Syncope in patients with transthyretin amyloid cardiomyopathy: clinical features and outcomes

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ABSTRACT

Background: We aimed to describe the clinical characteristics, underlying causes and outcomes of syncope in patients with transthyretin amyloid cardiomyopathy (ATTR-CM).

Methods: The clinical profile and underlying causes of syncopal episodes were reviewed in a cohort of 128 patients with ATTR-CM enrolled from January 2018 to June 2020 in a prospective multicentre registry in 7 hospitals of Galicia (Spain). After enrollment, patients were followed during a median period of 520 days. The effect of syncope on all-cause mortality was assessed by means of multivariate Cox´s regression.

Results: Thirty (23.4%) patients had a history of previous syncope as a clinical antecedent before being enrolled in the prospective phase of the registry, and 4 (3.1%) experienced a first episode of syncope thereafter. The estimated incidence density rate of syncope during the prospective follow-up period after registry enrollment was 71.9 episodes per 1000 patients-year (95% Confidence Interval (CI) 32.8– 111.1). The estimated overall prevalence of syncope was 26.6% (95% CI 18.9%–34.2%). Cardiac arrhythmias (n = 11, 32.3%), structural diseases of the heart or great vessels (n = 5, 14.7%), a neurally mediated reflex (n = 6, 17.6%), and orthostatic hypotension (n = 4, 11.8%) were identified as probable underlying causes of syncope; in 8 (23.6%) patients, syncope remained unexplained. Patients with syncope had increased non-adjusted all-cause mortality than patients without it (univariate hazard-ratio 3.37; 95% CI 1.43–7.94). When other independent predictors of survival were added to the survival model, this association was no longer statistically significant (multivariate hazard-ratio 1.81, 95% CI 0.67–4.84).

Conclusions: Syncope is frequent in patients with ATTR-CM. This study could not demonstrate an independent association between syncope and mortality in those individuals.

Abbreviations: ATTR-CM: Transthyretin amyloid cardiomyopathy; CI: Confidence Interval; HF: Heart Failure; HR: Hazard Ratio; IQR: Interquartile rank; LVEF: Left Ventricular Ejection Fraction; NTproBNP: N-terminal pro-brain natriuretic peptide; SD: Standard Deviation; 3,3-diphosphono-1,2-propanodicarboxylic acid.

KEYWORDS Syncope; cardiac amyloidosis; transthyretin; survival; arrhythmia

Introduction

Amyloidosis is a family of systemic disorders caused by the abnormal deposition of different types of proteins in organ tissues, including the heart [1,2]. Classically, light-chain amyloid cardiomyopathy associated to hematological disorders has been the most studied and characteristic forms of cardiac amyloidosis [3]. However, nowadays the most frequently diagnosed form of cardiac amyloidosis is the one due to the myocardial deposition of the serum protein transthyretin [4], which itself is subclassified as wild-type transthyretin amyloid 99m Tc-DPD: technetium-99m-labeled cardiomyopathy (ATTR-CM) or *variant (hereditary)* ATTR-CM [3,5].

The diagnosis of ATTR-CM may be done invasively, based on the demonstration of transthyretin deposition in endomyocardial or extracardiac biopsies in patients with typical findings on cardiac imaging studies [6]. However, the diagnosis of ATTR-CM is most frequently done non-invasively, by means of the combination of a positive cardiac nuclear scintigraphy with technetium-labeled bisphosphonates together with the absence of a detectable monoclonal protein in serum and urine immunofixation electrophoresis and serum-free light chains assay [7].

Heart failure (HF) with preserved or mildly reduced left ventricular ejection fraction (LVEF) is the most typical clinical presentation of amyloid cardiomyopathy [8]; arrhythmias, angina, and thromboembolic events are also frequent. Extracardiac involvement of the tendons – in wild-type ATTR- CM – and peripheral nerves – in variant ATTR-CM – is characteristic of the disease and may precede by several years the development of cardiac symptoms [9].

Syncope is common in patients with amyloid cardiomyopathy, and it has been associated with poor prognosis in the light chain subtype [10]; orthostatic hypotension [11] and cardiac arrhythmias [12] have been described as frequent underlying mechanisms. The previously reported prevalence of syncope in patients with ATTR-CM varies from 8% to 21.5% [4,13].

The description of clinical characteristics and outcomes of syncope in patients with amyloid cardiomyopathy is limited to a couple of small retrospective studies focused on patients with light chain amyloidosis [10,14]. To the best of our knowledge, the mechanisms and prognostic implications of syncope in patients with ATTR-CM have not been studied yet, beyond a few anecdotal case reports [15–17].

We aimed to make a comprehensive description of the clinical features, underlying causes, and outcomes of syncope in a multi-institutional, prospective, Spanish cohort of patients with ATTR-CM.

