaki H, Nakamura M, et al. A different amyloid formation mechanism: de novo oculoleptomeningeal amyloid deposits after liver transplantation. *Transplantation*. 2004;77:345–349.
13. Terazaki H, Ando Y, Nakamura M, et al. Variant transthyretin in blood circulation can transverse the blood-cerebrospinal barrier: qualitative analyses of transthyretin metabolism in sequential liver transplantation. *Transplantation*. 2001;72:296–299.
14. Beirão JM, Malheiro J, Lemos C, et al. Impact of liver transplantation on the natural history of oculopathy in Portuguese patients with transthyretin (V30M) amyloidosis. *Amyloid*. 2015;22:31–35.
15. Sandgren O, Kjellgren D, Suhr OB. Ocular manifestations in liver transplant recipients with familial amyloid polyneuropathy. *Acta Ophthalmol*. 2008;86:520–524.
16. Maia LF, Magalhaes R, Freitas J, et al. CNS involvement in V30M transthyretin amyloidosis: clinical, neuropathological and biochemical findings. *J Neurol Neurosurg Psychiatry*. 2015;86:159–167.
17. Sekijima Y, Yazaki M, Oguchi K, et al. Cerebral amyloid angiopathy in posttransplant patients with hereditary ATTR amyloidosis. *Neurology*. 2016;87:773–781.
18. Charidimou A, Gang Q, Werring DJ. Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum. *J Neurol Neurosurg Psychiatry*. 2012;83:124–137.
19. Longhi S, Quarta CC, Milandri A, et al. Atrial fibrillation in amyloidotic cardiomyopathy: prevalence, incidence, risk factors and prognostic role. *Amyloid*. 2015;22:147–155.
20. Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J*. 2012;164:222–228 e221.
21. de Freitas AF. The heart in Portuguese amyloidosis. *Postgrad Med J*. 1986;62:601–605.
22. Koike H, Misu K, Sugiura M, et al. Pathology of early- vs late-onset TTR Met30 familial amyloid polyneuropathy. *Neurology*. 2004;63:129–138.
23. Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation*. 2009;119:2490–2497.

24. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003; 349:1019–1026.
25. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996;27:1760–1764.
26. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370:2467–2477.
27. Damy T, Maurer MS, Rapezzi C, et al. Clinical, ECG and echocardiographic clues to the diagnosis of TTR-related cardiomyopathy. *Open heart*. 2016;3:e000289.
28. Suhr OB, Holmgren G, Steen L, et al. Liver transplantation in familial amyloidotic polyneuropathy. Follow-up of the first 20 Swedish patients. *Transplantation*. 1995;60:933–938.
29. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.
30. Castano A, Drachman BM, Judge D, et al. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. *Heart Fail Rev*. 2015; 20:163–178.
31. Pilebro B, Arvidsson S, Lindqvist P, et al. Positron emission tomography (PET) utilizing Pittsburgh compound B (PIB) for detection of amyloid heart deposits in hereditary transthyretin amyloidosis (ATTR). [published online September 19, 2016]. *J Nucl Cardiol*. doi: 10.1007/s12350-016-0638-5.
32. Pilebro B, Suhr OB, Näslund U, et al. (99m)Tc-DPD uptake reflects amyloid fibril composition in hereditary transthyretin amyloidosis. *Ups J Med Sci*. 2016;121:17–24.
33. Lindqvist P, Olofsson BO, Backman C, et al. Pulsed tissue Doppler and strain imaging discloses early signs of infiltrative cardiac disease: a study on patients with familial amyloidotic polyneuropathy. *Eur J Echocardiogr*. 2006;7:22–30.
34. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100.
35. Salvi F, Pastorelli F, Plasmati R, et al. Brain microbleeds 12 years after orthotopic liver transplantation in Val30Met amyloidosis. *J Stroke Cerebrovasc Dis*. 2015;24:e149–e151.
36. Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. *Open heart*. 2016;3:e000279.
37. Saito T, Kawamura Y, Sato N, et al. Non-vitamin k antagonist oral anticoagulants do not increase cerebral microbleeds. *J Stroke Cerebrovasc Dis*. 2015;24:1373–1377.
38. Staerk L, Fosbøl EL, Lip GYH, et al. Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study. *Eur Heart J*. 2017;38:907–915.
39. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33:2719–2747.
40. Lewalter T, Kanagaratnam P, Schmidt B, et al. Ischaemic stroke prevention in patients with atrial fibrillation and high bleeding risk: opportunities and challenges for percutaneous left atrial appendage occlusion. *Europace*. 2014;16:626–630.
41. Hendrikx T, Rosenqvist M, Wester P, et al. Intermittent short ECG recording is more effective than 24-hour Holter ECG in detection of arrhythmias. *BMC Cardiovasc Disord*. 2014;14:41.