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Clinical features and survival in senile systemic amyloidosis: comparison to familial transthyretin cardiomyopathy

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Abstract

Senile systemic amyloidosis (SSA) features cardiomyopathy resulting from amyloid deposits of wild-type transthyretin (TTR). From 1994 to 2009, 82 patients with SSA were diagnosed at our center; 79 were men (96%) and median age at diagnosis was 73.8 years (range, 59.1–86.0). Most patients (77/78) presented with abnormal echocardiography; median values for interventricular septal thickness and left ventricular ejection fraction were 16 mm (range, 9–24) and 50% (range, 20–70), respectively. Fat aspirates were positive for amyloid in 27% of patients. Mean levels of brain natriuretic peptide ($n = 41$) and troponin I ($n = 19$) were 422 ± 279 pg/ml and 0.151 ± 0.107 pg/ml. Median survival was 4.3 years (95% CI, 3.7–5.0). SSA and familial TTR cardiomyopathy were compared; survival distribution was significantly different across groups (log-rank test = 11.97, p-value = 0.0075). We conclude that patients with SSA are primarily men who present with dominant cardiac involvement at an older age than patients with familial TTR cardiomyopathy.

Introduction

Cardiac dysfunction is a significant health issue in an aging population. One in four individuals over the age of 80 years has cardiac amyloid deposits and this occurrence is fatal in 10% of cases [1,2]. Senile systemic amyloidosis (SSA) causes a restrictive cardiomyopathy that has been described primarily in elderly men [3]. Cardiac amyloid deposits in SSA are composed of wild-type transthyretin (TTR) [4]. The data described in this report are from a cross-sectional and longitudinal (5-year) study of patients with SSA evaluated at our center. The goals are to accurately characterize the clinical features of SSA in a large clinical population and to detail the biochemical nature of circulating and deposited forms of wild-type TTR in SSA.

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Methods

The study group consisted of patients evaluated at the Boston Medical Center Amyloid Clinic between 1994 and 2009. Informed consent for data and sample collection was obtained from patients with prior approval from the Boston University Medical Campus Institutional Review Board. A diagnosis of SSA was based on the following criteria: Congo red positive tissue biopsy, confirmation of TTR amyloid deposits in the tissue biopsy by immunohistochemistry or immunogold staining, negative testing for a plasma cell dyscrasia (ruling out AL), and proof that a pathologic TTR mutation or variant was not present by DNA sequencing or mass spectrometric analysis. Cardiac function was assessed by echocardiogram. Electrocardiogram (ECG), brain natriuretic peptide (BNP), and troponin I levels were also determined. Patients were diagnosed with cardiac involvement if they had clinical symptoms of heart failure and/or interventricular septal thickening ≥12 mm on echocardiogram without a history of hypertension. When cardiac symptoms occurred as the major manifestation of amyloidosis, patients were considered to have dominant cardiac involvement. Renal involvement was present if a 24-h urinary protein excretion was >1.0 g and/or renal insufficiency was not attributed to cardiac dysfunction. Survival was measured as the time from tissue diagnosis of amyloidosis until death; survival curves were estimated using the Kaplan–Meier method. The log-rank test was used to compare the survival distributions in SSA and mutant TTR forms of cardiomyopathy, ATTR-T60A, -S77Y, and -V122I. When appropriate, hazard ratios were used to characterize differences between survival curves. Cox regression was used to test the significance of age-adjusted hazard ratios. All analyses were conducted in SAS 9.1 (SAS Institute, Inc, Cary, NC) and statistical significance was $p < 0.05$.

Results and discussion

Between 1994 and 2009, more than 2000 patients ≥60 years were evaluated for a diagnosis of amyloidosis at our center; 82 (4%) were diagnosed with SSA. The clinical characteristics and cardiac findings are presented in Table I. Patients with SSA were predominantly men (79/82) and had a median (range) age at diagnosis of 73.8 (59.1–86.0) years. Cardiac involvement was featured in 80/82 of the group. Cardiomyopathy was the presenting feature in almost the entire (77/78) group; 70/72 had dominant cardiac involvement. In 19 patients with SSA and a history of hypertension, 18 had cardiac involvement; of these, 11/18 had a heart biopsy positive for amyloid and TTR, 5/18 had severe cardiomyopathy with a septal thickness of 16–20 nm unquestionably suggesting SSA, and 2/18 had less severe cardiomyopathy that was attributed to amyloid when the echocardiographic images were reviewed by the cardiologist. Other clinical signs of amyloidosis, including carpal tunnel syndrome, peripheral neuropathy, autonomic neuropathy, and renal involvement were rare. The frequency of detecting amyloid deposits in fat aspirates was low (27%). Median survival was 46.0 months (95% CI, 36.0–61.0).