Methods

Description of the study

The AMI-GAL study (*Registro de AMIloidosis Cardiaca de GALicia*; in English, *Registry of Cardiac Amyloidosis of Galicia*) is a prospective observational registry of patients with amyloid cardiomyopathy, whose recruitment started on 1 January 2018, in 7 public hospitals in Galicia, a region located in the north-west of Spain. The Committee of Ethics in Clinical Research of the Autonomous Community of Galicia approved the protocol of the study, which has been described elsewhere [18,19]. Written informed consent is being collected from patients enrolled in this prospective registry. The investigation is being conducted according to the Declaration of Helsinki.

The diagnosis of ATTR-CM can be made invasively, by means of an endomyocardial biopsy or an extracardiac biopsy that showed unequivocal signs of

Transthyretin deposition in a patient with typical cardiac imaging findings or it can be done non-invasively, by means of a positive technetium-99 m-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) nuclear scintigraphy that shows grade 2 or grade 3 cardiac uptake in a patient with typical cardiac imaging findings and no evidence of monoclonal protein in serum-free light chains assay and urine and serum immunofixation electrophoresis [7]. In patients with ATTR-CM, genetic studies are recommended to differentiate between the *wild-type* and *variant* subtypes of the disease, but it is not mandatory for including patients in the registry.

Syncope

In this study, syncope was defined as a transient loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery [20]. Local investigators were responsible for registering both the previous history of syncope – i.e. syncopal episodes that had occurred before the inclusion of the

patient in the registry – as well as incident episodes of syncope – i.e. those that occurred during subsequent follow-up after the inclusion of the patient in the registry–. Granular information regarding clinical presentation and underlying causes of syncope were recorded from clinical records. Given that the AMI-GAL study was conceived as a general registry of patients with cardiac amyloidosis, the diagnostic approach and therapeutic management of syncopal episodes was determined by local practices, rather than based on a predetermined protocol.

Syncope was considered related to a *structural cardiac cause* in patients who presented, coexisting with ATTR-CA, an underlying structural disorder of the heart or the great vessels, which is typically recognized as a primary hemodynamic cause of syncope, like severe aortic stenosis, cardiac tamponade, obstructive hypertrophic cardiomyopathy, aortic dissection or pulmonary embolism. *Arrhythmic syncope* was diagnosed when the transient loss of consciousness was coincident in time and attributable to a cardiac rhythm disturbance, which is a recognized primary cause of syncope, either bradyarrhythmic – Mobitz II second-degree atrioventricular block, third-degree atrioventricular block, asystole, prolonged sinus arrest, slow junctional rhythm, slow idioventricular rhythm – or tachyarrhythmic – sustained ventricular tachycardia, supraventricular tachycardia with fast ventricular rate–. In this study, the term cardiac syncope makes reference to syncopal episodes due to either structural cardiac causes or cardiac arrhythmias.

In the absence of an underlying structural or arrhythmic cause of syncope, *neurally mediated reflex syncope* was suspected if the episode of transient loss of consciousness was precipitated by pain, fear, or standing and was associated with typical progressive prodromes like pallor, sweating, and/or nausea (*vasovagal type*); if it occurred during or immediately after typical triggers like micturition, gastrointestinal stimulation – swallow, defecation –, cough, sneeze, or post-exercise (*situational type*); or if it was triggered by cervical stimulation and carotid sinus massage was positive and reproduced symptoms (*carotid sinus syndrome*). *Orthostatic hypotension* was considered as the most likely cause of syncope when the transient loss of consciousness occurred shortly after standing from supine/sitting position and the active standing maneuver revealed significant orthostatic hypotension. Syncopal episodes that did not qualify for any of these clinical categories were classified as *unexplained syncope*.

Study follow-up

Patients were followed prospectively since the date of their inclusion in the registry to 30 September 2020 or to the date of death, whatever occurred first. Causes of death were collected from clinical records or medical certificates of death. Cardiovascular deaths were those caused by arrhythmia, refractory HF, cerebrovascular disease, arterial or venous thromboembolism, peripheral artery disease, or complications of a cardiovascular procedure, as well as unexplained sudden deaths.

Statistical analysis

In this manuscript, categorical variables are presented as number and proportions, while continuous variables are presented as mean ± standard deviation (SD) or median (interquartile rank (IQR)), depending on their adequation to normality. Comparisons among groups were performed by means of the Chi-squared test or the Fisher´s exact test for the former variables, and by means of T-student´s or Mann-Whitney´s tests for the latter variables, as appropriate.

Syncope was considered as a binary variable (yes/no) for survival analyses. Long-term survival curves of patients with and without syncope were depicted by means of Kaplan-Meier´s method and compared by means of the log rank test.

Multivariable Cox´s regression was used to control the effect of potential confounders on the statistical association observed between syncope and survival. For this purpose, syncope was considered in the model as a time-varying covariable. First, we sought to identify the independent predictors of survival in our population, so we conducted a backward stepwise analysis with a p-out criterion <0.10. In the initial step of the backward stepwise procedure, we included all clinical variables that were judged as potential confounders either on the basis of their known association with outcomes or either on the basis of an asymmetric distribution between patients with and without syncope – i.e. age, United Kingdom clinical stage [21], prior hospitalization due to heart failure, chronic pulmonary obstructive disease, NYHA class III or IV, previous pacemaker implantation, intraventricular conduction delay, left-atrium dimension, maximum wall thickness, serum bilirubin, beta-blocker use. As a result of this process, three variables were identified as independent predictors of survival in our cohort – NYHA class III or IV, prior

hospitalization due to heart failure and beta-blocker use. Adjusted hazard ratio for all-cause mortality for patients with syncope vs. patients without syncope was obtained from a multivariable model in which syncope was entered, together with these three independent prognostic predictors.

Statistical analyses were performed with SPSS 25 and Stata 14. Statistical significance was set as a p-value <0.05.

Results

Study population

Since 1 January 2018 to 30 June 2020, 128 patients with ATTR- CM were included in the AMI-GAL registry. Among them, 110 (85.9%) patients represented newly diagnosed cases of ATTR-CM – i.e. patients diagnosed with the disease after the date of beginning of the registry–, while 18 (14.1%) patients represented prevalent cases of ATTR-CM – i.e. patients who had been diagnosed with the disease before 1 January 2018 and who were followed at participating centers–. The median (IQR) time elapsed since the diagnosis of ATTR-CM until the inclusion of the patient in the registry was 0 (IQR 0–0) days for newly diagnosed cases and 671 (IQR 394–1018) days for prevalent cases.

All patients enrolled in the registry had a positive ^{99m}Tc-DPD scintigraphy. ATTR-CM was diagnosed non-invasively in 108 (84.4%) patients and invasively in 20 (15.6%) patients. Invasive diagnoses were made on the basis of a positive endomyocardial biopsy in 19 patients, and on the basis of a positive abdominal fat biopsy in 1 patient.

Genetic testing was performed in 117 (91.4%) patients with ATTR-CM; p.Val50Met mutations in the transthyretin gene were found in 2 (1.6%) of them, who were diagnosed from variant ATTR-CM. One hundred fifteen (89.8%) patients with negative genetic testing were diagnosed from wild-type ATTR- CM; in the remaining 11 (8.6%) patients with ATTR-CM who did not undergo genetic testing, the subtype of the disease could not be determined.

Frequency of syncope

Before their inclusion in the prospective phase of the registry, 30 (23.4%) patients presented a history of previous syncope – i.e. those patients had experienced syncopal episodes before being enrolled in the registry–. Among them, 12 (9.4%) patients had a previous history of relapsing syncope (≥2 previous episodes of syncope).

In four patients with a history of previous syncope before registry enrollment, syncope had occurred subsequently after the diagnosis of ATTR-CM. In 25 of the remaining 26 patients with a history of previous syncope, the clinical evaluation of syncope had included a transthoracic echocardiogram, which constantly showed left ventricular hypertrophy. However, a definite diagnosis of ATTR-CM was only reached at that moment as a result of the diagnostic work-up for syncope in seven patients, while it was deferred by several months or years in the rest of them. The median time elapsed from the first syncopal episode to the definite diagnosis of ATTR-CM was 940 days (95% CI 64–2016).

After their enrollment in the registry, patients were followed prospectively during a median period of 520 days (IQR 334–684). Over this prospective follow-up period, 8 (6.2%) patients experienced a total of 13 episodes of syncope. Four of these eight patients had a previous history of syncope before registry enrollment, while the other four had not. The incidence density rate of syncope during prospective follow-up after registry enrollment was 71.9 episodes per 1000 patients-year (95% Confidence Interval (CI) 32.8–111.1).

Considering both their past clinical history before registry enrollment and the prospective follow-up period after registry enrollment, 34 out of the 128 studied patients with ATTR-CM had at least one syncopal episode. Thus, the overall prevalence of syncope in the study population was 26.6% (95% Confidence Interval (CI) 18.9%–34.2%).

Baseline clinical characteristics of patients with and without syncope

Table 1 shows the baseline clinical characteristics of patients with ATTR-CM who suffered at least one episode of syncope, as compared with patients who did not.

Patients with syncope presented a significantly higher total bilirubin than patients without syncope ($p = 0.023$), as well as longer PR ($p = 0.041$), longer QRS ($p = 0.008$) and longer

corrected QT (p = 0.025) intervals at 12-lead electrocardiograms. The prevalence of previous pacemaker implantation (p = 0.027) was also significantly higher in patients with syncope.