In the 80 patients with cardiac involvement, 86% had heart failure symptoms with NYHA Functional Class > I. An abnormal ECG was found in 93% of patients and nearly all (99%) had an abnormal echocardiogram. Patients had cardiomyopathy with thickened left ventricular walls; the median interventricular septal thickness was 16 mm. Clinical markers

of cardiac involvement were markedly elevated; mean levels of BNP ($n = 41$) and troponin I ($n = 19$) were 422 pg/ml and 0.151 pg/ml, respectively.

The characteristics of SSA were compared to features in patients with amyloidotic cardiomyopathy related to mutant forms of TTR including T60A ($n = 48$), S77Y ($n = 13$), and V122I ($n = 35$). As in SSA, men were over-represented in the three ATTR groups (63%, 69%, and 77%). For T60A, S77Y, and V122I, median ages at diagnosis were 64.1 (54.9–82.9), 63.8 (51.7–74.3), and 70.0 (53.6–92.5) years compared to 73.8 (59.1–86.0) years in SSA. Gender and age distributions were different across groups ($p < 0.001$). Median survivals (95% CI) in ATTR due to T60A, S77Y, and V122I were 59.0 (41.0–121.0), 62.0 (38.0–165.0), and 41.0 (24.0–48.0) months and 5-year survival percentages (95% CI) were 49.1 (29.9–65.8), 54.5 (22.9–78.0), and 30.7 (13.0–50.5). The Kaplan–Meier survival curves for all groups are shown in Figure 1. Survival differences were significant across all groups ($p = 0.008$) for unadjusted analyses. When the data were adjusted for age, there was no significant difference ($p = 0.337$).

In summary, patients with SSA are predominantly men who present with dominant cardiac involvement as evidenced by an abnormal echocardiogram, ECG, and/or cardiac biomarker measurements. Heart failure is a more frequent manifestation than arrhythmia. Compared to ATTR, SSA is diagnosed at an older age. The median survival in SSA is <4 years which is similar to ATTR-V122I, but significantly different when compared to ATTR-T60A and ATTR-S77Y, in which median survivals are ≥5 years.

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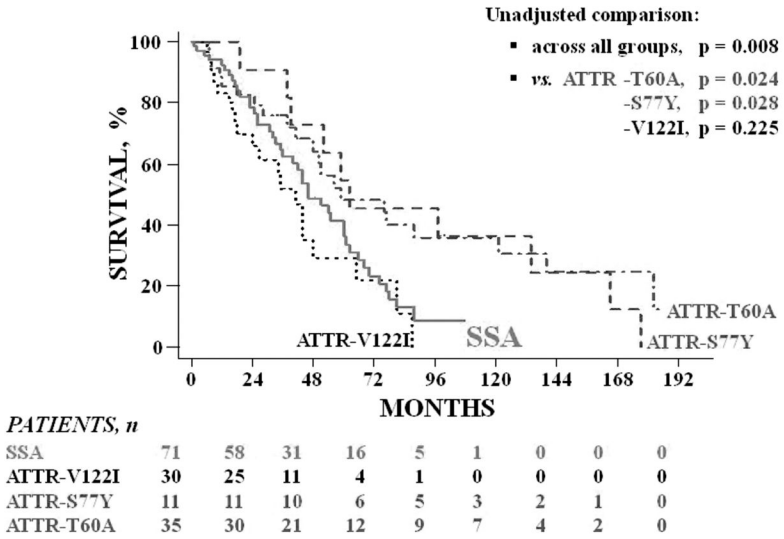

Figure 1.

Kaplan–Meier analysis of the probability of survival for patients with SSA *versus* ATTR.

Table I

Features of cardiac amyloidosis in patients with SSA.

Feature	Number
Clinical characteristics	*N* = 82
Age at diagnosis (years), median (range)	73.8 (59.1–86.0)
Male, *n* (%)	79/82 (96%)
Cardiomyopathy, *n* (%)	77/78 (99%)
Dominant cardiac involvement, *n* (%)	70/72 (97%)
History of hypertension, (%)	19/74 (26%)
Carpal tunnel syndrome, *n* (%)	5/80 (6%)
Peripheral neuropathy, *n* (%)	7/75 (9%)
Autonomic neuropathy, *n* (%)	4/74 (5%)
Renal involvement, *n* (%)	2/75 (3%)
Amyloid deposits in fat aspirate, *n* (%)	20/75 (27%)
Survival (months), median (95% CI)	46.0 (36.0–61.0)
Cardiac findings	*N* = 80
NYHA Functional Class > I, *n* (%)	68/79 (86%)
Abnormal ECG, *n* (%)	67/72 (93%)
Low voltage, *n* (%)	22/67 (33%)
Supraventricular arrhythmias, *n* (%)	37/65 (57%)
Abnormal echocardiography, *n* (%)	77/78 (99%)
Interventricular septal thickness (mm), median (range)	16 (9–24)
Left ventricular ejection fraction, % median (range)	50% (20–70)
BNP (pg/ml), mean ± SD	422 ± 279 (*n* = 41)
Troponin I (pg/ml), mean ± SD	0.151 ± 0.107 (*n* = 19)