Patients with syncope also presented numerically higher prevalence of prior hospitalization due to HF (41.2% vs. 25.5%) and NYHA class III or IV (47.1% vs. 30.9%), as well as numerically higher mean ventricular wall thickness (18.4 vs. 17.3 mm) and mean left atrial dimension (48.3 vs. 45.8 mm), than patients without syncope; however, these differences did not reach statistical significance (p > 0.05 for all these contrasts).

Clinical profile and underlying causes of syncope

Table 2 shows the clinical profile, type, and presumed underlying causes and mechanisms of syncope in the study population.

The most frequent circumstances in which syncope occurred were during exertion (n = 11), while standing up (n = 8), while sitting down (n = 5), and shortly after postural changes (n = 5). Specific triggers of syncope like pain (n = 2) and cervical movements (n = 1) were infrequent.

Cardiac syncope was diagnosed in 16 (47%) patients, including 5 patients with syncope attributable to structural disorders of the heart or great vessels – 3 patients with severe aortic stenosis, 2 patients with pulmonary embolism – and 11 patients with syncope due to cardiac arryhtmias – third- degree AV block in 8 cases, second-degree Mobitz II AV block in 1 case, atrial fibrillation with fast ventricular rate in 1 case, and atrial flutter with fast ventricular rate in 1 case–.

Among 18 (53%) patients in whom a cardiac cause of syncope was not detected, a neurally mediated reflex was considered the most probable underlying mechanism of fainting in 6 (17.6%) cases, while 4 (11.8%) cases were attributed to orthostatic hypotension.

The underlying cause of syncope remained unexplained in 8 (23.5%) patients. In these subjects, the diagnostic work-up included 24-hour electrocardiographic monitoring in five cases and the implantation of a subcutaneous loop recorder in one case. The remaining two patients with unexplained syncope were scheduled straightforward to

prophylactic pacemaker implantation, due to the presence of bifascicular block at their baseline electrocardiograms.

Permanent pacemakers were also implanted in all nine patients who experienced syncope due to bradyarrhythmias, as well as in two patients with neurally mediated syncope – one case due to the presence of bifascicular block and one case due to carotid sinus syndrome.

Relapsing syncope

Nineteen (55.9%) out of 34 patients with syncope suffered ≥2 episodes of fainting. Relapsing syncope was attributed to a neurally mediated mechanism in four patients and to orthostatic hypotension in three patients. Cardiac causes of relapsing syncope were bradyarrhythmias (n = 5), tachyarrhythmias (n = 1), and aortic stenosis (n = 2). All patients with relapsing syncope of a cardiac origin stopped fainting after the cardiac cause of syncope was corrected, except 1 patient with a first episode of syncope due to third degree atrioventricular block who underwent pacemaker implantation and who suffered a subsequent episode of syncope due to orthostatic hypotension several months later. An underlying cause of syncope could not be identified in four patients, who were diagnosed with relapsing syncope of an unknown origin.

Survival

At the end of the prospective follow-up period of the study, 21 (16.4%) patients with ATTR-CM had died. Figure 1 shows the cumulative estimates of the long-term survival of patients with or without syncope, obtained by means of the Kaplan–Meier´s method. Patients with syncope had statistically significant lower survival as compared to both by means of the log rank test (p = 0.0003).

By means of univariate Cox´s regression, we estimated an unadjusted hazard ratio for all-cause mortality for patients with syncope vs. patients without syncope of 3.37 (95% CI 1.43–7.94). When other independent predictors of survival were added to the multivariable model – NYHA class III or IV, prior hospitalization due to HF and beta-blocker use–, the association between syncope and all-cause mortality was no longer statistically significant (adjusted HR 1.81, 95% CI 0.67– 4.84). Univariate and multivariate HR of all variables, which were assessed as potential confounders that could

affect the statistical association between syncope and mortality are presented in the *Supplemental Figure 1*.

Causes of death

Table 3 shows a description of the mode of death in patients who presented syncopal episodes and in those who did not. A total of 17 (80.9%) deceases were due to cardiovascular causes, with refractory HF and sudden death the most frequent. Syncope was a major contributor of death in one patient with recurrent neurally mediated vasovagal syndrome who died due to sequelae of head trauma following a syncopal episode.

Discussion

To the best of our knowledge, this is the first study that assessed in a comprehensive manner the clinical profile, underlying causes, and outcomes of syncope in patients with ATTR-CM. Roughly more than one-quarter of patients with ATTR-CM included in our multicentre registry experienced at least one syncopal episode, either as a previous antecedent before enrollment or during subsequent follow-up; in near one-half of these individuals, cardiac arrhythmias and structural diseases of the heart or great vessels that coexisted with ATTR-CM were identified as the most probable underlying causes of fainting. Patients with ATTR-CM and a history of syncope presented lower non-adjusted long-term survival; however, the antecedent of syncope was no longer an independent predictor of all-cause mortality after multivariable adjustment for potential confounders.

In our prospective cohort of patients with ATTR-CM, most of them wild type, we estimated an overall prevalence of syncopal episodes of 26.2% and an annualized incidence rate of 7.1%. In the American cohort of the international Transthyretin Amyloidosis Outcomes Survey [13], 8% patients with variant ATTR-CM (p.Val112Ile) and 12.2% patients with wild-type ATTR- CM had antecedents of syncope before enrollment. The prevalence of syncope was 21.5% in a small, single-center, historical cohort study of patients with ATTR-CM in A Coruña, Spain [5].

Variations in the reported prevalence of syncope are conditioned by heterogeneous reporting methods and the different clinical profiles of the studied populations.

Remarkably, the patients included in our registry were older than those enrolled in the American cohort [13]. In the general population, the frequency of syncope increases with age [22]; in octogenarians, the annualized incidence of syncope approaches 2% and its prevalence may exceed 20% [23].

Despite syncope is rather common in patients with ATTR- CM, it has been infrequently described as the clinical presentation of the disease. In the two previous single-center reports, syncope was the initial symptom of ATTR-CM in 4.4% [24] and 6% [25] patients, respectively. In our cohort, a definite diagnosis of ATTR-CM was made as the result of a clinical evaluation for syncope in 5.5% patients. However, most patients with a history of previous syncope who were enrolled in our study already showed signs of significant left ventricular hypertrophy in the echocardiographic evaluation performed for evaluation of syncope. This fact suggests that the diagnosis of ATTR-CM might be initially overlooked in a significant proportion of these individuals, so syncope might be a more frequent presentation of the disease than previously thought.

Cardiac arrhythmias [26], and more specifically bradyarrhythmias, were the most frequent underlying mechanisms of syncope in our study. Baseline electrocardiograms of patients with ATTR-CM and syncope frequently showed prolonged PR and QRS intervals, bundle-branch blocks and/or bifascicular blocks; not surprisingly, advanced atrioventricular block was the underlying cardiac rhythm in all cases of bradyarrhythmic syncope. A high incidence of conduction disorders leading to pacemaker implantation has been reported in patients with ATTR-CM [12]; also, advanced atrioventricular block followed by pulseless activity has been described as a frequent terminal event preceding cardiovascular death in patients with light-chain amyloid cardiomyopathy [14]. In our study, no syncopal episode was attributable to ventricular arrhythmias, contrary to what has been described by other authors [27].

In subjects with structurally normal hearts, supraventricular tachycardia rarely causes syncope. However, in patients with systolic dysfunction and/or restrictive physiology, a sudden loss of atrial contribution to ventricular loading, together with a significant shortening of the duration of ventricular diastole, may result in an abrupt reduction of cardiac output, hypotension, and fainting. This was the most likely underlying mechanism of syncope in two patients of our study, in which paroxysmal atrial fibrillation or flutter with fast ventricular rate were detected during the episode.

Cardiac amyloidosis often coexists with, or predisposes to, other structural diseases of the heart or great vessels, which themselves may cause syncope. Heart valve amyloid infiltration may lead to valve dysfunction; indeed, severe aortic stenosis was assumed as the underlying cause of syncope in three patients in our study. A study suggested that ATTR-CM could be present in up to 16% patients with severe aortic stenosis referred for transcatheter aortic valve implantation [28].

A neurally mediated reflex and/or orthostatic hypotension were assumed as the most probable underlying mechanisms of syncope in a substantial proportion of patients in whom a structural or arrhythmic cause was not detected. Orthostatic intolerance due to autonomic neuropathy [29] is characteristic of patients with light chain amyloid cardiomyopathy and of patients with variant ATTR-CM; it is less frequent, but it may also occur, in elderly patients with wild-type ATTR-CM, especially in those treated with vasodilators or diuretics. Neurally mediated reflex syncope is largely the most frequent cause of syncope in the general population [22]; it may also affect patients with ATTR-CM, in whom it often coexists with orthostatic intolerance, and may cause severe symptoms [12].

A few cases of syncope registered in our study remained unexplained after diagnostic work-up. Most of these patients experienced exertional syncopal episodes, which have been also described in individuals with light chain amyloid cardiomyopathy and might be triggered by dynamic left ventricular outflow obstruction or by myocardial ischemia due to coronary microvascular dysfunction [10].

In our study, patients with ATTR-CM and a history of syncope showed increased non-adjusted all-cause mortality as compared with the rest of the cohort; however, syncope did not retain a statistically significant independent prognostic value after multivariable adjustment. Patients with syncope showed signs of more advanced cardiac disease, with numerically higher (not statistically significant) prevalence of previous HF hospitalization and advanced NYHA classes, as well as higher ventricular wall thickness and left atrial dimension. This fact might explain, at least partially, the increased non-adjusted risk of death observed in these individuals; indeed, cardiovascular causes accounted for most of the deaths registered during long-term follow-up. Furthermore, the frequent use of pacemakers in our cohort might have reduced the potential negative prognostic impact of syncope.

However, a history of syncope was identified an independent predictor of mortality in a prospective multi-institutional study of 472 patients with cardiac amyloidosis who carried an implantable defibrillator [30], while recent syncope was independently associated with increased mortality in a prospective, single-center Italian study of 48 consecutive patients with cardiac amyloidosis [31]. Unfortunately, the type of amyloid was not reported in these studies [30,31], so no specific conclusions can be extracted from them for the specific population of patients with ATTR-CM.

This study has a few limitations. First, our analysis is based on a general registry of patients with cardiac amyloidosis, which was not designed for the specific aim of this investigation. Second, the inclusion of patients with the variant ATTR- CM was anecdotal; moreover, the lack of genetic testing prevented us to identify the specific subtype of the disease in 9% of the studied subjects. Third, the diagnostic and therapeutic approaches of syncope was not homogeneous and depended on local practices of participating centers; it is possible, indeed, that a higher use of long-term electrocardiographic monitoring devices could have increased the diagnostic yield in patients with unexplained syncope. Fourth, the baseline clinical variables of ATTR-CM patients were collected at the time of their inclusion in the registry; given that a significant number of syncopal events had occurred prior to enrollment, we could not explore potential causative associations. We recognize that evaluating the clinical characteristics of remote episodes of syncope may be difficult. We conducted a comprehensive review of past medical records of all patients with a history of previous syncope, which were fully accessible for the research team in all cases. Syncopal episodes considered for the study were those for which the patient consulted to a physician and so, those that motivated a specific clinical evaluation, which was reflected in patients´ medical records. We cannot rule out that some patients presented syncopal episodes for which they did not consult and so were not evaluated by a physician and were not mentioned in patients´ medical records. Finally, the small sample size, short follow-up, and limited number of events of this study prevented us from making a separate analysis of the impact of syncope on the risk of different specific modes of death. Given these limitations, our results must be considered only as hypothesis generating and require further confirmation.

In conclusion, our study suggests that syncope is a frequent clinical manifestation in patients with ATTR-CM. In this population, underlying causes of syncope include cardiac arrhythmias, coexisting structural diseases like aortic stenosis, and syncope attributable to orthostatic hypotension and/or neurally mediated reactions. In our cohort, patients with ATTR-CM and syncopal episodes showed signs of a more advanced cardiac disease and higher non-adjusted all-cause mortality; however, this study could not demonstrate an independent prognostic effect of syncope on survival.

Future studies based on a wider use of long-term monitoring devices are warranted in order to define the optimal therapeutic management of syncope in patients with ATTR-CM, especially in those that remain unexplained after the initial diagnostic work-up.

Acknowledgments

Five investigators of this study (G. B-C., E. B-C., I. G-O., A. V-R., and M.G. C-L.) are members of the Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBER-CV) of the Instituto de Salud Carlos III Spanish Ministry of Science and Innovation, Spanish Government.

Disclosure of financial/other conflicts of interest

G. B-C. received travel grants, speaker fees, and a research grant from Pfizer (not related to the present study). E. B-C. received speaker fees from Pfizer.

A reviewer of this manuscript has disclosed speaker fees from Pfizer, Alnylam. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Funding

This study was founded by means of a competitive research grant from the Sociedad Gallega de Cardiología (SOGACAR) and an independent research grant from Pfizer (ID number 54963821).

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Table 1. Baseline clinical characteristics of study participants.

	With syncope (n = 34)	Without syncope (n = 94)	P-value
Clinical history			
Age (years), mean ± standard deviation	81.6 ± 6.5	80.8 ± 5.8	0.520
Women, n (%)	6 (17.6%)	22 (23.4%)	0.486
Time elapsed since the diagnosis of cardiac amyloidosis (days)	189 ± 432	81 ± 261	0.178
Hypertension	26 (76.5%)	61 (64.9%)	0.215
Hypercholesterolemia	19 (55.9%)	56 (59.6%)	0.708
Diabetes mellitus	6 (17.6%)	21 (22.3%)	0.565
Coronary artery disease	5 (14.7%)	12 (12.8%)	0.773
History of atrial fibrillation or flutter	18 (52.9%)	54 (57.4%)	0.650
Cardiac pacemaker	10 (29.4%)	12 (12.8%)	0.027
Prior hospitalization due to heart failure	14 (41.2%)	24 (25.5%)	0.087
Cerebrovascular disease	7 (20.6%)	13 (13.8%)	0.352
Chronic obstructive pulmonary disease	1 (2.9%)	15 (16%)	0.068
Peripheral artery disease	3 (8.8%)	7 (7.4%)	0.725
Tendinopathy	13 (38.2%)	33 (35.1%)	0.745
Peripheral neuropathy	0	2 (2.1%)	0.538
Clinical status			
United Kingdom clinical stage**			0.417
Stage I	16 (48.5%)	47 (51.6%)	

Stage II	13 (39.4%)	26 (28.6%)	
Stage III	4 (12.1%)	18 (19.8%)	
New York Heart Association Class III or IV	16 (47.1%)	29 (30.9%)	0.090
Exploratory signs of congestión	22 (64.7%)	50 (53.2%)	0.246
Right-sided	21 (61.8%)	43 (45.7%)	
Left-sided	11 (32.4%)	28 (29.8%)	
Systolic blood pressure (mm Hg)	124 ± 21	126 ± 16	0.594
Heart rate (beats per minute)	75 ± 15	73 ± 14	0.554
Electrocardiography			
PR duration (msec)*	231 ± 47	207 ± 36	0.041
QRS duration (msec)*	124 ± 23	110 ± 23	0.008
QTc duration (msec)*	474 ± 32	456 ± 35	0.025
Intraventricular conduction delay	25 (73.5%)	52 (55.3%)	0.063
Left anterior fascicular block	4 (11.8%)	14 (14.9%)	
Left posterior fascicular block	0	2 (2.1%)	
Right bundle branch block	3 (8.8%)	7 (7.4%)	
Left bundle branch block	4 (11.8%)	11 (11.7%)	
Right bundle branch block + anterior left fascicular block	7 (20.6%)	6 (6.4%)	
Right bundle branch block + posterior left fascicular block	0	2 (2.1%)	
Ventricular pacing	7 (20.6%)	10 (10.6%)	
Cardiac imaging			
Left ventricular ejection fraction (%)	52.1 ± 12.3	53 ± 12.6	0.708
Left ventricular end-diastolic diameter (mm)*	43.8 ± 8.8	43.7 ± 6.6	0.955
Maximum wall thickness (mm)	18.4 ± 3.2	17.3 ± 3	0.061

E/E´ ratio*	16 ± 5.3	14.8 ± 5.4	0.300
Transmitral flow*			0.870
Normal	1 (2.9%)	1 (1.1%)	
Prolonged relaxation	7 (20.6%)	16 (17%)	
Pseudonormal	3 (8.8%)	10 (10.6%)	
Restrictive	12 (35.3%)	27 (28.7%)	
Unknown (atrial fibrillation)	9 (26.5%)	32 (34%)	
Not measured	2 (5.9%)	8 (8.5%)	
Left atrium dimension (mm)*	48.3 ± 5.9	45.8 ± 6.5	0.053
Tricuspid annulus plain systolic excursion (mm)	16.2 ± 3.9	16.8 ± 3.8	0.441
Pericardial effusion	8 (23.5%)	16 (17.6%)	0.453
Moderate or severe valvular heart disease	14 (41.2%)	36 (38.3%)	0.768
Aortic stenosis	6 (17.6%)	10 (10.6%)	
Aortic regurgitation	1 (2.9%)	3 (3.2%)	
Mitral regurgitation	5 (14.7%)	13 (13.8%)	
Tricuspid regurgitation	7 (20.6%)	22 (23.4%)	
Laboratory tests			
Hemoglobin (g/dl)	13.5 ± 1.5	13.8 ± 1.7	0.465
Creatinin (mg/dl)	1.24 ± 0.39	1.34 ± 1.14	0.594
Bilirubin (mg/dl)	1.39 ± 0.99	0.99 ± 0.84	0.023
Albumin (g/dl)	4.21 ± 0.41	4.19 ± 0.36	0.800
NTproBNP (ng/ml)*	3789 ± 2847	4087 ± 4363	0.716
Therapies			
Tafamidis	20 (58.8%)	48 (51.1%)	0.437

Beta-blocker	13 (38.2%)	52 (55.3%)	0.088
Angiotensin converter enzyme inhibitor	5 (14.7%)	19 (20.2%)	0.612
Angiotensin 2 receptor blocker	9 (26.5%)	21 (22.3%)	0.626
Mineralocorticoid receptor antagonist	8 (23.5%)	28 (29.7%)	0.487
Loop diuretic	25 (73.5%)	70 (74.5%)	0.915
Thiazide	8 (23.5%)	13 (13.8%)	0.191
Digoxin	0	6 (6.4%)	0.340
Amiodarone	2 (5.9%)	3 (3.2%)	0.608
Calcium channel blockers	1 (2.9%)	5 (5.4%)	0.494
Oral anticoagulant	18 (52.9%)	56 (60.2%)	0.502
Aspirin	6 (17.6%)	9 (9.6%)	0.210
Statin	18 (52.9%)	53 (56.4%)	0.729

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* Missing values: United Kingdom clinical stage (N = 4), PR interval (N = 71), QRS interval (N = 21), QTc interval (N = 26), left ventricular end-diastolic diameter (N = 4), E/E´ relation (N = 18), transmitral flow (N = 51), left atrial dimension (N = 1), NTproBNP (N = 4).

** Stage I = NTproBNP≤3000 pg/ml and glomerular filtration rate ≥45 ml/min.

Stage III = NTproBNP>3000 pg/ml and glomerular filtration rate <45 ml/min.

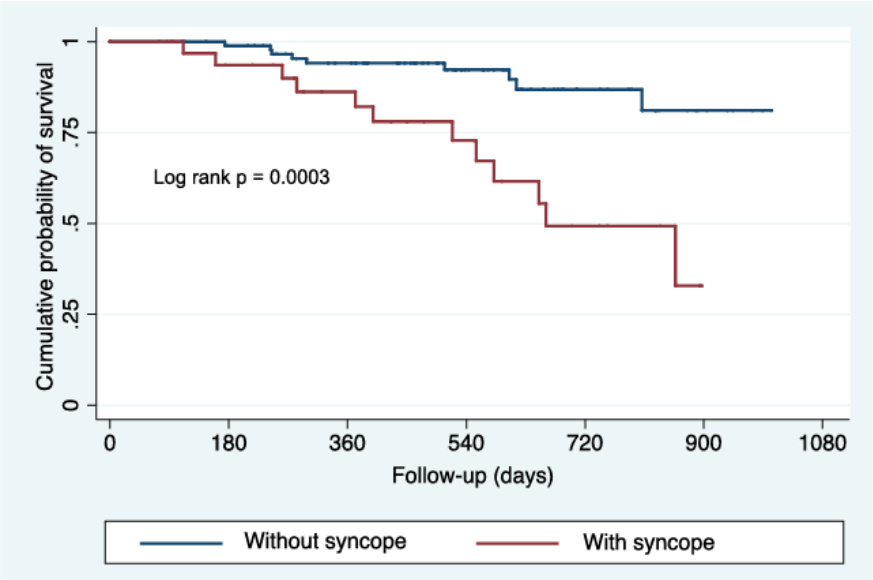
Stage II = Patients not classified as stage I or stage III.

Gillmore J, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J 2018; 39: 2799–2806.

Table 2. Clinical presentation and underlying causes of syncope.

Type of syncope	No. patients with syncope	No. patients with ≥2 episodes of syncope	Circumstances and triggers	Specific etiologies
Structural cardiac/ vascular	5	2	On exertion (n = 3) While standing up (n = 1) After postural change (n = 1)	Aortic stenosis (n = 3) Pulmonary embolism (n = 2)
Arrhythmic	11	6*	While sitting down (n = 4) On exertion (n = 3) While standing up (n = 2) While sleeping (n = 1) Circumstances not recorded (n = 1)	Atrial fibrillation with fast ventricular rate (n = 1) Atrial flutter with fast ventricular rate (n = 1) Third-degree AV block (n = 8) Mobitz II second-degree AV block (n = 1)
Neurally mediated	6	4	While standing up (n = 3) Triggered by pain (n = 2) Triggered by cervical movements (n = 1)	Vaso-vagal reflex (n = 5) Carotid sinus syndrome (n = 1)
Orthostatic	4	3	After postural change (n = 4)	Orthostatic hypotension (n = 4)
Unexplained	8	4	On exertion (n = 5) While standing up (n = 2) While sitting down (n = 1)	Unknown (n = 8)

*One patient with a first episode of syncope due to third degree atrioventricular block presented a subsequent episode of syncope after pacemaker implantation, which was attributed to orthostatic hypotension.



With syncope (N at risk)	34	28	21	14	6	0	0
Without syncope (N at risk)	94	87	73	43	19	6	0

Figure 1. Kaplan-Meier estimates of the cumulative probability of survival in patients with transthyretin amyloid cardiomyopathy with or without syncope. N, number of patients.

Table 3. Causes of death during prospective follow-up.

	With Syncope (n = 12)	Without syncope (n = 9)
Cardiovascular cause of death		
Refractory heart failure	7	3
Sudden death	2	2
Bowel ischemia	0	1
Lower limb ischemia	0	1
Ischemic stroke	0	1
Non-cardiovascular cause of death		
Malignancy	1	0
Infection	1	0
Mixed cause of death		
Head trauma due to syncope	1	0
Unknown cause of death	0	1